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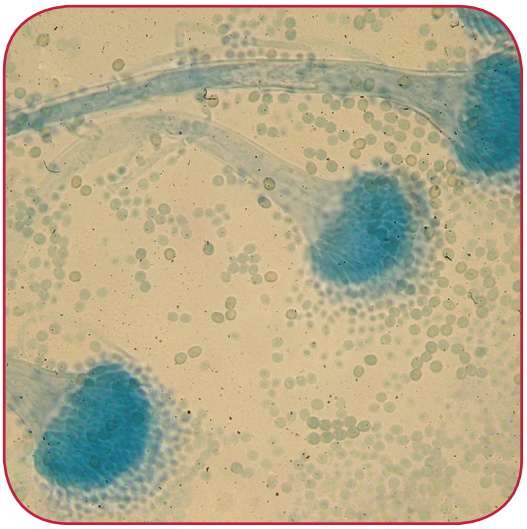

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COMMENTARY
Facial transplantation: from the early trials to ethical and clinical guidelines

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Abstract
Facial transplantation is a complex technique that involves a number of risks. However, although it is not a lifesaving transplant, for individuals in dramatic conditions due to severe facial disfigurements, it constitutes the only possibility of recovering an acceptable quality of life. For this reason, even from an ethical point of view, it is considered an important therapeutic resource, provided it is conducted in rigorously-controlled conditions.

Key words
- ethics
- organ
- transplantation
- risk

Organ transplantation is one of the most important medical developments to have taken place in recent decades. The number of individuals who benefit from this therapeutic resource every year continues to rise.

For a number of years now, in addition to organ transplants, multi-tissue transplants have also been possible. In these procedures, a number of tissues are harvested from a donor cadaver and used to reconstruct parts of the recipient's body. Although multi-tissue transplants are not life-saving procedures, they can allow huge improvements in the recipient's quality of life.

The first multi-tissue transplant was performed on 23 September 1998 when, at the Édouard-Herriot Hospital in Lyon, a team led by Jean-Michel Dubernard transplanted the right hand (harvested from a deceased forty-one-year-old man) on to forty-eight-year-old New Zealander Clint Hallam, who had undergone an amputation.

Dozens of hand, upper limb and even lower limb transplants have been performed since.

Of the various types of multi-tissue transplants, facial transplants are particularly complex from a technical standpoint and, above all, raise important ethical questions [1].

Those who are eligible for face transplants are carefully-selected individuals who have severe facial disfigurations for various reasons and for whom there are no longer any alternative conventional plastic surgery or reconstruction options [2]. These individuals have severe limitations when expressing themselves, in their interpersonal relationships and when breathing and eating. So far, a few dozen face transplants have been conducted around the world. In most cases, the transplant regards a limited part of the face below the eyes, including the cheeks down to the chin. All those cases approved for facial transplantation had extremely serious lesions, for which there were no reconstruction options.

The first face transplant was performed in France at Amiens university hospital on 27 November 2005 by two teams (led by surgeons Jean-Michel Dubernard and Bernard Devauchelle). The patient (Isabelle Dinoire, a 38-year-old mother-of-two whose face had been mauled by her Labrador) was transplanted the tip of a nose, lips and chin [3, 4].

The second face transplant was performed on 14 April 2006 at Xijing military hospital in the city of Xian, in northern China, on a thirty-year-old patient, Li Guoxing, who had been attacked by a bear in 2004 [5]. This case was more complex than the previous transplant performed in France: two-thirds of the patient's face were completely disfigured and the transplant involved a cheek, upper lip, nose and one eyebrow. The patient was discharged on 30 July 2006.

Although the techniques used have improved over time, facial transplantation is still a highly complex procedure. Suffice to think that for the first facial transplant performed in Canada (in spring 2018 by surgeon Daniel Borsuk on a patient who had lost his nose and upper jaw in a hunting accident), it took 12 hours to harvest the tissues from the donor, 16 hours to prepare the recipient and 18 hours for the transplant.

From a clinical standpoint, the issues connected with a highly complex procedure are obvious: "Facial allografts could fail in the short or the long term. Technical failure, immunological problems, and poor selection of patients are significant risks" [6].

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Given the limited number of transplants performed to date, few follow-up data are available. Some of the data available highlight the numerous risks. For example, a group of French researchers followed the results of seven patients who received transplants between 2000 and 2009. Four of them had suffered firearm injuries to the face, one had suffered burns and two had had facial tumours. Over an average of six years' follow-up, two patients died (one due to failure of the transplant and infections and another committed suicide just over three years after the transplant). All the patients experienced episodes of rejection and the surviving patients continued taking high doses of steroids for years after the surgical procedure [7].

Face transplants also raise serious ethical issues, especially as regards self-identification, interpersonal relationships and social involvement [8, 9].

Further important issues regard the donor, the consent expressed while he/she was alive and the family's assent.

The recipient's mental health makes a crucial contribution to the success or failure of a face transplant. For this reason, subjects have to be chosen very carefully. Indeed, the multidisciplinary transplant teams involved always include psychologists and social workers.

When face transplants were in their early days, a number of authoritative institutions had expressed their opinion against face transplants.

For example, in Great Britain, face transplantation was first proposed on 25 November 2002 by surgeon Peter Butler, of the Royal Free Hospital in London, for a twenty-three year-old woman, called Elizabeth, who had a very serious road traffic accident on 21 September 2001. An opinion was sought of the Royal College of Surgeons, which published its opinion in November 2003 (the opinion was subsequently updated in November 2006) [10]. The report identified a number of issues that were particularly serious from a technical and scientific, psychological and ethical point of view. The Royal College came to the following conclusions: "The working party believes that until there is further research and the prospect of better control of these complications it would be unwise to proceed with human facial transplantation. Equally this conclusion does not underestimate the suffering of those patients who might be tempted by the prospect of facial transplantation. This conclusion is not adverse to facial transplantation. Indeed, it acknowledges the need to recognise it as a possible future treatment. It simply means that the work should take a much more incremental approach than some of the current hype surrounding it has suggested" [11].

On 19 February 2002, the French Comité Consultatif National d'Éthique (CCNE) was consulted regarding the topic by Laurent Lantieri, a plastic surgeon employed at the Henri Monor Hospital in Crétil, who proposed a protocol for facial transplantation. On 6 February 2004, the CCNE published its opinion, which highlighted the related issues [12] and whose conclusions were largely negative: "(T)here are ambiguities for both donors and recipients. Facial transplantations are not the same as organ transplantation and are far indeed from the graft of limbs. That is why they should not be practised before further and complimentary research have made it possible to evaluate with precision the risks inherent to this type of intervention, and to validate the results" [13].

Although the practice should still be considered experimental, over a decade after these positions were adopted, the results obtained are encouraging. For example, according to the data published in the American Journal of Transplantation in January 2015, olfactory and eating abilities were restored in 100% of cases, whereas the ability to breathe, talk, and control facial expressions improved in 93%, 71% and 76% of cases, respectively [14].

The utmost caution is required. However, the encouraging results and the fact that the transplant is the only possible way to recover certain functions and to restore the possibility of social relationships for individuals with severe facial disfigurements, lead us to consider facial transplantation an important therapeutic resource and one for which there are no alternative options.

The technique is also becoming a reality in Italy. Indeed, on 21 May 2015, the National Transplant Centre (Centro Nazionale Trapianti) submitted its project "Partial or complete facial allograft for the treatment of complex disfigurements secondary to burns, traumas, malformations and tumours" to the Ethics Committee of the Italian National Institute of Health (Istituto Superiore di Sanità) for assessment. Italian regulations (at the time an agreement dated 14 February 2002 [15], which was subsequently renewed in 2018 [16]), indeed, require that for experimental transplants the National Transplant Centre must acquire the opinion of the Ethics Committee and consult the Italian National Health Council (Consiglio Superiore di Sanità). The Italian National Institute of Health Ethics Committee approved the protocol on 4 August 2015. Despite being aware that the technique is still in the experimental stage, that there are considerable risks and that it is not a lifesaving transplant, the Committee attached special importance to the fact that this kind of transplant may constitute the only possibility for restoring an acceptable quality of life for those in dramatic conditions [17]. Subsequently, on 10 November 2015, the Italian National Health Council also expressed its favourable opinion, expressing a need for "the inclusion, in the consent form, of the possibility of performing subsequent fine-tuning procedures, in order to obtain the best possible result" [18].

This new transplantation frontier constitutes, for a very limited number of people with very severe disfigurements, the only possibility of improving their quality of life. The selection of candidates for transplantation, as well as the donors, must be particularly stringent. The use of this technique must therefore remain a rare event.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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REFERENCES

1. Edwards JA, Mathes DW. Facial transplantation: a review of ethics, progress, and future targets. Transplant Research and Risk Management. 2011;3(1):113-25.
2. Khalifian S, Brazio PS, Mohan R, et al. Facial transplantation: the first 9 years. Lancet. 2014;384(9960):2153-63.
3. Devauchelle B, Badet L, Lengelé B, et al. First human face allograft: early report. Lancet. 2006;368(9531):203-9.
4. Dubernard JM, Lengelé B, Morelon E, et al. Outcomes 18 months after the first human partial face transplantation. N Engl J Med. 2007;357(24):2451-60.
5. Xijing Hospital. Press release. 14 April 2006.
6. Butler PE, Hettiaratchy S, Clarke A. Managing the risks of facial transplantation. Lancet. 2006;368(9535):561-3.
7. Lantieri L, Grimbert P, Ortonne N, et al. Face transplant: long-term follow-up and results of a prospective open study. Lancet. 2016;388(10052):1398-407.
8. Lantieri L, Hivelin M, Audard V, et al. Feasibility, reproducibility, risks and benefits of face transplantation: a prospective study of outcomes. Am J Transpl. 2011;11(2):367-78.
9. Coffman KL, Siemionow MZ. Face transplantation: psychological outcomes at three-year follow up. Psychosomatics. 2013;54(4):372-8.
10. Kmietowicz Z. Face transplants should not be done without more research. BMJ. 2003;327(7425):1184.
11. The Royal College of Surgeons. Facial transplantation. Working Party report 2nd edition. November 2006. Available from: www.rcseng.ac.uk/-/media/files/rcs/library-and-publications/non-journal-publications/facial-transplantation-2006.pdf.
12. Houssin D. Libre propos en réaction à l'avis du Comité Consultatif National, d'Éthique sur les allontransplantations de tissu composite au niveau de la face. Les Cahiers du Comité Consultatif National d'Éthique. 2004;39:36.
13. Comité Consultatif National d'Éthique. Avis 82. L'allotransplantation de tissu composite (ATC) au niveau de la face (Greffe totale ou partiale d'un visage). 6 February 2004. Available from: www.ccne-ethique.fr/sites/default/files/publications/avis082.pdf.
14. Fischer S, Kueckelhaus M, Pauzenberger R, et al. Functional outcomes of face transplantation. Am J Transpl. 2015;15(1):220-33.
15. Conferenza permanente per i rapporti tra lo Stato, le Regioni e le Province autonome di Trento e di Bolzano. Accordo tra il Ministro della Salute, le Regioni e le Provincie autonome di Trento e Bolzano14 febbraio 2002. Repertorio atti n. 1388 del 14 febbraio 2002. Accordo tra il Ministro della Salute, le Regioni e le Province autonome di Trento e Bolzano sui requisiti delle strutture idonee ad effettuare trapianti di organi e di tessuti e sugli standard minimi di attività di cui all'articolo 16, comma 1, della legge 1 aprile 1999, n. 91 recante "Disposizioni in materia di prelievi e di trapianti di organi e di tessuti". Gazzetta Ufficiale della Repubblica Italiana – Serie Generale 3 ottobre 2002;143(232):34-5.
16. Conferenza permanente per i rapporti tra lo Stato, le Regioni e le Province autonome di Trento e di Bolzano. Accordo, ai sensi dell'articolo 2, comma 1, lettera b), e 4 comma 1, del decreto legislativo 28 agosto 1997, n. 281, tra il Governo, le Regioni e le Province autonome di Trento e Bolzano sulla proposta del Ministero della Salute sul documento recante "Programma Nazionale Donazione di Organi 2018-2020". 14 dicembre 2017. Available from: www.normativasanitaria.it/jsp/dettaglio.jsp?id=62572.
17. Comitato Etico dell'Istituto Superiore di Sanità. Parere sul protocollo "Trapianto allogenico parziale o completo di faccia per il trattamento di difetti complessi da ustioni, traumi, malformazioni e oncologici". 4 August 2015. Confidential document.
18. Consiglio Superiore di Sanità. Parere su "Protocollo sperimentale di trapianto allogenico parziale o completo di faccia per il trattamento di difetti complessi da ustioni, traumi, malformazione e oncologici". 10 November 2015. Confidential document.

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ORIGINAL ARTICLES AND REVIEWS

An international study of middle school students' preferences about digital interactive education activities for promoting psychological well-being and mental health

Antonella Gigantesco[1], Gabriella Palumbo[1], Magdalena Zadworna-Cieślak[2], Isabella Cascavilla[1], Debora Del Re[1], Karolina Kossakowska[3] and WST European Group*

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**The members of the WST European Group are listed before the References*

Abstract

Introduction. The present study investigated students' preferences about technology tools and digital education activities to be used in classroom to facilitate the implementation of a mental health promotion program.

Method. Students' preferences have been elicited during one session focus group lasting 60 minutes. Overall, 26 focus groups, facilitated by 33 teachers, were organized in 9 schools of five European countries. Overall, 283 students who attended the first, second and third year of middle school (aged 10-15 years) volunteered to participate in the focus groups.

Results. The majority of preferences indicated smartphone to communicate or to get information and tablet for a better use in classroom. Collaborative games have been considered as more useful and beneficial compared to the other digital educational activities proposed.

Conclusions. Teachers require further insight into the pedagogical role of ICT and training. There is a need to encourage them to provide opportunities to allow students to use technology to solve problems or develop abilities for a better socio-emotional functioning and, ultimately, mental health.

Key words

- psychological well-being
- mental health
- school
- pedagogical tools
- educational ICT tools

INTRODUCTION

Poor mental health in childhood and adolescence is associated with health and social problems such as school failure, delinquency, and substance misuse, and this increases the risk of adverse outcomes in adulthood [1]. World Health Organization (WHO) has estimated that up to 20% of children and adolescents worldwide suffer from a problem of psychological or behavioural development and one in eight suffers from a mental disorder [2]. Interventions that promote positive mental health may provide young people with the necessary life skills, support, and resources to accomplish their potential and to deal with adversity for preventing mental health disorders [3]. Schools are one of the most important communities where young people mental health can be promoted [4, 5]. The literature suggests that mental health promotion programs in schools produce long-term benefits for young people, especially if these programs are conducted as part of school activities and adopt a wider approach, namely, the ones that promote generic psychosocial competence and life skills instead of focusing on specific behavioural prob-

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lems [6-10]. Life skills [11] are psychosocial competencies that help people to be more aware in the process of decision-making, solving problems, thinking critically and creatively, communicating effectively, developing safe relationships, understanding the emotions of others, and managing their lives in a healthy and productive manner.

According to the UNICEF report, computer and communication technologies are now fixtures of youth culture [12]. Modern technology has transformed the experience of growing up of adolescents. For a generation of young people, technology has assumed a substantial stake in their social and educational lives [13]. Teens all over the world are growing up in a world in which the Internet, smartphones, text messaging, television and video games, and other technologies dominate their communication and are an integral part of everyday life. Due to the enormous development of technologies, this era could also be called the Age of Technology [14]. Many educational researchers have affirmed that young people have different learning styles and communication technologies preferences because of their fluency in communication technology skills [15]. Because of this, they urge schools and educators to respond to these students' preferences in ways that may be significant for education. For example, teachers may leverage students' capabilities with technologies to implement these technologies inside the school to be used for disseminating life skills programs finalized to positive mental health youth development.

We here report the findings collected within the framework of the Project "Well-School-Tech", for middle secondary school education, funded by the Erasmus+ Program for School Education. The Projects' European partners were Vilniaus Kolegija, University of Applied Sciences (VIKO), Vilnius (Lithuania); Promimpresa (Italy); Istituto Superiore di Sanità (Italian National Institute of Health), Rome (Italy); University of Lodz, Lodz (Poland); Europa Training, Plymouth (United Kingdom); European Center for Quality, Sofia (Bulgaria). The objectives of the project were: 1) to exchange good practices for mental well-being management in school context, in order to collect methodologies aimed at students' well-being with the direct support of the actors involved in the well-being and learning process of students, i.e. teachers and parents; 2) to provide students with tools to manage mental well-being, improve communication skills, increase self-awareness and problem solving abilities; 3) to produce high quality resources for teachers and professionals and improve their competencies to deal with diversified groups of students, making use of new technologies and learner-centred pedagogical approaches.

With the active participation of the students, the pedagogical methods proposed by partners had to be adapted in multimedia technologies tools (website, video, applications), available in five European languages.

As a one part of the project, the present study has been conducted, with the help of some teachers, in order to provide a comprehensive picture of students' technology experiences and identify the most appropriate multimedia technologies tools for their age group. Specifically, the study aimed to investigate: 1) middle school students' technology experiences inside and outside the school; 2) their preferences about digital education activities to use in classroom, to put into action a structured program aimed at promoting psychological well-being.

For the purpose, the Well-School-Tech Project research team solicited several focus groups, consisting of students, who attended middle secondary schools, to be conducted in all the countries involved in the Well-School-Tech Project.

MATERIALS AND METHODS

Study design and participants

A descriptive qualitative design was employed for this study using a semi-structured focus group interview for data collection.

Several eligible schools were contacted in early 2017. Once contact had been established, each project research team in their own country illustrated the project and the study to students and teachers in each school. Overall, 9 middle lower schools located in Plymouth (UK), Sofia (Bulgaria), Lodz (Poland), Caltanissetta (Italy), and Vilnius (Lithuania) expressed an interest in the study. A designated teacher in each school carefully recruited students who attended the schools from the first, second and third-year of middle school (aged 10-15 years). Overall, 283 students volunteered to participate in the study *(Table 1)*.

All students who consented to participate in the study also consented to attend a focus group interview. Approval for the study and signed written informed consent was obtained from the parents of all the participant students prior to commencement of the focus groups. According to the countries' legislations, this study did not need formal ethical approval because it was an informative cross-sectional purely observational study. In any case, the study was conducted according to the international guidelines and ethical codes of the Belmont Report and the Oviedo Convention. The focus groups were conducted during the 2017-2018 school year between November and December 2017.

Procedure

Information regarding students' preferences about devices and digital education activities were elicited during one session focus group lasting 60 minutes. Overall, 26 focus groups, facilitated by 33 teachers, were organized in the 9 schools which volunteered to participate to the study. Each focus group included a number of students ranging from 8 to 17 years old. Two facilitators conducted each focus group. One facilitator conducted the interview, while the other (called co-facilitator) recorded process notes; specifically, s/he took careful notes of verbal expressions to aid the subsequent data analysis and interpretation. A focus group template was provided to facilitators by the project team at Italian National Institute of Health (Istituto Superiore di Sanità – ISS) to support and facilitate them in the implementation of a standardized methodology to conduct focus groups (*Box 1* and *Box 2*).

The facilitators were equipped with a guide with in-

Table 1
Schools and students involved in the focus groups

	Bulgaria	Lithuania	Poland	United Kingdom	Italy	All Countries
Schools (no.)	1	1	1	5	1	9
Classrooms (no.)	3	4	3	5	5	20
Teachers (no.)	10	4	4	5	10	33
Focus groups (no.)	5	3	8	5	5	26
Gender of students M/F	33/23	20/32	35/28	27/35	28/22	143/140
Age of students						
<11 years	0	19	1	58	0	78
11-12 years	25	12	29	0	35	101
13-14 years	31	0	33	4	15	83
>14 years	0	21	0	0	0	21

formation on how to present these activities to students using practical examples.

At the end of each focus group, the facilitators reviewed records and presented data to their project partner coordinator using a Focus Group Report *(Figure 1)*.

Each project partner coordinator summarized all the reports received by his facilitators using a summary focus group report and sent it to Italian National Institute of Health (ISS).

Two ISS's researchers analysed all the reports coming from all countries independently, to identify emerging key themes, differences, and correspondences in the data. Finally, they drafted and provided a final report to all the project partners.

Data analysis

Analyses were conducted across the whole dataset (all countries). Descriptive analyses on students' preferences were performed considering the five questions that were targeted in the Focus Group Report *(Figure 1)*.

Box 1
Focus group schedule *(for facilitators)*

Opening focus group
- To introduce the focus group, a standard statement is recommended to ensure that each group receives the same information and nothing important is missed out *(see for guideline: Informative statements for opening focus group in Box 2)*.

Introducing the topic of psychological well-being
- Ask students if they have ever heard the word "psychological well-being" or "mental health" and what this could mean to them.
- Allow 5/10 minutes to let students express freely their thoughts.
- Explain that psychological well-being refers to feeling good about themselves and with others (with family and friends), developing self-confidence and self-esteem, being optimistic, being able to solve problems and conflicts, and recognizing emotions in order to avoid stress, aggression, anxiety, or low mood.
  Mental health does not mean only suffering from a mental illness. Everyone needs to take care of his mental health, in the same way that people need to take care of their physical health. Mental health is about being emotionally "healthy" and does not always refer to someone with a mental "illness".

Discussing about electronic devices and choice of the favorite one
- Ask students the following questions, and please, be informed about the devices available in your school:
  - Which devices do you usually like to communicate or get information (laptop, smartphone or tablet)?
  - Which devices do you think is better for use in classroom to acquire some new skills for improving your psychological well-being?
- Allow 10/15 minutes to let students express freely their thoughts.
- Accurately transcribe all individual contributions to the focus group interview.
- Write on Focus Group Report the electronic devices chosen by students (register all the comments and if there is a consensus or not on the electronic devices that students prefer).

Discussing about digital interactive educational activities
- Introduce and make examples for each digital interactive educational activity *(see the list of activities in Box 3)*
- Ask students the following questions, for example:
  - Which activity would you like?
  - Which activity do you think would be useful to improve your psychological well-being?
  - Do you think that a specific activity among those listed can be more beneficial than others?
- Allow 15/20 minutes to let students express freely their thoughts.
- Accurately transcribe all individual contributions to the focus group interview.
- Write on Focus Group Report the digital education activities that students choice (register all the comments and if there is a consensus or not on the activity that students prefer).

Box 2
Informative statements for opening focus group *(for facilitators)*

- Welcome to the focus group for students. You are invited here together with other students to discuss the use of digital resources for educational purposes at school. Today's work is part of a bigger project that develops and examines a school-based programme, which will be used by teachers in schools to promote students' psychological well-being.
- Part of the project involves developing ideas for the inclusion of digital interactive educational activities in this programme to see how well they work in school settings.
- Today we will ask your opinion on the relevance, usefulness and effectiveness of some educational activities that should be used for learning skills that may enable students to better deal with everyday life and to cope with life stress.
- We are interested in your opinions. As such there are no wrong answers, there are only your opinions about digital resources, which one of them you like more, or you think could work better, etc. The aim of this focus group is to gather suggestions from you in order to better understand what we need to develop further in the program and what does not need to be changed. Please speak freely and allow others to speak freely too.
- We treat these focus groups and the data collected as confidential. We would like to record these focus groups, mainly through notes and through digital recordings. We will keep them safely and only the transcriptionist and myself will listen to them.
- Is everything clear or is there anything important I have missed?

This template provided the facilitators with information and guidance to open focus groups, introduce the topic of psychological well-being and encourage students to talk openly about their opinions, experiences and preferences, using predetermined interview questions. These included questions that facilitators answered to achieve a comprehensive assessment of students' preferences for 8 interactive educational digital supported activities (*see the list in Box 3*).

Results are reports with frequencies and percentages. Chi-square test was used to compare countries for students' choices about devices.

RESULTS

Data in *Table 2* show that the majority of preferences concerned smartphone (61%) as the device students like more for communicating or getting information, while for a better use in classroom, about 54% of preferences pertained to tablet.

With regard to communicating or getting information, there were differences in the students' preferences among countries (2-sided chi-square: 77 323; df = 8; $p < 0.001$), in particular among Poland, Bulgaria and UK. In fact, Polish and Bulgarian youth declared to not completely prefer laptop/computer for communicating and getting information. In Poland also tablet was not popular to this aim. On the contrary, UK students preferred more tablet than other devices.

Also with regard to the use of devices in classroom, there were differences in the students' preferences among countries (2-sided chi-square: 114 389; df = 8; $p < 0.001$). In fact, youth from Bulgaria and Italy did not completely choose smartphone, while it was the most

Session Date ..... **Country** ..... **School name** ..... **Facilitator name** ..... **Co-facilitator name** ..... **Classroom**		**Age group (years)**: < 11 ☐ 11-12 ☐ 13-14 ☐ > 14 ☐ **Participating students no.** ☐☐ **Male students no.** ☐☐ **Female students no.** ☐☐
Students' choices		
	Device *(one or more choices)*	
Which devices do you usually like to communicate or get information (laptop, smartphone or tablet)?		
Which device do you think is better for use in classroom to acquire some new technical skills for improving your psychological well-being?		
	Digital education activity *(one or more choices)*	
Which activity would you like?		
Which activity do you think would be useful to improve your psychological well-being?		
Do you think that a specific activity among those listed can be more beneficial than others?		

Figure 1
Focus Group Report (Edited by facilitators and/or co-facilitators).

Box 3
The interactive educational digital supported activities presented to students

1. Collaborative games/solution to find
2. Role play
3. Score/competition
4. Online videos (already existing resources) about addressed subjects
5. Story with multiple choices and solutions
6. Interactive exercices/multiple choice test
7. Task based approach/mission to accomplish/objective to achieve
8. Questions/survey

popular device for Polish and Lithuanian adolescents. Similarly to Bulgarian and Italian youth, UK youth declared to prefer more tablet or laptop/computer than smartphone.

With regard to the preferences for digital interactive educational activities that students liked, about 29% concerned online videos. A very high percentage of preferences for activities that students thought useful pertained to collaborative games (46%). With regard usefulness, overall, there were no remarkable differences in the students' major preference among the different countries involved, except for Lithuanian students who thought useful collaborative games as much as online videos.

Among the preferences for activities that students thought more beneficial than others, the higher percentage (about 40%) also concerned collaborative games. Although collaborative games received overall the largest preference with regard to beneficial effects, comparison among the different countries showed that there were some differences. In fact, for Italian and Lithuanian students they did not represent the major choice. These students more frequently indicated as preferable role-play, multiple choice test (Italy) and competition and online videos (Lithuania) *(Table 3)*.

Overall, collaborative games were considered by students as more useful and also beneficial compared to the other activities proposed.

DISCUSSION AND CONCLUSIONS

In 2001, Mark Prensky, an American media researcher and author of computer games, introduced the terms *digital natives* and *digital emigrants* [16]. Not without a reason, these terms are more and more often cited in the works dealing with the issues of modern technologies in the educational context. *Digital natives* in contact with information technologies are like native speakers speaking their mother tongue. They are able to move naturally in the Internet environment, operate a computer and various mobile devices. Such constant access to the Internet and communication channels, or mobile phones, of course may carry certain risks [17-20], but they are not the subject of current study.

There is no doubt that the participants of our research were *digital natives* – a generation of children born and grown up in the world of digital technologies. They are 21st-century students who no longer want to use only traditional teaching methods but recognize smartphones, computers and laptops as powerful tools for transforming learning.

The predominance of the smartphone as a communication and information tool among the vast majority of surveyed students in the present study probably is the result of the trend in the development of smartphones: increasing technical capabilities of devices, faster access to the Internet, and most of all – their commonness. It has to be noted however that there were some differ-

Table 2
Students' choices about devices (because students could indicate 1 or more options the sum is not equal to 283)

Devices that students like for communicating or getting information	Smartphone	Tablet	Laptop/Computer
Bulgaria	56	16	0
Poland	44	0	0
Italy	40	18	18
United Kingdom	17	27	18
Lithuania	29	14	9
Total	**186**	**75**	**45**
Devices that students think are better for use in classroom	**Smartphone**	**Tablet**	**Laptop/Computer**
Bulgaria	0	36	20
Poland	42	54	0
Italy	0	24	21
United Kingdom	3	38	21
Lithuania	26	17	9
Total	**71**	**169**	**71**

Table 3
Students' choices about digital education activities (because students could indicate 1 or more options the sum is not equal to 283)

	Collaborative game	Role-play	Competition	Online videos	Story with multiple choices	Multiple choice test	Task based approach	Questions
				Activities that students like				
Bulgaria	0	16	20	36	0	20	40	0
Poland	0	19	17	39	0	37	39	0
Italy	12	2	7	12	0	13	0	0
UK	3	11	16	20	6	4	2	0
Lithuania	14	3	8	20	0	3	4	0
Total	**29**	**51**	**68**	**127**	**6**	**77**	**85**	**0**
				Activities that students think useful				
Bulgaria	56	0	0	0	0	36	20	0
Poland	44	16	0	0	0	10	18	0
Italy	22	6	2	9	1	1	0	2
UK	25	8	3	7	5	5	7	4
Lithuania	16	3	8	14	0	4	1	2
Total	**163**	**33**	**13**	**30**	**6**	**56**	**46**	**8**
				Activities that students think more beneficial than others				
Bulgaria	56	0	0	0	20	0	20	36
Poland	44	16	0	0	0	10	0	0
Italy	4	19	0	2	2	10	0	0
UK	20	10	6	11	3	3	3	6
Lithuania	8	7	11	13	0	7	4	2
Total	**132**	**52**	**17**	**26**	**5**	**30**	**27**	**44**

ences among countries given that the data obtained in the UK suggest that UK students preferred tablets.

In 2016, Digital Virgo and Comecode, in cooperation with the Mobile Institute, conducted the first study in Poland dedicated to children up to 14 years of age in the mobile world. The results, published in the report SmartKids [21], are quite consistent with the results of the present study. In fact, out of 714 parents taking part in that survey, as many as 82% of them confirmed the use of mobile devices by their children. The study also showed that 1/4 children use their own devices, 52% use parents' smartphones or tablets, and 48% use their own or shared with parents. A study conducted on Italian students also showed that smartphones and tablets are the most frequently used devices (51% and 44% respectively) [22]. Another study which involved almost 3500 participants from seven European countries (Belgium, Denmark, Ireland, Italy, Portugal, Romania and the United Kingdom), reported that about 46% of children aged 9-16 years was a smartphone's owner [23]. A study conducted in USA on over 4500 parents of children in primary and middle secondary schools reported that about 45% of children aged 10-12 years had their own smartphone [24]. Moreover, on average, US teens aged 13-18 engage with screen media (from watching television or online videos to reading online and using social media) for more than 6.5 hours each day; and mobile devices account for almost half this time [25].

It seems that the smartphone is the most familiar device for the youngest users, followed by tablets. There may be a feedback relationship, the majority of children and adolescents want to use a smartphone as a communication and information search tool because most often they use it to communicate with others and surf the Internet.

In the present study, it is interesting to note that Polish and Bulgarian students did not at all indicate the laptop or home computer as a useful device for communicating or searching for information. According to the Concise Statistical Yearbook of Poland [26] on 8000 households, nearly 80% are in possession of a computer (or laptop), thus it is difficult to explain its low popularity among school youth. We are rather inclined to assume that the smartphone, as more "handy", seems to be more attractive to young people. Also a hypothesis about gender differences seems to be worth further exploration. For example, in a study conducted by Sozio *et al.* [27], Brazilian girls will be more likely to use mobile phones than boys (54% and 50%, respectively) and this trend was also observed in other Countries,

for example in Hungary [28] and Japan [29]. This is not consistent with the results of the present study in which, as previously said, smartphone represented the preferred communication and information tool across all surveyed students, except UK students, who had a preponderance of female compared to male students. At the same time, it should be noted that there was a preponderance of female students also in Lithuanian sample of students, however, in this latter case, similarly to Brazil, Japan and Hungary, the main choice was the smartphone, although to a lesser extent to the other Countries surveyed in the present study.

A recent Polish research conducted in 2017 among a representative sample of teenagers [30] (named Teenagers 3.0 report) shows that Polish female teenagers use the Internet more often and intensive than boys, both at home, on the way from home to school, with friends, and in public places, where Wi-Fi is available. Mobile technology allows them to use Internet anywhere and anytime. The average time that Polish girls spend in Internet connection with a smartphone is 211.5 minutes daily, for boys – 165.2 minutes. However, boys use their computer and game console more often. The authors explain these results by the fact that girls use smartphone conveniently for maintaining social relationships more than boys do, while boys more often play online games, for which a desktop computer is more suitable [30]. These differences seem to be worth further exploration because they also concern adult women and men. According to the studies of Andone *et al.* [31] female use smartphones for longer than male adults, with a daily mean of 166.78 minutes vs. 154.26 minutes.

At the same time, not consistently with these results, another study on Polish primary school students showed that among teenagers (11-14 years), 14.3% of boys would like to use smartphones also during lessons and only 2.9% of girls would do it. The opposite situation has been recorded in the case of the preference to use tablets instead of traditional textbooks – 17.1% of girls and 3.6% of boys declared it [32]. The results of the Teenagers 3.0 report [30] help us to better understand differences in the use of information and communication technologies (ICT) by gender. For example, boys more often than girls enjoy or want to use the Internet to improve knowledge for academic purposes while girls to read and/or run blogs, contact friends and search social networking sites. Among girls, the Internet use with social purposes is usually inappropriate during school lessons, hence perhaps their lower attitude towards the use of smartphone in classroom compared to boys.

Interestingly, in the present study, despite the abovementioned primacy of smartphone, about 54% of preferences pertained to tablet as a better tool to use in the classroom. This is not entirely consistent with the results of other Polish studies on the use of modern technologies in secondary school. In fact, Plebańska and Halska [33] reported that among the technologies mentioned by young Polish students as the most commonly used in classroom, an interactive whiteboard took the first place, and on the second place there was a laptop/computer. Smartphones, tablets and mobile applications were much less frequently mentioned by students, although their presence indicated a certain tendency to change. This might be due to lack of confidence in facilitating students to use these tools, some teachers not recognizing the educational value of these type of technologies, or school policy not allowing them to use these types of technologies [34]. Various factors may influence the generation gap between teachers and students in classrooms, i.e., teacher's perceptions and opinions on technology, the requirement to update pedagogy with a focus on technology, the availability of professional training for integrating technology effectively in school [35]. Many teachers are not experts in a broad array of technological tools and they are not comfortable allowing students to independently build their knowledge using technology [36]. While, usually, students think that computers, laptops, smartphones, iPods, videos, interactive whiteboards or Internet are technological tools to be used in classroom, teachers are slower to embrace new forms of technology. Teachers' inexperience may generate a resistance to change, which in turn may affect their interest in training for using technology as educational tool in classroom. Teachers require insight into the pedagogical role of ICT and training, in order to use it in their educational activity. According to recent research [37] teachers who carried out a ICT course are more effective in teaching by using technology tools as opposed to those that have no accomplished such training. A school in Ireland reported that teachers who did not acquire sufficient confidence with technology tools avoided using ICT. Consistently, some teachers in Canada confessed they were reluctant ICT users because they worried they might make a bad impression to students who knew more about technology than they did [38].

Nevertheless, the accelerated expansion of digital technologies has provided interesting perspectives in the educational landscape allowing innovation to take place in the education space. Approaches such as Modern Classrooms [39] or Future Classrooms [40] appear concepts that have been gaining prominence in the European educational context. They integrate the idea that nowadays classrooms must be seen as a learning laboratory, equipped with different new technology and materials, that enables the development of active learning activities, where autonomy and collaboration happen in a daily basis for each and every student. Using new technologies in the classroom can be a way to create positive education. The goal of positive education is to produce both well-being as well as to forward the traditional outcomes of schooling. Using the most popular ICT and devices, teachers can transmit optimism, trust, and a hopeful sense of the future, which will positively influence their students' perception of the world [41]. In the process of digital education activities such as collaborative games, role-play, online videos or task based approach and choices tests, students improve their individual skills; for example students can improve their decision-making by learning how to choose the best action plans from available options [42].

However, there are some barriers in implementing new technologies in the classroom to assist individual skills development. This might be due partially to the

fact that school related tasks currently require students to use technology only for searching information and writing papers. More rarely, teachers provide opportunities to allow students to use technology to solve problems or develop abilities for a better social and emotional functioning. The importance of integrating technology into the classroom has become a priority at most levels of the curriculum in many countries around the world. However, as said, teachers are generally time poor and often have limited knowledge in using technology for solving students' academic or psychosocial problems [43, 44]. This explains why they usually did not employ innovative pedagogical practices in their technology integration [34]. One of the helpful approaches would be peer-to-peer learning and support for teachers. For example, Lang [45] suggests a model of pedagogy of outreach – integrating knowledge of ICT teachers, generalist teachers, and students in the classroom. There is a need to encourage teachers to integrate technology for digital education activities to develop students' productivity as well as their emotional and social abilities [46].

The next stage of Well-School-Tech Project was to put into action a structured program aimed at promoting psychological well-being making use of technology and digital education activities. The programme for promoting psychological well-being and mental health focused mainly on teaching skills that enable students to cope satisfactorily with stress in their life and was inspired by Goleman's emotional intelligence model [47]. Goleman's model identified five domains of emotional intelligence: i) knowing your emotions; ii) managing your own emotions; iii) using emotions to motivate yourself; iv) recognising emotions of other people; v) managing relationships. The main contents of the program address skills such as defining personal goals, adopting effective communication skills, using negotiation, coping with stress, coping with anger, and resolving conflict. In the project, we designed some Internet-based digital education activities for enhancing the above mentioned skills and in the present study we assessed students' opinions on acceptability and usefulness of these activities. Among them, our findings show that students for the most part considered collaborative games as more useful and beneficial compared to the other activities proposed. According to Griffiths [48], gaming gets educational benefits not only in terms of entertainment value but also in increasing skills. Cecilia *et al.* [49] who have analysed the influence of gaming activities on cognitive performance of children found that the technological exposition in childhood enhanced learning, the autonomy in the use of technological tools and/or application represents a good practice to improve the learning abilities in developmental age.

The presented analyses are not free from limitations. First, the study design called for allowing students to provide *one or more choices* for questions regarding the choice of the preferred devices and for digital education activities. The results showed that indeed the majority of students from Bulgaria, Poland and Italy opted for more than one choice while UK and Lithuanian students, in the majority of cases, only opted for one single choice. Therefore, there was likelihood that some students did not understand the request or that the request to provide one or more choices was not enough emphasised in UK and Lithuania. Second, for the statistical analyses, the ISS did not have available individual data of the students; that is why it was not able to associate each choice or preference with the gender of student who expressed that choice or preference. In fact, the facilitators reviewed records and presented aggregate data to their project partner coordinator using a Focus Group summary Report *(Fig. 1)*. In this Report, facilitators only reported the total number of male and female students. Third, students represented by individual countries are not highly numerous, this does not allow us to draw universal conclusions, but we hope that it will contribute to further exploration of the topic.

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Authors' contributions

AG: study design, focus group analysis, statistical data analysis, literature analysis, draft and final revision of the manuscript. GP: study design, focus group analysis, collaboration to the preparation of manuscript, literature analysis. MZ-C: data collection, data interpretation, collaboration to the preparation and revision of manuscript, literature analysis. IC: focus group analysis, literature analysis. DDR: focus group analysis, literature analysis. KK: data collection, data interpretation, collaboration to the preparation and final revision of the manuscript, literature analysis.

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Declarations

The manuscript is original and no part of the manuscript has been published before, nor is any part of it under consideration for publication at another Journal.

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Conflicts of interest statement

The authors declare that they have no conflict of interest.

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REFERENCES

1. Jenkins R, Baingana F, Ahmad R, McDaid D, Atun, R. Social, economic, human rights and political challenges to global mental health. Ment Health Fam Med. 2011;8:87-96.
2. World Health Organization. Prevention of mental disorders. Effective interventions and policy options. Summary Report. Geneva: WHO; 2004. Available from: http://apps.who.int/iris/bitstream/handle/10665/43027/924159215X_eng.pdf?sequence=1&isAllowed=y.
3. Barry MM, Clarke AM, Jenkins R, Patel V. A systematic review of the effectiveness of mental health promotion interventions for young people in low and middle-income countries. BMC Public Health. 2013;13:835. doi: 10.1186/1471-2458-13-835
4. Puolakka K, Haapasalo-Pesu KM, Konu A, Åstedt-Kurki P, Paavilainen E. Mental health promotion in a school community by using the results from the well-being profile: an action research project. Health Promot Pract. 2012;15(1):6-12. doi: 10.1177/1524839912464876
5. Gigantesco A, Del Re D, Cascavilla I, Palumbo G, De Mei B, Cattaneo C, Giovannelli I, Bella A. A universal mental health promotion programme for young people in Italy. BioMed Res Int. 2015;2015:345926. doi: 10.1155/2015/345926
6. World Health Organization. Global School Health Initiative: Health Promoting Schools. Geneva: WHO; 1995. Available from: www.who.int/school_youth_health/gshi/en/.
7. World Health Organization. Skills for Health: The WHO Information Series on School Health, Document 9. Geneva: WHO; 2003. Available from: www.who.int/school_youth_health/media/en/sch_skills4health_03.pdf.
8. Greenberg MT. School-based prevention: current status and future challenges. Effective Educ. 2010;2(1):27-52. doi: 10.1080/19415531003616862
9. Jané-Llopis E, Barry M, Hosman C, Patel V. Mental health promotion works: a review. Promot Educ. 2005;Suppl 2:9-25, 61, 67. doi: 10.1177/10253823050120020103x
10. Zadworna-Cieślak M. Health behavior of young people – the role of psychological and family determinants. In: Sobczak A, Znajmiecka-Sikora M (Eds). Development in the perspective of the human science – opportunities and threats (pp. 69-83). Lodz: Lodz University Press; 2012.
11. UNICEF. International of Children Emergency Fund, 2012. Available from: www.unicef.org/evaldatabase/index_66242.html.
12. UNICEF. The States of the World's Children, 2017. Children in a digital world. Available from: www.unicef.org/sowc2017.
13. Koivusilta LK, Lintonen TP, Rimpela AH. The orientations in adolescent use of information and communication technology: A digital divide by socio demographic background, educational career, and health. Scand J Public Health. 2007;35(1):95-103. doi: 10.1080/14034940600868721
14. Collins A, Halverson R. The second educational revolution. Rethinking education in the age of technology. J Comput Assist Lear. 2010;26(1):18-27.
15. Thompson, P. The digital natives as learners. Technology use patterns and approaches to learning. Comput Educ. 2013;65:12-33. doi:10.1016/j.compedu.2012.12.022
16. Prensky M. Digital natives, digital immigrants. On the Horizon. 2001;9(5):1-6. Available from: www.marcprensky.com/writing/Prensky%20%20Digital%20Natives,%20Digital%20Immigrants%20-%20Part1.pdf.
17. Mok JY, Choi SW, Kim DJ, Choi JS, Lee J, Ahn H, Song WY. Latent class analysis on internet and smartphone addiction in college students. Neuropsychiatr Dis Treat. 2014;10:817-28. doi: 10.2147/NDT.S59293
18. Sprecher S, Hampton AJ, Heinzel HJ, Felmlee D. Can I connect with both you and my social network? Access to network-salient communication technology and get-acquainted interactions. Comput Human Behav. 2016;62:423-32. doi: 10.1016/j.chb.2016.03.090
19. Duke E, Montag C. Smartphone addiction, daily interruptions and self-reported productivity. Addict Behav Rep. 2017;6:90-5. doi: 10.1016/j.abrep.2017.07.002
20. Swain S, Behera I, Sahu M, Choudhury J. Mobile phone use among children and its impact on hearing. Our experience at a tertiary care teaching hospital. Pediatr Pol. 2018;93(2):117-20. doi: 10.5114/polp.2018.75061
21. Digital Virgo. Polska 2015. Smart Kids. Dzieci w mobilnym świecie ["Smart Kids" Report - the first study in Poland focusing on kids in the mobile world]. 2016. Available from: http://raport.digitalvirgo.pl/Smart_Kids_Raport.pdf.
22. Bozzola E, Spina G, Ruggiero M, Memo L, Agostiniani R, Bozzola M, Corsello G, Villani A. Media devices in pre-school children: the recommendations of the Italian pediatric society. Ital J Pediatr. 2018;44(1):69. doi: 10.1186/s13052-018-0508-7
23. Mascheroni G, Ólafsson K. The mobile Internet. Access, use, opportunities and divides among European children. New Media & Society. 2015;1-23. doi: 10.1177/1461444814567986
24. Nielsen Social Media Report. Social Studies. A look at the social landscapes. 2016. Available from: www.nielsen.com/content/dam/corporate/us/en/reports-downloads/2017-reports/2016-nielsen-social-media-report.pdf.
25. Mascheroni G, Ólafsson K. Net children go mobile. Risks and opportunities. (2. ed.). Milano: Educatt; 2014.
26. GUS. Concise Statistical Yearbook of Poland, 2016. Available from: https://stat.gov.pl/en/topics/statistical-yearbooks/statistical-yearbooks/concise-statistical-yearbook-of-poland-2016,1,17.html.
27. Sozio ME, Ponte C, Vitorino I. Children and Internet use: a comparative analysis of Brazil and seven European Countries. London: LSE-EU Kids Online; 2015. Available from: http://www2.fcsh.unl.pt/eukidsonline/docs/Brazil%20%20NCGM_COMPARATIVE%20REPORT.pdf.
28. Körmendi A. Smartphone usage among adolescents. Psychiatr Hung. 2015;30(3):297-302.
29. Nishida T, Tamura H, Sakakibara H. The association of smartphone use and depression in Japanese adolescents. Psychiatry Res. 2019;273:523-27. doi: 10.1016/j.psychres.2019.01.074
30. NASK, 2017. Raport z badania: Nastolatki 3.0 [Study report: Teenagers 3.0]. Retrieved from: https://akademia.nask.pl/publikacje/Raport_z_badania_Nastolatki_3_0.pdf.
31. Andone I, Blaszkiewicz K, Eibes M, Trendafilov B, Montag C, Markowetz A. How age and gender affect smartphone usage. In: Proceedings of the 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing. Heidelberg, Germany, September 12-16, 2016. Adjunct, pp. 9-12.
32. Kossakowska K, Zadworna-Cieślak M, Szczepanik M, Woszczak M. Physical activity and psychological well-being of Polish primary school students – preliminary report. Paper presented on the 24th Scientific Conference

– The International Disabled People's Day: Healthy Children-Healthy Europa, Zgorzelec, Poland; 2018, March.
33. Plebańska M, Halska B. Rola wykorzystania nowych technologii we współczesnych szkołach – rezultaty pierwszego etapu badań [The role of use of new technologies at contemporary schools – Results of the first stage of research]. KNUV. 2017;1(51):130-48. Available from: www.i.vistula.edu.pl/media/docs/nZbANjWkoeeyoMmrGkrL8SdCj.pdf
34. Hsu S. Who assigns the most ICT activities? Examining the relationship between teacher and student usage. Comput Educ. 2011;56(3):847-55. doi:10.1016/j.compedu.2010.10.026
35. Lisenbee PS. Generation gap between students' needs and teachers' use of technology in classrooms. J Literacy Technol. 2016;17(3):99-123.
36. Prensky M. The role of technology in teaching and the classroom. Education Technol. 2008;(Nov/Dec):1-3.
37. Winzenried A, Dalgarno B, Tinkler, J. The interactive whiteboard. A transitional technology supporting diverse teaching practices. Australasian J Education Technol. 2010;26(4):534-52.
38. Hennessy S, Ruthven K, Brindley S. Teacher perspectives on integrating ICT into subject teaching: commitments, constrains, caution, and change. J Curriculum Stud. 2005;37(2):155-92.
39. Leahy G. The Modern Classroom: strategic insights for school leaders. Blackburn, Lancashire: Promethean Editions; 2016.
40. European Schoolnet. About European Schoolnet, 2016. Available from: www.eun.org/about.
41. The Global Happiness Council. Global Happiness Policy Report 2018. New York: Sustainable Development Solutions Network; 2018. Available from: www.happiness-council.org/report/2018/.
42. Albert D, Steinberg L. Judgment and decision making in adolescence. J Res Adolesc. 2011;21(1):211-24. doi: 10.1111/j.1532-7795.2010.00724.x
43. Hew KF, Brush T. Integrating technology into K-12 teaching and learning: current knowledge gaps and recommendations for future research. Educ Technol Res Dev. 2006;55(3):223-52. doi:10.1007/s11423-006-9022-5
44. Hughes J. The role of teacher knowledge and learning experiences in forming technology-integrated pedagogy. J Tech Teach Educ. 2005;13(2):277-302.
45. Lang C, Craig A, Casey G. A pedagogy for outreach activities in ICT: Promoting peer-to-peer learning, creativity and experimentation. Br J Educ Technol. 2017;48:1491-501. doi: 10.1111/bjet.12501
46. Campbell T, Wang SK, Hsu HY, Duffy A, Wolf P. Learning with Web Tools, simulations, and other technologies in science classrooms. J Sci Educ Technol. 2010;19(5):505-11.
47. Goleman D. Emotional intelligence. New York, NY, USA: Bantam Books; 1995.
48. Griffiths M. The educational benefits of videogames. Educ Health. 2002;20:47-52.
49. Cecilia R, Di Giacomo D, Vittorini P, De la Prieta F. Influence of gaming activities on cognitive performances. In: Mascio T, Gennari R, Vittorini P. (Eds). Methodologies & Intelligent Systems for Technology Enhanced Learning. Cham, Switzerland: Springer; 2015. Vol. 374, pp. 67-72.

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Adolescents self-reported sleep quality and emotional regulation: a discordant twin study

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Abstract

Aim. This study explores the association between sleep quality and emotional regulation, and investigates the genetic and environmental bases of this association.

Methods. Three-hundred-eighty-two adolescent twins, from the Italian Twin Registry, and their parents filled the Youth Self-Report and Child Behavior Checklist questionnaires, from which the construct of Effortful Control (EC) was derived as a measure of emotional regulation. Twins were identified as "good" or "non-good" sleepers based on answers to the Sleep Disorders Questionnaire. EC levels were compared between same-sex sleep discordant twins.

Results. A significant association was detected between EC scores and sleep quality. When controlling for shared (fetal or early life) environmental factors and genetic background in the discordant twin analysis, this association weakened in dizygotic twins and disappeared in monozygotic twins.

Conclusion. Results support the association between sleep quality and EC in adolescence; furthermore, they suggest that sleep quality and emotional regulation may depend on common genetic or environmental factors.

Key words

- twin
- sleep quality
- effortful control
- self-regulation

INTRODUCTION

During the transition from childhood to adolescence, we observe dramatic changes in sleep patterns, which play an important role in growth and maturation, and in mental and physical health [1]. Adolescents, compared with children, generally start to feel sleepy later as a result of changes in the phase of circadian wake-sleep rhythms and of an enhanced capacity to sustain prolonged wakefulness [2]. During adolescence, the sleep need doesn't seem to decline while slow wave sleep (the homeostatic restorative component of sleep) decreases by approximately 40% relative to REM sleep [2]; so, to get the same amount of restorative sleep, adolescents' sleep duration should be longer compared with younger children's sleep. On the contrary, due to biological and psychosocial factors, it becomes shorter and of lower quality.

Investigating the determinants of changes in sleep duration and quality during adolescence is important, because poor sleep in adolescence may have detrimental effects on brain development due to the role of sleep in synaptic homeostasis, brain plasticity, and brain maturation. Indeed, several studies found associations between poor sleep and daytime sleepiness, maladaptive conducts, internalizing and externalizing symptoms, and poor school performance [3].

There is evidence from twin studies that genetic factors play a role in adolescents' sleep quantity and quality. For example, Te Velde *et al.* showed, in a Dutch adolescent twin sample, that sleep duration was influenced at the age 12 by genetic, shared environmental, and non-shared environmental factors with similar relative contributions, while at the age 20 it was influenced by non-shared environmental and genetic factors [4]. Another twin study in adolescence found a significant genetic influence on sleep problems [5].

Sleep changes in adolescence are affected by normative biological changes, by environmental factors, as well as by experience and temperament. Around the time of puberty a delay in circadian phase has been observed in humans and other mammals. The delay has been measured on behavioral daily rhythm (sleep and activity) as well as on physiological rhythms (metabolism and endocrinology). Gonadal hormones influence

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both the sleep-wake homeostatis and the circadian rhythm regulation of sleep [6]. In teenagers this is exacerbated by psycho-social and behavioral changes, such as the social media exposure and the use/abuse of caffeine and caffeine-laden products [7].

The relationship between sleep and temperament has been extensively studied in infants, toddlers and school age children. Fewer are the studies among adolescents. In a review paper, Willis [8] reports a robust association between sleep and anxiety in adolescents. In a longitudinal study of young adult twins, Alice Gregory and her team showed that while genetic effects play a modest role in insomnia and depression symptoms separately, they appear to play a more central role in concurrent and longitudinal associations between these phenotypes [9]. Higher neuroticism was reported for adolescent poor sleepers compared with good sleepers [10], and for junior high school students with later bedtimes, shorter sleep duration, more sleep problems and daytime sleepiness. According to Matthews [11], poor sleep quality in young adults is robustly associated with loneliness. A relatively recent study showed positive correlations of sleep problems with negative affectivity and sociability, and a negative correlation with effortful control [12]. Similar findings were reported by Lukowski and Milojevich [13] in a sample of university students; in their study, a poor global quality of sleeping was unrelated to extraversion, positively correlated to negative affect (sadness) and to orienting sensitivity (associative), and negatively correlated with effortful control.

Self-regulation represents a broad construct entailing attentional, cognitive, physiological, and behavioral processes that operate in concert to ensure an appropriate level of emotional, motivational, and cognitive arousal [14]. From a developmental perspective, researchers often investigate self-regulation using measures of effortful control [15]. The construct of effortful control (EC) reflects the temperamentally-based component of emotion-relevant self-regulation, and captures a set of control functions needed for voluntary and goal-directed behavior [16]. In terms of development, EC represents an early appearing component of child temperament [16]. Children high in EC reveal better social and emotional competence [17], are less likely to develop internalizing and externalizing symptoms, and show better school performances [18] compared to children with low EC. Furthermore, EC has been associated with indicators of psychological adjustment, such as optimism, self-esteem and happiness [19].

In a recent study conducted on the same sample, we showed substantial genetic influences on the EC measure [19]. Moreover, other previous twin studies found a substantial genetic component for the same measure in children [20] and in young adults [21].

Although the correlations between sleep quality and EC, found by Lukowski and Milojevich [13], could be due, at least in part, to shared genetic or environmental factors, no previous studies tested this hypothesis. Therefore, considering an adolescent sample from the Italian Twin Registry, we aimed to replicate the association between EC and sleep quality, and to explore the role of genetic and environmental factors in this association.

METHODS

Participants

Study subjects were twins aged 14-18 years previously enrolled in the Italian Twin Registry (ITR) [22]. Of about 1600 families contacted by mail, 389 families having a twin pair among their offspring agreed to participate filling in the CBCL/YSR questionnaires. The sample included 774 twins (385 complete pairs, 4 unmatched twins) of Caucasian origin. Of these, 281 (36.3%) were monozygotic (MZ) and 493 (63.7%) were dizygotic (DZ). Twins from respondent and non-respondent families were similar for gender, zygosity and age, as well as for age of the parents, whereas parents of participating twins were significantly more educated than parents in non-participating families.

Subsequently, following a new study hypothesis, a random sub-sample of the 389 families was administered the questionnaire to assess sleep quality, and 191 families sent it back.

Parents of twins received at home an invitation letter explaining the purpose of the study, an informed consent form to be signed and a number of questionnaires regarding the traits of interest to be filled by parents and/or twins. The protocol of this observational study was under the general framework of the ITR research activities, approved by the Ethics Committee of the Istituto Superiore di Sanità (ISS, Italian National Institute of Health).

Zygosity assessment

Zygosity of twin pairs was assessed by a standardized self-report questionnaire, which consists of items, filled by parents, about physical similarity and frequency of confusion of the twins by family members and strangers during infancy. This is a well-known method in twin studies that has been shown to be over 95% accurate [23].

Measures

We collected behavioral information through the Child Behavior Checklist/6-18 (CBCL) and Youth Self-Report/11-18 (YSR) questionnaires [24].

The CBCL is a standardized assessment of behavior problems based on responses to 113 items that are scored 0 ("not true"), 1 ("somewhat true"), or 2 ("very true") in describing the child's behavior by parents. The YSR is a standardized assessment tool widely used to report behavioral problems and social competence among adolescents; twins self-responded to the 118 test items, scored as in the CBCL. In the analyses, we simultaneously exploited the information from parents (CBCL) and adolescents (YSR) (see below, Statistical Analyses).

To calculate the variable "effortful control" (EC), we used 8 items from the 9-item measure (one item was excluded because it showed poor psychometric properties in preliminary analyses) introduced by Luengo-Kanacri *et al.* [25]. This 8-item subscale of the CBCL and YSR captures the construct of EC in the subdimensions of attentional focusing (three items) and inhibitory con-

trol (five items). This measure assesses processes related to emotional regulation, as well as the abilities to voluntarily focus and shift attention, to voluntarily inhibit or initiate behaviors such as delaying and planning. Sample items are: "He/she does not finish things he/she started", "He/she also talks when it is not his/her turn", and "His/her demands must be fulfilled immediately, easily frustrated". The items were reversed as appropriate: high scores indicated high EC. The reliability for the parent-version of the measure (CBCL) was 0.82 and for the YSR was 0.74. For the 8-item version of the EC scale, the reliability was 0.74, while it was 0.71 and 0.75 for inhibitory control and attentional focusing, respectively.

For the purposes of the analyses, a composite EC score was calculated based on CBCL and YSR (see below, Statistical Analyses).

Sleep quality was assessed by the Sleep Disorders Questionnaire, a brief self-report insomnia questionnaire including 18 yes/no questions on different sleep problems and 5 further questions concerning sleep habits [26]. The questionnaire was built according to DSM-IV and ICSD-R criteria for sleep problems; both these classifications assign a crucial role to the subjective complaint of insufficient or inadequate sleep. This assessment tool showed good convergent validity with respect to the global score of the Pittsburgh Sleep Quality Index (PSQI) in a sample of general practitioners' patients [26]. In order to define the quality of sleep during the last month, we considered only those 10 of the 23 items measuring the specific sleep symptoms of insomnia, excessive sleepiness, sleep apnea and parasomnia that were the target of our study. The first three questions concern symptoms of insomnia, the fourth question concerns non restorative sleep, while the other questions investigate excessive sleepiness (5-7), sleep apnea (8) and parasomnias (9, 10).

We defined the absence of "good sleep" on the basis of at least one positive response to the following ten items: 1) Did you take more than half an hour to fall asleep? 2) While sleeping, do you wake up often or do you remain awake for more than 30 min? 3) Have you woken up early, that is, more than an hour before you expected to? 4) Have you had non restorative sleep, that is as if you haven't slept at all? 5) Did you have problems staying awake during the day? 6) Did you have irresistible sleep attacks during the day? 7) Have you had an excessive need to sleep (10 h weren't enough)? 8) Have you realized or has someone told you that you stop breathing for a few seconds while you're sleeping? 9) Do you often (more than 3 times a month) have nightmares or dreams that cause a lot of anxiety? 10) Have there been episodes of sleep walking or of any other unusual behavior during sleep?

This definition allowed us to discriminate subjects who did not show any kind of problems ("good sleepers") from those showing slight, moderate or severe sleep problems ("non-good sleepers").

Twin pairs were considered discordant for sleep quality when one twin was a good sleeper (i.e. reported no sleep problems) while his/her co-twin was a non-good sleeper (i.e. reported at least one problem).

Statistical analyses

Descriptive analysis was performed on twins as individuals to report means (with standard deviations) and frequencies.

Confirmatory Factor Analysis was applied to the 8 items of CBCL and YSR related to EC to estimate factor scores of the total EC scale and its subscales (attentional focusing and inhibitory control) separately for parent-reported and self-reported data. These scores were then averaged to obtain a composite EC score to be used in all subsequent analyses.

Robust regression taking account of the non-independence of data within twin pairs and including age and gender as covariates was applied on twins as individuals to estimate the association between EC and sleep quality.

Monozygotic (MZ) and dizygotic (DZ) pairs discordant for sleep quality were identified, and the estimated mean EC (and related subscales) factor scores in twins and co-twins, separately for MZ and DZ pairs, were compared using Student t test for paired samples.

DZ twins share on average 50% of their genetic background, while MZ twins are genetically identical. Furthermore, both MZ and DZ twins share the fetal and the early-life environment. Thus, the study of twins discordant for exposure to a putative risk factor (i.e. one twin in the pair is exposed, the other twin is not exposed) allows one to investigate if there is an association between exposure and outcome while matching exposed and unexposed twins for age, genetic background (partially for DZ twins, totally for MZ twins), as well as for intra-uterine and childhood within-family environment. In particular, this design allows one to understand if and to what extent an observed association between exposure and outcome is due to genetic and/or environmental effects shared by exposure and outcome (i.e. genetic and/or environmental confounding effects). Basically, three possible scenarios can occur: 1) the exposure is causally related to the outcome and no genetic or shared environmental confounding effects are involved; in this case, exposure and outcome are expected to be significantly associated with the same strength at the individual level, as well as within DZ and MZ discordant pairs; 2) the exposure is not a causal factor and its relation with the outcome is totally due to shared genetic and environmental effects (total confounding); in this case, exposure and outcome are expected to be significantly associated at the individual level, but the association is expected to weaken in DZ pairs (partially matched for genetic background, and totally matched for pre-natal and early-life environment), and to disappear in MZ pairs (totally matched both for genetic background and for pre-natal and early-life environment); 3) the exposure has a partial causal effect on the outcome; in this case, a significant association between exposure and outcome is expected at the individual level, but the exposure effect is expected to be reduced and persistent in both MZ and DZ pairs (partial confounding effects) [27]. In our study, the exposure variable is sleep quality and the outcome variables are EC and its subscales.

All analyses were performed with the Stata software (version 13).

RESULTS

A total of 191 twin pairs (120 MZ pairs, 71 DZ pairs), representing ages 14 through 18, provided information on sleep quality. Ninety-nine percent of twins were attending school.

Among the subjects, 120 twins (31.4%) were identified as good sleepers, of whom 33.3% were male and about 63.3% were MZ. The remaining sample (n = 262) included those subjects who showed at least one sleep problem (1-2 problems, 39%; 3-4 problems, 38%; 5-6 problems, 16%; more than 6 problems, 7%). Demographic characteristics, zygosity and mean EC (and related subscales) factor scores of good and non-good sleepers are reported in *Table 1*.

No gender differences were observed for sleep quality (chi-square test, p = 0.16). Moreover, age was not correlated with EC (r = -0.06, p = 0.25) or sleep quality (r = -0.02, p = 0.65).

Twins with a good sleep quality had higher temperament factor scores (i.e. EC and the subscales "attentional focusing" and "inhibitory control") compared to those with sleep problems. Accordingly, age and gender adjusted correlations between the number of sleep problems endorsed by the subjects and EC or related subscales were negative and significant [r = -0.26 (p <0.0001) for EC; r = -0.18 (p <0.001) for attentional focusing; r = -0.27 (p <0.001) for inhibitory control]. Adjusting by age and gender, sleep quality (1 = "good sleeper", 0 = "non-good sleeper") was significantly associated with EC factor scores (β = 0.33, p <0.001) and with EC subscales scores ($\beta_{Attentional}$ = 0.29, p <0.001, $\beta_{Inhibitory}$ = 0.28, p <0.001); moreover, females showed higher EC scores compared to males (p <0.05).

Among all same sex twin pairs, 33 were discordant for sleep quality *(Table 2)*. Of these, 17 were DZ pairs and 16 were MZ pairs. Compared to co-twins with sleep problems (non-good sleepers), twins without any sleep problem (good sleepers) showed higher mean EC levels in both MZ and DZ pairs.

Larger intra-pair differences in DZ compared to MZ discordant pairs emerged. In particular, the mean difference in EC score was 0.32 (paired t test, p = 0.05) in DZ pairs, partially matched for genetic background, and decreased to a non-significant 0.17 in MZ pairs, fully matched for genetic background (paired t test, p = 0.46). Therefore, these results show that, besides accounting for age and gender, when controlling also for shared (fetal or familial) environmental factors and genetic background, the association between EC and sleep quality weakened in DZ pairs and disappeared in MZ pairs. Similar results were obtained for EC subscales.

DISCUSSION

Over several years, researchers pointed to the association of adolescents' inadequate sleep quality and irregular sleep patterns with behavioral problems in the area of emotional self-regulation, such as negative moods, increased likelihood of stimulant use, higher levels of risk taking behaviors, poor school performance, and increased risk of unintentional injuries. This association drew attention on the possible causal link between sleep problems and emotional dis-regulation, which would be of relevance in the design of interventions aimed to improve emotional self-regulation.

Overall, our results confirmed at individual level the association of quality of sleeping with emotional regulation and its components [13]. However, since the association is weaker in DZ pairs and disappears in MZ pairs, these results do not seem to support a direct causal link between sleep quality and emotional regulation as measured by effortful control, and suggest that genetic and shared environmental factors may confound this association observed also in other studies. In other words, our data seem to support the idea that quality of

Table 1
Demographic characteristics and factor scores of effortful control (and related subscales) according to sleep quality

	Sleep quality						Overall sample		
	Non-good sleepers (N = 262 twins)			Good sleepers (N = 120 twins)			(N = 382 twins)		
	N	Mean ± SD or %	Range	N	Mean ± SD or %	Range	N	Mean ± SD or %	Range
Gender, male	139	53.05%		76	63.33%		215	56.28%	
Age, years	262	16.37 ± 1.22	14 ; 18	120	16.34 ± 1.24	14 ; 18	382	16.37 ± 1.22	14 ; 18
Age, percentiles									
25th		15.3			15.2			15.2	
50th		16.6			16.4			16.6	
75th		17.5			17.5			17.5	
Zygosity									
MZ	80	30.53%		40	33.33%		120	31.41%	
DZ same sex	103	39.31%		39	32.50%		142	37.17%	
DZ opposite sex	79	30.15%		41	34.17%		120	31.41%	
Effortful control	262	-0.04 ± 0.82	-2.82 ; 1.22	120	0.30 ± 0.69	-3.14 ; 1.22	382	0.06 ± 0.80	-3.14 ; 1.22
Attentional focusing	261	-0.05 ± 0.82	-2.62 ; 1.01	120	0.23 ± 0.69	-2.32 ; 1.01	381	0.04 ± 0.79	-2.62 ; 1.01
Inhibitory control	262	-0.03 ± 0.79	-2.78 ; 1.08	120	0.28 ± 0.66	-3.05 ; 1.08	382	0.07 ± 0.76	-3.05 ; 1.08

SD: standard deviation; MZ: monozygotic; DZ: dizygotic.

Table 2
Comparison of good and non-good sleepers in terms of effortful control (and related subscales)

	Discordant same-sex DZ pairs					Discordant MZ pairs				
	N	Good sleepers	Non-good sleepers	Difference	P*	N	Good sleepers	Non-good sleepers	Difference	P*
		Mean (SD)	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)	Mean (SD)	
Effortful control	17	0.44 (0.61)	0.11 (0.64)	0.32 (0.62)	0.05	16	0.27 (0.67)	0.10 (0.87)	0.17 (0.87)	0.46
Attentional focusing	17	0.44 (0.53)	0.10 (0.69)	0.34 (0.76)	0.09	16	0.21 (0.72)	-0.05 (0.76)	0.26 (0.69)	0.15
Inhibitory control	17	0.32 (0.63)	0.09 (0.56)	0.23 (0.63)	0.16	16	0.25 (0.55)	0.20 (0.83)	0.04 (0.88)	0.85

* One-sample t test; SD: standard deviation; MZ: monozygotic; DZ: dizygotic.

sleeping and emotional regulation may depend upon a common set of genetic and environmental causes. This result may reinforce the evidence found by Diaz *et al.* [28] that EC moderates the relation between sleep and academic achievement in children: children with low EC need plenty of sleep in order to be successful at school. Furthermore, looking from the other direction, Berger *et al.* [29] found that sleep duration moderates the association between children's temperament and academic achievement. These phenotypes might have then a complex genetic and environmental architecture, and our findings suggest the need to investigate deeply the composite relation between sleep and children's EC: in the absence of a causal dependency between sleep quality and emotional regulation, difficulties in sleeping behavior may not represent a good direct target for regulation-enhancing interventions.

The results of our study should be interpreted in the light of the following main limitations: a) the use of self-reported data; b) our strict classification of subjects as good sleepers (and therefore our broad classification of subjects as non-good sleepers), which is new and does not allow comparisons with other studies; c) the dependency of our results on the arbitrary definition used for sleep quality; d) the low number of discordant pairs; however, the (high-degree) genetic and environmental matching of subjects may partly counterbalance the reduction in power imposed by a limited sample size.

Although the cross-sectional study design did not allow us to resolve the directionality of the association between EC and sleep quality, we were able to show a possible dependency of emotional regulation and quality of sleeping upon common genetic and environmental factors. As regards the modifiable factors, a crucial role in the expression of both these phenotypes is played by parenting style and family functioning [30, 31], which may thus represent two of the key environmental exposures common to the twin pair.

Our results may have significant implications for theories aimed to explain the links between sleep quality and emotional regulation; furthermore, they highlight the need to identify the relevant common environmental exposures in order to plan interventions aimed to improve both sleep quality and emotional regulation.

Author's contribution statement

EM: planned and performed statistical analysis, contributed interpreting the results and writing the manuscript. GA: discussed the results and contributed to the final manuscript. DD: collected data, aided in interpreting the results. CF: performed statistical analysis, contributed interpreting the results and writing the manuscript. MF: aided in data collection and contributed to database preparation. CV: contributed to the phenotypes definition and commented on the paper. MAS: contributed to the design and implementation of the research and provided critical feedback. All authors read and approved the final manuscript.

Conflict of interest statement

Authors have no conflicts of interest to disclose.

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REFERENCES

1. Carskadon MA. Sleep in adolescents: the perfect storm. Pediatr Clin North Am. 2011;58(3):637-47. doi: 10.1016/j.pcl.2011.03.003.37
2. Moore M, Meltzer LJ. The sleepy adolescent. Causes and consequences of sleepiness in teens. Paediatr Respir Rev. 2008;9(2):114-21. doi: 10.1016/j.prrv.2008.01.001
3. Fallone G,Owens JA, Deane J. Sleepiness in children and adolescents. Clinical implications. Sleep Med Rev. 2002;6(4):287-306.
4. te Velde SJ, van der Aa N, Boomsma DI, et al. Genetic and environmental influences on individual differences in sleep duration during adolescence. Twin Res Hum Genet. 2013;16(6):1015-25. doi: 10.1017/thg.2013.74
5. Moore M, Slane J, Mindell JA, et al. Genetic and environmental influences on sleep problems: a study of preadolescent and adolescent twins. Child Care Health Dev. 2011;37(5):638-41. doi: 10.1111/j.1365-2214.2011.01230.x

6. Hagenauer MH, Perryman JI, Lee TM, Carskadon MA. Adolescent changes in the homeostatic and circadian regulation of sleep. Dev Neurosci. 2009;31(4):276-84. doi: 10.1159/000216538
7. Carskadon MA, Tarokh L. Developmental changes in sleep biology and potential effects on adolescent behavior and caffeine use. Nutr Rev. 2014;72(Suppl. 1):60-4. doi: 10.1111/nure.12147. Review.
8. Carskadon MA, Tarokh L. Developmental changes in sleep biology and potential effects on adolescent behavior and caffeine use. Nutr Rev. 2014;72 (Suppl. 1):60-4. doi: 10.1111/nure.12147. Review.
9. Willis TA, Gregory AM. Anxiety disorders and sleep in children and adolescents. Sleep Med Clin. 2015;10(2):125-31. doi: 10.1016/j.jsmc.2015.02.002
10. Monroe LJ, Marks PA. MMPI differences between adolescent poor and good sleepers. J Consult Clin Psychol. 1977;45(1):151-2.
11. Matthews T, Danese A, Gregory AM, Caspi A, Moffitt TE, Arseneault L. Sleeping with one eye open: loneliness and sleep quality in young adults. Psychol Med. 2017;47(12):2177-86. doi: 10.1017/S0033291717000629
12. Moore M, Slane J, Mindell JA, et al. Sleep problems and temperament in adolescents. Child Care Health Dev. 2011;37(4):559-62. doi:10.1111/j.1365-2214.2010.01157.x
13. Lukowski AF, Milojevich HM. Sleep quality and temperament among university students: differential associations with nighttime sleep duration and sleep disruptions. Behav Sleep Med. 2015;13(3):217-30. doi: 10.1080/15402002.2013.855214
14. Blair C. Diamond A. Biological processes in prevention and intervention. The promotion of self-regulation as a means of preventing school failure. Dev Psychopathol. 2008;20(3):899-911. doi: 10.1017/S0954579408000436
15. Rueda MR, Posner MI, Rothbart MK. The development of executive attention. Contributions to the emergence of self-regulation. Dev Neuropsychol. 2005;28(2):573-94. doi: 10.1207/s15326942dn2802_2
16. Rothbart MK, Rueda MR. The development of effortful control. In: Developing individuality in the human brain. A tribute to Michael I. Posner. Mayr U, Awh E, Keele S (Eds). Washington, DC: American Psychological Association; 2005. pp. 167-188.
17. Eisenberg N, Valiente C, Morris AS, et al. Longitudinal relations among parental emotional expressivity, children's regulation, and quality of socioemotional functioning. Dev Psychol. 2003;39(1):3-19.
18. Brock LL, Rimm-Kaufman SE, Nathanson L, et al. The contributions of "hot" and "cool" executive function to children's academic achievement and learning-related behaviors, and engagement in kindergarten. Early Child Res Quart. 2009;24(3):337-49. doi: 10.1016/j.ecresq.2009.06.001
19. Fagnani C, Medda E, Alessandri G, et al. The genetic architecture of effortful control and its interplay with psychological adjustment in adolescence. J Res Pers. 2017;68:5-14.
20. Lemery-Chalfant K, Doelger L, Goldsmith HH. Genetic relations between effortful and attentional control and symptoms of psychopathology in middle childhood. Infant Child Develop. 2008;17:365-85. doi: 10.1002/icd.581
21. Yamagata S, Takahashi Y, Kijima N, Maekawa H, Ono Y, Ando J. Genetic and environmental etiology of effortful control. Twin Res Hum Genet. 2005;8:300-6. doi: 10.1375/1832427054936790
22. Brescianini S, Fagnani C, Toccaceli V, et al. An update on the Italian Twin Register. Advances in cohort recruitment, project building and network development. Twin Res Hum Genet. 2013;16(1):190-6. doi: 10.1017/thg.2012.85
23. Goldsmith HH. A zygosity questionnaire for young twins: a research note. Behav Genet. 1991;21(3):257-70.
24. Achenbach TM, Rescorla LA (Eds). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Centre for Children, Youth & Families; 2001.
25. Luengo-Kanacri BP, Pastorelli C, Eisenberg N, et al. The development of prosociality from adolescence to early adulthood: The role of effortful control. J Pers. 2013;81(3):302-12. doi: 10.1111/jopy.12001
26. Violani C, Devoto A, Lucidi F, et al. Validity of a Short Insomnia Questionnaire. The SDQ. Brain Res Bull. 2004;63(5):415-21.
27. McGue M, Osler M, Christensen K. Causal inference and observational research. The utility of twins. Perspect Psychol Sci. 2010;5(5):546-56.
28. Diaz A, Berger R, Valiente C, Eisenberg N, VanSchyndel S, Tao C, Spinrad TL, Doane LD, Thompson MS, Silva KM, Southworth J. Children's sleep and academic achievement. The moderating role of effortful control. Int J Behav Dev. 2017;41(2):275-84. doi: 10.1177/0165025416635284
29. Berger RH, Diaz A, Valiente C, Eisenberg N, Spinrad TL, Thompson MS, Hernández MM, VanSchyndel SK, Southworth J. Sleep duration moderates the association between children's temperament and academic achievement. Early Educ Dev. 2018;29(5):624-40. doi: 10.1080/10409289.2017.1404884
30. Buckhalt JA1, El-Sheikh M, Keller PS, Kelly RJ. Concurrent and longitudinal relations between children's sleep and cognitive functioning: the moderating role of parent education. Child Dev. 2009;80(3):875-92. doi: 10.1111/j.1467-8624.2009.01303.x
31. El-Sheikh M, Tu KM, Erath SA, Buckhalt JA. Family stress and adolescents' cognitive functioning: sleep as a protective factor. J Fam Psychol. 2014;28(6):887-96. doi: 10.1037/fam0000031

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The impact of a school-based multicomponent intervention for promoting vaccine uptake in Italian adolescents: a retrospective cohort study

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Abstract

Background. In Italy, the National Immunization Prevention Plan recommends for adolescents between ages 11 and 18 several vaccines, however their adherence is below the expected coverage. School-based delivery strategies might represent an alternative to primary care settings. This study aims to evaluate the impact of a school-based intervention aimed to increase the vaccination uptake among Italian secondary class students.

Methods. One of the four schools in which a school-based multicomponent intervention was previously carried out has been matched with a control school in the same geographical area. Students' coverage for mandatory and recommended vaccinations was assessed before and after an 8 months period using the Local Health Authority Immunization Register.

Results. Seven hundred and fifty-five resident students in the RM Local Health Authority were included: 265 from the intervention school, 490 from the control school. At baseline, the two schools were comparable for grades and sex distribution; the intervention school had significant higher immunization rates for Meningococcal B, but lower ones for the 4th dose of dTap. After eight months, higher percentage of students received the HPV (30.5% *vs* 13.8% of females; p = 0.003) Meningococcal C (6.0% *vs* 2.0%; p = 0.005) and Meningococcal B (14.7% *vs* 0.3%; p <0.001) vaccines in the intervention school compared with control. The pre-post differences between the two schools in the immunization rates were significantly higher in the intervention school for the HPV, Meningococcal C and B vaccines.

Conclusions. This study demonstrates that a school-based health promotion project was effective in improving the recommended vaccines uptake among adolescents with potential interesting implication for the national target attainment. Considering the importance of informing and educating, innovative school-based health promotion programs could represent an excellent opportunity for the Local Health Authorities to get in touch with a hard-to-reach target. Performance in offering the vaccination in school facilities should be evaluated.

Key words
- immunization
- school
- adolescents
- students
- vaccine uptake

INTRODUCTION

Vaccines are universally recognized as one of the most effective instruments for the primary prevention of infectious diseases, but in recent years vaccination delay or refusal is putting at risk the high level of immunization rates achieved in the past. This phenomenon, namely vaccine hesitancy, could be due to multiple levels of factors that influence parental vaccine confidence

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and acceptance [1]. Apart from the risk perception of the diseases and the confidence on vaccines, the WHO SAGE Working Group on Vaccine Hesitancy pointed out "convenience" as a possible explanation related to the ease of access to immunization in terms of location and time [2]. Immunizing adolescents represent globally a struggle despite national routine recommendations. In Italy, the National Immunization Prevention Plan recommends for adolescents between 11 and 18 years the following vaccines: diphtheria, tetanus, and acellular pertussis (dTpa), catch-up strategies for measles, mumps and rubella (MMR); Meningococcal C conjugate in subjects not vaccinated during childhood, two/three-dose schedule against HPV (only for females); a two-dose schedule against varicella in subjects unvaccinated or with negative history for the disease [3]. Regardless, respectively 52.9%, 53.9%, 74.9%, 75.0% and 16.0% of 16 years old adolescents received the fifth dose of dTap, the second dose of MMR, the first dose of rubella and mumps and one dose of Meningococcal C [4]. HPV vaccine coverage rates ranged from 72.1% for the 1999 birth cohort to 52.4% for the 2002 birth cohort (even if the latter is not still definitive) [5]. The coverage for the remaining available vaccines is lower than 10%, in particular 2.4% for varicella [4].

With the availability of newer vaccines and greater attention to providing booster doses of routine vaccines to older children, schools are becoming a more widely used platform for immunization [6]. In several countries, school-based health centres represent an alternative to primary care settings and have been shown to minimize common obstacles, such as parents missing work, therefore increasing immunization rates [7-10].

Despite the relevant success of the extraordinary measles catch-up campaign in several Regions, which include also the MMR vaccine delivery in elementary and middle schools, [11], Italy does not have a well-structured school-based immunization program. Furthermore, with the gradual shelving of the scholastic preventive medicine [12], Italian students are losing several opportunities to receive trustworthy information regarding vaccination and, consequently, protection against vaccine preventable diseases. This kind of activity has been delegated to the paediatricians, which usually visit their older patients only if they have health issues. Eventually, the Local Health Authority, in respect of its own autonomous organization, could implement voluntarily, but no more mandatory, school-based health promotion campaign, which are usually target to contrast non-communicable diseases, to promote healthy lifestyle and to fight dependencies.

For all these reasons, the Public Health Institute of the Università Cattolica del Sacro Cuore of Rome decided to design a project called "VacciniAmo le Scuole" (Let's school get vaccinated), which proposes to evaluate and enhance parents' and students' knowledge and attitudes of prevention regarding vaccine-preventable diseases in collaboration with the Italian Ministry of Education and the Local Health Authorities. Preliminary results provided further evidence about school-based health promotion programs as an effective strategy for improving knowledge and attitudes about this issue [13].

Since the original study design did not consider a control group, definitive conclusions about the project impact on the general vaccine coverage among the target population couldn't be carried out. The present study aimed to overcome this limitation evaluating the impact of a school-based multicomponent intervention on the adherence of Italian secondary school students to adolescent recommended vaccination. In this study, we hypothesized that the school involved in the VaccinAmo le Scuole project reported significantly higher rates of immunization of recommended vaccinations for adolescents compared with a school who did not receive the health promotion intervention (the control group).

METHODS

The intervention: VacciniAmo le Scuole project

The VacciniAmo le Scuole project was conducted in 2015 in four secondary schools in three Italian Regions (Lazio, Basilicata and Sicily), with the support of the local health authorities (ASL Roma A (now ASL Roma 1), ASL Roma B (now ASL Roma 2), ASM Matera and ASP Palermo). Each class received a 90 minutes health promotion intervention, which includes a theoretical introduction and a second part more interactive using the role-play technique, and a pre-post questionnaire [14]. Students' parents received at home a similar questionnaire, which includes a section requesting their informed consent and invitation to a meeting with the project team. All the health promotion activities have been carried out in deep collaboration with each representative of the local health authorities. After the school interventions, each Local Health Authority arranged to receive students and parents at least one day in their surgery to carry out the recommended vaccinations for adolescents. Detailed information regarding the project and its results are under submission separately. The VacciniAmo Le Scuole project was approved by the Ethical Committee of the Local Health Authorities "Roma 1" (Ref. n. 513 CE Lazio1 – Rome, 02/03/2017).

Study design and schools recruitment

The impact of the school-based multicomponent intervention VacciniAmo le Scuole was tested using a retrospective cohort design, comparing the aggregated immunization coverage in one of the schools in which the VacciniAmo le Scuole has been performed (intervention school) to a matched school from the same geographical area.

The intervention school was selected from the four schools participating in the VacciniAmo le Scuole according to the number of students involved in the project and the availability of a comparison school in the same geographical area. Only the school in the ASL ROMA1 respected these inclusion criteria. Consequently, its referent recruited a control school from the same administrative area, according to geographic vicinity and with similar socio-demographic characteristics. In this way the control school could be considered similar both in terms of the attending students (including from a socio-demographic point of view), both in terms of its relationship with the ASL. As a matter of

fact, apart from the VacciniAmo le Scuole intervention, for every registered student of both the schools received yearly a personalized letter, which informs each one regarding his own immunization status.

The intervention school has 413 registered students, but only 284 participated in the VacciniAmo le Scuole project and have been included in this study. All the 517 students registered in the control school have been included in this study.

The main outcomes were the proportion of students receiving each vaccination mandatory/recommended for adolescent, namely the 5th dose of dTap, the 2nd dose of MMR, a dose of HPV (among girls), one dose of Meningococcal C (in subjects not vaccinated during childhood). Furthermore, because in 2015 the ASL ROMA1 was pursuing also the Meningococcal B vaccine, the proportions of students who received at least one dose of this vaccine were investigated as a secondary outcome. Finally, also the proportion of students receiving at least one among the above-mentioned vaccines has been evaluated as a secondary outcome because it represents a proxy of the opportunity to meet experts from the local health authority which can provide students with the best knowledge on vaccine preventable diseases for them. Because of the shifting from three to two doses schedule (only for the new cohorts of 12 years old girls whom initiated the HPV vaccination in 2015), the outcome regarding the HPV vaccine was considered as the initiation or the completion of a 2-dose HPV series. The vaccination against varicella was excluded because of the impossibility to assess the negative history for the disease in the students. It should be underlined that in people aged 11 to 18 years the above-mentioned mandatory/recommended vaccinations are free of charge, while the Meningococcal B vaccination are offered under a discounted payment because in 2015 it is not yet included in the National Immunization Plan.

All the outcomes were evaluated in both intervention and control schools just before and at 8 months since the implementation of the VacciniAmo le Scuole project.

Data sources

The head of the two schools provided the student list with information on their school grade. Students' coverage for mandatory and recommended vaccinations was assessed using the Local Health Authority Immunization Register, which routinely collected data deriving from the national Immunization Program for residents within their administrative boundaries. Students were not counted in the analysis if they were resident in another local health authority, because lack of information regarding immunization history and administration. That's led to the exclusion of 46 non-resident students in the ASL ROMA1 (19 students in the intervention school and 27 in the control school, p = 0.393).

The two above-mentioned data sets were merged using the student's tax code as key and the observations were made anonymous assigning a casual numerical code.

Students' vaccination history was ascertained before the program started in the intervention school (February, the 15th) and again after 8 months (from February, the 16th until October, 15th). Eight months have been considered as the follow-up period until the end of the scholastic year, giving two additional months to take into account that during the summer holidays parents could postpone the decision to vaccinate their children.

Students were considered to be already immunized if they had at baseline the appropriate number of doses for each immunization recommended in the National Immunization Plan (4 or 5 doses of dTap, 2 doses of MMR, at least 2 doses of HPV only for girls, at least 1 dose of Meningococcal C or B). For the dTap the information regarding the immunization status was calculated for a 4th dose, which should be completed at the age of 5-6 years old, and for the 5th dose, which should be administered every 10 years after the 4th dose (so around 15-16 years), but that is usually co-administered during the first access to the immunization center after 11 years old to make the vaccination schedule easier.

Among the students who were not already fully immunized, the ones who received the expected doses were recorded and a comparison between pre and post intervention coverage was done. For the dTap the 5th dose was considered the expected one and students that have already received it were considered fully immunized.

Statistical analysis

Descriptive data were summarized through absolute and relative frequencies for categorical variables and through means and Standard Deviations (SD) for continuous variables.

Chi Square was used to compare differences between variables of interest at baseline. Overall and stratified vaccine uptake rates between the two schools were compared using two sample tests of proportions. Furthermore, to take into account the baseline immunization coverage, the same statistical test was used to compare within and between differences in the vaccine specific pre-post immunization rates.

Statistical significance was set for p value <0.05 and all statistical tests were two-sided. Statistical analysis was performed using Intercooled Stata 12 for Macintosh (Stata Corporation Lakeway, USA, 2007).

RESULTS

755 resident students in the ASL ROMA1 were included in this study, 265 from the intervention school, 490 from the control school. Their mean age was 12.3 (±1.0) years and 48.1% of them were girls. The school grades and sex distribution did not differ between the two schools. At baseline, the intervention school had significant higher immunization rates for Meningococcal B, but lower ones for the 4th dose of dTap. Among the 755 students, 40.4% needed 1 or more vaccines, significantly more in the intervention school (46.0%) than in the control one (37.3%). Characteristics of the schools as well as baseline immunization rates are shown in *Table 1*.

Table 2 reports the results of the intervention under study after eight months. A higher proportion of girls not already fully immunized for HPV received the HPV vaccine in the intervention group (30.5% *vs* 13.8%; p

Table 1
Characteristics and baseline immunizazion rates of the two schools included in the study

		School		p (chi2)
		VacciniAmo	Control	
Residents (N = 755)		265	490	0.393
Sex (% of Females)		130 (49.4%)	(240) 48.9%	0.906
School Grade	I	93 (35.9%)	163 (33.3%)	0.359
	II	94 (35.9%)	158 (32.2%)	
	III	78 (28.2%)	169 (34.5%)	
Immunization status (Students Already Immunized)	dTap (4 doses)	210 (79.3%)	429 (87.6%)	**0.003**
	dTap (5 doses)	18 (6.8%)	38 (7.8%)	0.498
	MMR (2 doses)	202 (76.2%)	398 (81.2%)	0.105
	HPV (at least 2 doses - females)	49 (37.7%)	110 (45.8%)	0.131
	Men C (at least 1 dose)	98 (43.2%)	177 (36.1%)	<0.071
	Men B (at least 1 dose)	15 (5.7%)	0 (0.0%)	**<0.001***
	Already Immunized for all the above	143 (54.0%)	307 (62.7%)	**0.020**

* Fisher' exact test.

= 0.003). Similarly, a higher proportion of students received Meningococcal C (6.0% *vs* 2.0%; p = 0.005) and B (14.7% *vs* 0.3%; p <0.001) vaccines *(Table 2)* in the intervention group respect to the control. Although not statistically significant, a higher proportion of students received at least one of the mandatory/recommended vaccines in the intervention respect to the control school (41.2% *vs* 33.9%; p = 0.149).

The sex and the school grade of the students not already fully immunized that received individual vaccines are shown in *Figure 1*. Only one male student of the 3rd year received the second dose of MMR (not shown in *Figure 1*). Excluding HPV vaccines, usually males receive more vaccinations than females (57%, 75% and 64%, respectively for dTap, MenC and MenB). DTap uptake is higher in 3rd year students, while HPV and MenB is higher in the first class students (*Figure 1*).

Lastly, we compared the immunization coverage rates before and after the intervention under study. Results reported in *Table 3* are consistent with those reported in *Table 2*. The intervention school reported a significant increase in the HPV, Meningococcal C and B immunization rates (+11% (p = 0.002); +8.1% (p = <0.001) and +3.7% (p = 0.008), respectively. In particular, girls in the intervention school had lower HPV coverage at baseline (37.7% *vs* 45.8%), but they reached higher immunization rates at 8 months after the project implementation (56.2% *vs* 53.3%).

Table 2
Results of the intervention VacciniAmo le Scuole as proportion of students undergoing vaccination among those not already fully immunized *

Individual vaccines	VacciniAmo N (%)	Control N (%)	p
DTP	28 (11.3)	54 (11.9)	0.796
MMR	1 (1.6)	0 (0.0)	0.406**
HPV (females)	25 (30.5)	18 (13.8)	**0.003**
MenC	19 (14.7)	1 (0.3)	**<0.001****
MenB	15 (6.0)	10 (2.0)	**0.005**
At least One (DTP, MMR, HPV, MenC, MenB)	61 (41.2)	79 (33.9)	0.149

* The denominator of each cell is represented by the difference between the included students and the students already immunized with the specific vaccination (showed in *Table 1*). ** Fisher' exact test.

DISCUSSION

Currently, most countries in the world deliver nationally recommended vaccines to adolescents primarily through school-based vaccination centers. This approach has largely overcome missed opportunities for vaccinating adolescents in traditional healthcare settings allowing higher coverage for most of the available vaccination than in delivering systems based on the community sector or private practice [15]. Other Authors highlighted that school based educational intervention helped improve vaccination coverage among adolescents regardless of the venue of vaccination [16].

In Italy, despite this growing evidence and the large public offer of vaccinations, there is no national program in place to promote vaccine uptake on a school level that remains globally underused with a consequent inadequate access to preventive health care for adolescents. Nevertheless, the unexpected decrease in national immunization rates and the newly adopted National Vaccination Plan could enhance Regional and Local Autonomy to reinforce their efforts in this field, requiring country specific information regarding feasibility and efficacy of tailored school programs.

VacciniAmo le scuole is an innovative multicomponent health promotion program that as been shown effective in improve knowledge and attitudes towards vaccine preventable diseases among young Italian adolescents with an overall high acceptance among teachers and students [13], which is in agreement with previously published papers [17]. However, no evidence was

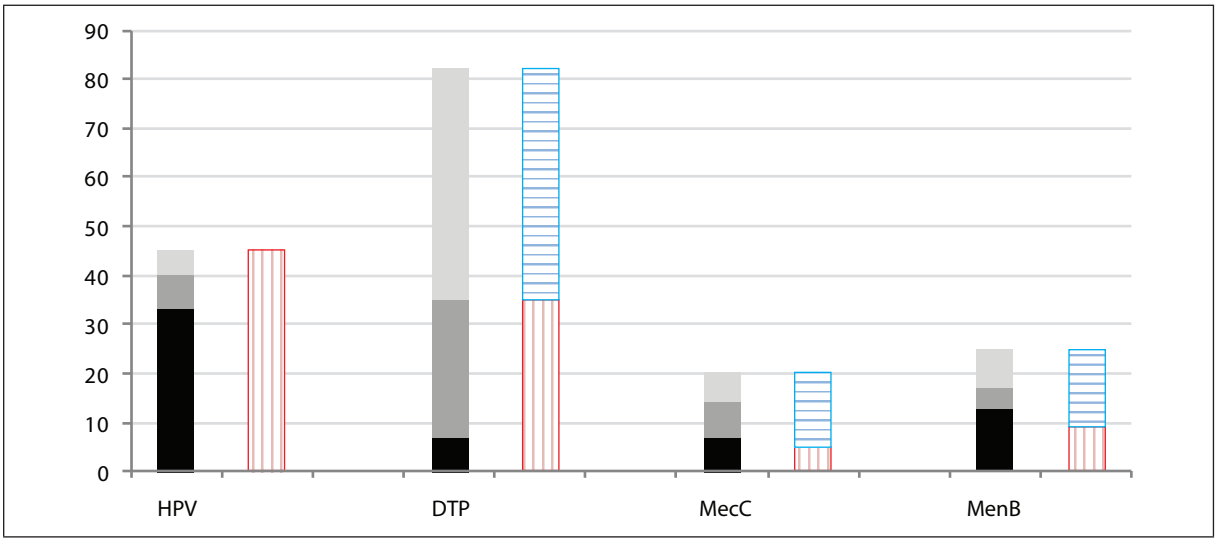

Figure 1
Students not already fully immunized receiving individual vaccines, stratified according school grades (first column: black = 1st year; grey = 2nd year; light grey = 3rd year) and sex (second column: vertical red line = Females; horizontal light blue line = Males).

available regarding its efficacy in improving the vaccine uptake among program participants that is evaluated in this retrospective cohort study in comparison to a standard-of-care approach.

Eight months since its implementation, vaccination coverage for most of the recommended vaccinations was higher in intervention school than in the control one. That's particularly true for HPV vaccination among girls, but also for Meningococcal C and B vaccines. For all these vaccines, as already shown by different authors, the higher uptake has been recorded in younger students [15, 18]. Furthermore, we recorded a higher uptake of Meningococcal C and B vaccines among males, which has been suggested due to the more vaccinations required for females [19].

The 5th dose of TdaP has been required by a small proportion of students, mostly in the third school grade and without differences between the two schools, presumably because parents and students was waiting for the proper schedule, which is usually administered a couple of year later. Similarly, the 2nd dose of MMR vaccine is required only by one student in the intervention school, with unsuccessful coverage, which remained around 80% in both schools, quite far from the 95% target identified in the national plan for eliminating measles and congenital rubella syndrome [20]. In this study we do not have information regarding the students history nor the specific serum antibodies, and it should not be excluded that the wild disease has already affected most of these students.

Additionally, despite the higher rate of students receiving at least 1 vaccine in the intervention school (41.2% vs 33.9%) that exceeded the control school in the overall coverage for all the investigated vaccines, it should be said that both the schools remain far from the national targets. Even if we have no insight into why necessary vaccines were missed, one possible reason relies on the fact that the vaccinations have been administered in a different location than in the ambulatory of the school. This reason should be taken into strong consideration when implementing a school-based health promotion program while the opportunity

Table 3
Within and between schools differences in the immunization coverage pre and post the intervention VacciniAmo le Scuole

	Post intervention immunization coverage (within-schools pre-post difference)				Between-schools pre-post differences	
	VacciniAmo	P	Control	P	VacciniAmo - Control	P
dTap (5th dose)	17.0% (+10.2%)	**<0.001**	18.8% (+11.0%)	**<0.001**	-0.8%	0.725
MMR (2nd dose)	76.6% (+0.4%)	0.919	81.2% (+0.0%)	1.000	+0.4%	0.174
HPV (females)	56.2% (+18.5%)	**0.003**	53.3% (+7.5%)	0.100	+11.0%	**0.002**
MenC	51.5% (+8.3%)	0.074	36.3% (+0.2%)	0.947	+8.1%	**<0.001**
MenB	11.3% (+5.7%)	**0.019**	2.0% (+2.0%)	**0.002**	+3.7%	**0.008**

to receive the health intervention is delayed in space and time [21, 23].

The success in increasingthe actual vaccination rates could be attributed to several factors. First, the health promotion intervention has been carried out using innovative and interactive approach, namely the role play, which has been very appreciated by the schools [14]. Secondly, the intervention has been developed in deep collaboration with the local health authority. For this reason, it is tailored according to the local needs and all the project team has been available to address students, parents and teachers' concerns regarding vaccination along the project period. Finally, while most of the school-based programs have been focused on a specific vaccine (usually the HPV), this project has been developed to increase the awareness and the coverage of all the recommended vaccination for adolescent.

This study has several limitations. Generalization should be done with caution because the setting is limited to a couple of urban schools and a small number of adolescents. Student's randomization is not possible due to the specific school setting. Additionally, the control school has been matched as much as possible for socio demographic characteristics and the two groups did not show significant difference at baseline for sex and school grade. Also the immunization status at baseline is quite balanced between the two schools, with some vaccine coverage higher in the intervention school (Meningococcal C and B), but others higher in the control one (dTap, MMR and HPV). Finally, even if the immunization registry is a high reliable source of information, it is limited to vaccination administered within the local health authority boundaries. For this reason we had to limit our sample to the residents within the local health authority and we cannot exclude, even if it is unlikely, we lose some information on students who decided to be vaccinated outside the ALS Roma 1.

This study demonstrates that the school-based multicomponent health promotion project VacciniAmo le Scuole was effective in improving the recommended vaccines among adolescents with potential interesting implication for the national targets attainment. Larger and multi-centric studies may help to understand the real advantages when a school-based model of immunization delivery is implemented in Italy. Even thought Italy has recently passed a law to make mandatory 10 vaccinations and to make vaccination a school requirements for children under the age of 16, multicomponent school based immunization campaigns could be helpful to overcome several well-known barriers to adolescent immunization, such as the need for parents to miss work or the opportunity for the ASL to get in touch with a hard-to-reach target, as well as to increase the population confidence in the health institutions [24].

CONCLUSIONS

Our results suggest that innovative school-based health promotion intervention could increase adolescent specific vaccination uptakes and coverage. The Local Health Authorities should implement and evaluate similar school-based interventions to give Italian students trustworthy information regarding vaccination and, consequently, being protected against vaccine preventable diseases. Better results could be reach offering the vaccination in school facilities.

Author's contribution statement

All authors have made substantial contributions to the analysis and interpretation of data and have approved the final version of the manuscript. Andrea Poscia and Antonietta Spadea has been involved in the conception and design of the study and in the data acquisition, Andrea Poscia and Roberta Pastorino analyzed the data and drafted the article and Antonietta Spadea, Stefania Boccia and Walter Ricciardi revising it critically for important intellectual content.

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Conflict of interest statement

The Authors declare they have no potential conflicts of interest to disclose.

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REFERENCES

1. Di Pietro ML, Poscia A, Teleman AA, Maged D, Ricciardi W. Vaccine hesitancy: parental, professional and public responsibility. Ann Ist Super Sanità. 2017;53(2):157-62. doi: 10.4415/ANN_17_02_13
2. World Health Organization. Summary WHO SAGE Conclusions and Recommendations on Vaccine Hesitancy. Geneva: WHO; January 2015. Available from: www.who.int/immunization/programmes_systems/summary_of_sage_vaccinehesitancy_2pager.pdf?ua=1
3. Italia. Ministero della Salute. Piano Nazionale Prevenzi-

one Vaccinale 2012-2014. Available from: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=466
4. ICONA Working Group. ICONA 2008: Indagine di COpertura vaccinale NAzionale nei bambini e negli adolescenti. Roma: Istituto Superiore di Sanità; 2009. (Rapporti ISTISAN 09/29).
5. Bonanni P, Ferro A, Guerra R, Iannazzo S, Odone A, Pompa MG, Rizzuto E, Signorelli C. Vaccine coverage in Italy and assessment of the 2012-2014 National Immunization Prevention Plan. Epidemiol Prev. 2015;39(4 Suppl. 1):146-58.
6. Hayes KA, Entzel P, Berger W, et al. Early lessons learned from extramural school programs that offer HPV vaccine. J School Health. 2013;83(2):119-26.
7. Rickert VI, Auslander BA, Cox DS, Rosenthal SL, Rupp RE, Zimet GD. School-based HPV immunization of young adolescents: Effects of two brief health interventions. Hum Vacc & Immunother. 2015;11(2):315-21. doi: 10.1080/21645515.2014.1004022
8. Ito T, Takenoshita R, Narumoto K, Plegue M, Sen A, Crabtree BF, Fetters MD. A community-based intervention in middle schools to improve HPV vaccination and cervical cancer screening in Japan. Asia Pacif Fam Med. 2014;13:13.
9. Lim WT, Sears K, Smith LM, Liu G, Levesque LE. Evidence of effective delivery of the human papillomavirus (HPV) vaccine through a publicly funded, school-based program: the Ontario Grade 8 HPV Vaccine Cohort Study. BMC Pub Health. 2014;14:1029.
10. Wilson SE, Harris T, Sethi P, Fediurek J, Macdonald L, Deeks SL. Coverage from Ontario, Canada's school-based HPV vaccine program. The first three years. Vaccine 2013;31:757-62.
11. Sammarco S, Ciriminna S, Casuccio N, et al. Copertura vaccinale e andamento epidemiologico del morbillo in Sicilia. Not Ist Super Sanità 2005;18(6):i-ii.
12. Italia. Ministero della Salute. Documento finale del gruppo di lavoro costituito con decreto del Ministro della Salute in data 13 Ottobre 2004 per la semplificazione delle procedure relativamente alle autorizzazioni, certificazioni ed idoneità sanitarie. Available from: www.epicentro.iss.it/discussioni/obsolete/pdf/Documento%20EBP%20finale.pdf .
13. Poscia A, La Milia DI, de Meo C, Azzolini E, Spadea A, Annona C, Mangia ML, Casuccio N, Ricciardi W, Boccia S. Promote immunization among high school students: the school-based project "VacciniAmo le Scuole". Eur Pub Health. 2016;26(S1):190-1.
14. Bartolucci S, Distefano FA, Ungari J, et al. Il role play al servizio della promozione della salute tra gli studenti delle scuole medie: il progetto pilota "VacciniAmo le Scuole". Abstract Book of the SItI 48° National Conference. 2015:75.
15. Ward K, Quinn H, Bachelor M, Bryant V, Campbell-Lloyd S, Newbound A, Scully M, Webby R, McIntyre PB. Adolescent school-based vaccination in Australia. Commun Dis Intell Q Rep. 2013;37(2):E156-67.
16. Gargano LM, Pazol K, Sales JM, et al. Multicomponent interventions to enhance influenza vaccine delivery to adolescents. Pediatrics. 2011;128(5):e1092-99. doi: 10.1542/peds.2011-0453
17. Grandahl M, Rosenblad A, Stenhammar C, et al. School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study. BMJ Open 2016;6:e009875. doi: 10.1136/bmjopen-2015-009875
18. Quinn HE, McIntyre PB. The impact of adolescent pertussis immunisation 2004 to 2009 – lessons from Australia. Bull WHO. 2011;89:666-74.
19. Kempe A, Barrow J, Stokley S, Saville A, Glazner JE, Suh C, Federico S, Abrams L, Seewald L, Beaty B, Daley MF, Dickinson LM. Effectiveness and cost of immunization recall at school-based health centers. Pediatrics. 2012;129(6):e1446-52. doi: 10.1542/peds.2011-2921
20. Italia. Ministero della Salute. Piano nazionale per l'eliminazione del morbillo e della rosolia congenita (PNEMoRc) 2010-2015. Intesa Stato-Regioni 23 marzo 2011. Available from: www.salute.gov.it/imgs/C_17_pubblicazioni_1519_allegato.pdf .
21. Shah PD, Gilkey MB, Pepper JK, Gottlieb SL, Brewer NT. Promising alternative settings for HPV vaccination of US adolescents. Expert review of vaccines. 2014;13(2):235-46. doi: 10.1586/14760584.2013.871204
22. Di Nardo F, Calabrò G.E, Ianuale C, et al. Capturing the chance for pneumococcal vaccination in the hospital setting. Ann Ist Super Sanità. 2017;53(4):291-8. doi: 10.4415/ANN_17_04_04
23. Desiante F, Russo C, Giorgino A, et al. Universal proposal strategies of anti-HPV vaccination for adolescents: comparative analysis between school-based and clinic immunization programs. *J Prev Med Hyg*. 2017;58(3):E225-30.
24. de Waure C, Sisti G, Poscia A, Ricciardi W. Il nuovo Piano Nazionale Prevenzione Vaccinale e i LEA: cosa cambia? Ig Sanità Pubbl. 2017;73(5):405-18.

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Behavioral responses in people affected by alcohol use disorder and psychiatric comorbidity: correlations with addiction severity

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Abstract

Aim. In this study, we investigated in people suffering from alcohol use disorder (AUD) with or without dual diagnosis (concomitant psychiatric disability) how they feel their dependence condition. We predicted that AUD people with a dual diagnosis could feel potentiated their addiction.

Methods. Alcohol habits and psychiatric conditions of 183 AUD men and 62 AUD women were measured by using the DSM-5, the severity of alcohol dependence questionnaire (SADQ), the alcohol anamnesis and psychiatric examination by the symptom check list 90-R (SCL-90-R).

Results. We have shown that alcohol drinking does not correlate with both psychiatric examination and self-reported psychopathology. SADQ shows that severe alcohol dependence correlates with highest psychiatric symptoms and with the levels of alcohol consumption.

Conclusions. This finding suggests that high SADQ scores may represent a tool to early disclose only patients with dual diagnosis. SADQ may provide information to address pharmacological interventions because revealing aspects of the dark side of addiction potentiated by AUD associated psychopathology.

Key words

- alcohol use disorders
- dual diagnosis
- addiction
- psychiatric comorbidity
- symptom check list 90-R

INTRODUCTION

People suffering from Alcohol Use Disorder (AUD) frequently show behavioral impairments and related psychiatric disruptions (dual diagnosis) [1-12], In the early studies of the Cloninger group, two subtypes of alcoholism have been described. The type I, affecting both men and women, could have genetic or environmental bases, usually starting at an early age, and causing either mild or severe alcohol dependence [13]. The type I was characterized by loss of control over drinking, binge drinking, guilt about drinking and progressive severity of alcohol abuse. The personality traits of type I were high harm avoidance and low novelty seeking, the person drinks to relieve anxiety. Instead, the type II is primarily genetic [5] affects men more often than women, and mainly sons of male alcoholics, the alcohol problems appear before age 25 and often begins during adolescence or early adulthood. Type II is characterized by the inability to abstain from alcohol. Type II is also associated with criminal behavior and with a history of antisocial acts. Relatively to personality traits, type II is characterized by high novelty seeking, person drinks to induce euphoria. Psychopathological dysfunction and sociopathy and often coexist in type II. In fact, type II alcoholism has more emotional regulation difficulties and a lot of social problems, than type 1 alcoholism, that can contribute to developing psychiatric disorders [14].

Depression, anxiety and personality disorders are of-

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ten associated with alcoholism and contribute to craving and relapse [2, 6, 15-21]. AUD people with dual diagnosis are reported to be high users of the health care system [22] and to have a more severe course of alcohol dependence [23, 24] than AUD people without a dual diagnosis [17, 25]. Indeed, the comorbid condition of psychiatric impairments and AUD may predict both relapsing shorter time and increasing treatment drop-out [26-28]. Dual diagnosis and alcohol addiction severity are crucial at-risk factors for relapse and drop-out events [29-31], but only a few studies concurrently investigated their related conditions. Such studies used self-administered questionnaires as the symptom check list 90-R (SCL-90-R) [32] and the severity of alcohol dependence questionnaire (SADQ) [33] to assess psychiatric condition and alcohol addiction magnitude. However, for assessing the levels of alcohol addiction previous studies [34-36] mostly investigated only the SADQ total score but without considering the analysis of the questionnaire subscales. Such analyses may provide subtle indications to disclose that certain drinking problem domains are closely related to crucial aspects of dependence [37, 38]. Thus, the aim and novelty of this study was to analyze in a cohort of about 250 AUD people the relationship between psychiatric diseases and the severity of alcohol dependence using not only the behavioral responses to self-administered questionnaires (SADQ and SCL-90-R) but also the clinical examinations carried out by psychiatrists and physicians with long-lasting expertise in psychiatry and alcohol addiction by using the DSM-5 criteria and ad hoc tools for measuring real drinking habits as life drink history (LDH) and time line follow back (TLFB) according to the standardized methodology of the Italian guidelines for the treatment of alcohol addiction [39, 40]. We predict that AUD people with dual diagnosis could feel potentiated their addiction. Potential gender differences were also investigated.

MATERIALS AND METHODS

AUD people recruitment

AUD participants were recruited in the Latium Region Alcohol Referral Center at Policlinico Umberto I, Sapienza University Hospital, in Rome, Italy during a 15 days-long day-hospital period. All participants met the DSM-5 criteria for AUD. According to the indications of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) we considered "at-risk" drinkers people drinking up to 4 drinks per day or 14 per week for men (in Italy 1 drink = 12 g), more than 3 drinks per day or 7 drinks per week for women (in Italy 1 drink = 12 g). NIAAA defines heavy drinking as 5 or more standard drinks in a day for a man and 4 or more standard drinks in a day for a woman [41]. AUD people enrolled in the study were 245 *(Table 1)*, 74.6% (n = 183) of them were men and their mean age was 47.20 ± 10.8 years and 62 (25.4%) women (48.15 ± 10.28 age in years). The 81.6% of AUD people were Italians, the 39.8% were married and 31% were single. The mean age of onset of alcohol problems was 28.99 ± 10.96 years. The AUD group reported an average of 17.95 ± 12.88 years of problem drinking and an average of 13.99 ± 10.86 drinks per day during the month prior to the admission to the treatment unit. 40% of the cases had completed at least 8 years of schooling.

Patients were divided into two groups: AUD patients without a dual diagnosis as referred to the SCL-90-R and as evaluated by the psychiatrist examination (n = 74; 58 men and 16 women) and AUD patients with a dual diagnosis (n = 171; 125 men and 46 women). Such differences between the number of recruited men and women may be explained to the fact that AUD men tend to ask for help more often than AUD women [42] even though the same women could show a more serious psychiatric condition [43].

The 171 AUD patients with dual diagnosis present-

Table 1

Description of the two groups of AUD patients with and without dual diagnosis divided for gender, enrolled in the study. Data are expressed as means ± SD, as median or as percentage. CAD = cumulative abstinence duration; SES = socio-economic status (1 up to 5000 euro per year; 2 from 5000 to 10 000 euro; 3 from 10 000 to 20 000; 4 over 20 000). According to NIAAA for men alcohol risk consumption begins with more than 4 drinks on any single day and more than 14 drinks per week. 1 drink = 12 g of alcohol in Italy. For the Educational Level, 1 represents no scholastic degree, 2 Primary School (8 years of compulsory formal education), 3 Secondary School (5 years of formal education), 4 University degree

	AUD patient without dual diagnoses		AUD patient with dual diagnoses	
	Men (n = 58)	Women (n = 16)	Men (n = 125)	Women (n = 46)
Age	48.40 ± 9.76	49.79 ± 10.25	46.65 ± 11.25	47.61 ± 10.35
Educational level [1 low – 4 high]	2.11 ± 0.49	2.33 ± 0.62	2.30 ± 0.69	2.44 ± 0.62
SES [1 low – 4 high]	2.24 ± 0.31	2.43 ± 0.18	2.34 ± 0.35	2.28 ± 0.28
Age of first consumption	28.97 ± 10.78	31.38 ± 9.26	26.89 ± 10.68	32.93 ± 11.58
Years of critical consumption	19.52 ± 14.01	16.50 ± 10.98	19.20 ± 13.26	14.23 ± 11.09
Alcohol preference (%)				
wine	50.3	44.1	52.6	44.6
beer	30.9	28.5	31.6	29.4
spirit	15.8	25.8	16.4	27.4
Abstinence days before the test [CAD]	5.63 ± 8.976	9.33 ± 11.672	5.11 ± 7.964	5.64 ± 7.312
Previous use of psychoactive substances [%]	30.9	17.1	32.1	16.3
Smoking [daily number of cigarettes]	17.8 ± 11.76	16.43 ± 11.98	17.1 ± 11.95	16.75 ± 12.78

ed different psychiatric conditions: most of them, the 49.7%, present a bipolar disorder followed by the 28.8% that present a mood disorder, the 8.9% present an anxiety disorder, the 8.8% present a personality disorder. Only the 2.3% present psychotic symptomatology and the 1.5% present adjustment disorders.

Table 1 shows also the differences in the sociodemographic and alcohol variables between the two groups of AUD patients with and without a dual diagnosis for gender.

Exclusion criteria for all participants included history of head injury, loss of consciousness, history of organic mental disorder, present assumption of psychoactive drugs as cocaine, opioids, amphetamine, other recreational drugs, anxiolytics, euphoriants, antipsychotics, barbiturates, antidepressants, hallucinogens-data based on urine toxicology), seizure disorder or central nervous system diseases and no sign of hypertension at the time of recruitment. Breath alcohol level was measured by using Alcoscan AL7000. During the 15-day long hospitalization period, alcohol consumption was also analyzed by the presence of Ethylglucoronide in the urine [44]. Psychiatric examination and self-administered interviews were carried out between day 7 and day 8 of the two weeks day-hospital period. The study was approved by the University Hospital ethical committee and informed consent was signed by each participant and all the study procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983, for human experimentation. The clinical diagnosis for dual diagnosis and the clinical diagnosis for alcohol addiction were carried out by different specialists unaware of the final group assignment of the patients according to the psychological and cognitive assessments by self-report questionnaires (see below).

Clinical assessment for a dual diagnosis

Psychiatric examination by DSM-5 criteria for dimensional assessment and diagnosis of mental disorders (based on descriptions, symptoms and other criteria for diagnosing mental disorders) [45] in AUD people was carried out to assess the presence of psychiatric disorders. A psychiatric examination was carried out between day 7 and day 8 of the 15-day long day-hospital period for a first diagnostic orienting as stated before. Then, the psychiatrist, when the patients concluded the detox period, performs a second evaluation to confirm or modify the diagnosis (between day 15 and 20 after the end of the day-hospital). The last diagnosis was used to confirm the classification of the two groups of AUD patients without and with dual diagnosis.

Clinical assessment for alcohol dependence

AUD magnitude and the lifetime alcohol consumption were assessed by clinicians by using LDH, TLFB and the DSM-5 Severity Scale for Alcohol Use Disorder.

LDH [46] is a retrospective, interview-based procedure, used to identify patterns of alcohol use, abuse, and dependence beginning with the onset of regular drinking and ending with the individual's current drinking pattern [46-48].

TLFB [49, 50] is used as a clinical and research tool to obtain a variety of quantitative estimates of alcohol and other drugs' use in the last month.

Both LDH and TLFB were administered by physicians with a long-lasting experience on alcohol addiction after the disappearing of the withdrawal symptoms according to a set of specific evidence, such as elevated blood pressure, tachycardia, tremor, sweating and no alcohol presence (see also the above-described methods).

The DSM-5 diagnostic criteria for alcohol use disorder [45] is used to designate mild (2-3), moderate (4-5), and severe (≥ 6) dependence. The AUD diagnosis was determined by analysing the number of AUD criteria of the past 12 months. DSM-5 defined AUD symptoms included: 1) tolerance, 2) withdrawal, 3) substance taken in larger amounts/longer period than intended, 4) persistent desire or unsuccessful attempts to decrease/control use, 5) a great deal of time spent obtaining, using or recovering from effects of alcohol, 6) social, occupational, or recreational activities given up or reduced because of use, 7) use despite knowledge of physical or psychological problems caused or exacerbated by use, 8) recurrent failure to fulfil major role obligations, 9) recurrent use in hazardous situations, 10) craving/strong desire to use the substance, 11) continued use despite social/interpersonal problems.

Psychological and cognitive assessments by self-report questionnaires

Self-report measures were carried out to investigate the psychological and cognitive functioning and the severity of the dependence. AUD people provided different self-report assessments under the supervision of a psychologist with a long-lasting training in alcohol addiction. In particular, we analysed the mini-mental state examination (MMSE), the vocabulary subtest of the WAIS-R, the SCL-90-R and the SADQ.

The MMSE [51] is a brief 30-point questionnaire, the most frequently used assessment methods for the estimation of cognitive function, and it has been shown to have adequate reliability and validity to screen for cognitive impairment. The raw score needs to be corrected for educational attainment and age [52].

The vocabulary subtest of the WAIS-R [53] is considered to be one of the best indicators of general intelligence and is used to assess the verbal intellectual functioning in clinical practice. The WAIS-R vocabulary subtest consists of the meaning definition of 40 words.

The SCL-90-R [54] is a 90-item self-report symptom inventory designed to reflect psychological symptom patterns of psychiatric and medical patients. Each item of the questionnaire is rated on a 5-point scale of distress from 0 (none) to 4 (extreme). The SCL-90-R used in the present investigation consists of the following nine primary symptom dimensions and a global severity index (GSI): somatization (SOM, which reflects distress arising from bodily perceptions), obsessive-compulsive (OC, which reflects obsessions-compulsions symptoms), interpersonal sensitivity (IS, which reflects feelings of personal inadequacy and inferiority in comparison with others), depression (DEP, which reflects depressive symptoms, as well as lack of motivation), anxiety (ANX, which reflects anxiety symptoms and ten-

sion), hostility (HOS, which reflects thoughts, feelings, or actions that are characteristic of negative affective states of anger, aggression, irritability, rage, and resentment), phobic anxiety (PHO, which reflects symptoms of persistent fears as responses to specific conditions), paranoid ideation (PAR, which reflects symptoms of projective thinking, hostility, suspiciousness, and fear of loss of autonomy), and psychoticism (PSY, which reflects a broad range of symptoms from mild interpersonal alienation to dramatic evidence of psychosis) [32, 55, 56]. The SCL-90-R presents three global indices: global severity index (GSI) designed to measure overall psychological distress; positive symptom distress index (PSDI) designed to measure the intensity of symptoms and positive symptom total (PST) reporting the number of self-reported symptoms. However, the GSI is the single best indicator of the current level or depth of an individual's disorder. It combines information concerning the number of symptoms reported with the intensity of perceived distress. The SCL-90-R takes between 12 and 20 min to complete. The internal consistency coefficient α values for the nine symptom dimensions ranged from a low of 0.77 for psychoticism to a high of 0.90 for depression. In an Italian study, the internal coherence for all subscales showed alpha values ranging between 0.70 and 0.96 [57]. Based on the Italian version of the SCL-90-R [58] the *T* cut-off level used in the present study to discriminate AUD people with dual diagnosis *vs* AUD without dual diagnosis people was set to $T \geq 55$ in the GSI score. The SCL-90-R was completed in the presence of psychologists who provided clarifications when necessary.

The SADQ [33, 59, 60] is a short, easy-to-complete, self-administered, 20-items questionnaire designed to measure the severity of dependence on alcohol as formulated by Edwards & Gross [61]. There are five subscales each including four items: physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption, and rapidity of reinstatement. The physical withdrawal, withdrawal relief drinking, alcohol consumption, and rapidity of reinstatement subscales are specially focused on the physical aspects of alcohol dependence while the affective withdrawal subscales refers to affective aspects of alcohol dependence. Each item is scored on a 4-point scale, ranging from almost never to nearly always, resulting in a corresponding score of 0 to 3. Thus, the total maximum score possible is 60 and the minimum is 0 [33, 62]. A score greater than 30 indicates severe alcohol dependence; scores ranging from 16 and 30 indicate the presence of moderate alcohol dependence. Above 16 a mild dependence was assessed [63].

Statistical analysis

Data were analyzed using SPSS. Descriptive analyses were conducted to evaluate the characteristics of the enrolled participants. TLFB, LDH, SCL-90-R, SADQ and DSM-5 data were analyzed by two-way ANOVA to determine differences between AUD people with or without a dual diagnosis. Gender differences were also considered as a main factor. Post-hoc comparisons were carried out by using the LSD testing. Pearson bivariate correlations were calculated between SADQ scores and psychopathological indicators and alcohol variables (years of alcohol abuse, the age of onset, total alcoholic units in the last month, the daily alcoholic units in the last month).

RESULTS

Sample characteristics

AUD people characteristics are described in *Table 1*. All recruited AUD people fulfilled the criteria for severe alcohol dependence (8.84 ± 1.99 – mean number of DSM-5 positive criteria) as assessed by using DSM-5 criteria and resulting heavy drinkers according to NIAAA (14.38 ± 11.16 – mean number of daily alcohol units).

AUD people were compared for gender in all investigated parameters *(see Table 2)*. Since no statistical differences were found between males and females in the analysed factors, except, as expected, for the drunk alcoholic units (higher in men) and the depression dimension of the SCL-90-R (elevated in women), the gender factor was not considered in the other reported results.

Dual diagnosis and drinking parameters

AUD with dual diagnosis and AUD people without dual diagnosis did not differ in alcohol consumption habits resulting, however, both groups heavy drinkers according to the NIAAA criteria (daily alcohol units: 15.06 ± 11.57 *vs* 12.79 ± 10.06 and monthly alcohol units consumed: 425.94 ± 322.95 *vs* 365.97 ± 279.43 respectively). Moreover, AUD with dual diagnosis and AUD people without dual diagnosis displayed comparable addiction severity (9.09 ± 2.07 *vs* 8.18 ± 1.59 - mean number of DSM-5 positive criteria).

SCL-90-R scores and SADQ

Table 3 shows the relationship between the levels of dependence measured by SADQ (mild, moderate and severe) and the SCL-90-R primary symptoms and the GSI. AUD patients with severe dependence had significantly higher mean scores in the psychopathological SCL-90-R domains.

Post-hoc tests show that somatization, depression, hostility, paranoid ideation, psychoticism, obsessive-compulsive, interpersonal sensitivity, anxiety and the GSI were significantly higher in AUD people with severe and moderate dependence when compared with mild dependence (ps < 0.05). Post-hocs also reveal differences between moderate and mild addiction in somatization, obsessive-compulsive, interpersonal sensitivity, anxiety, hostility and the GSI (ps < 0.05).

SCL- 90-R scores and psychiatric examination

Table 4 shows the ANOVA data between SCL-90-R scores, as dependent variables, and the psychiatric examination by a specialist in order to disclose AUD people with dual diagnosis and AUD people without a dual diagnosis. The results evidence significant differences between the two groups for each dimension (ps < 0.01 in the ANOVA) with the highest values in AUD patients with dual diagnosis.

Table 2
Differences between AUD patients without and with dual diagnosis for gender in self report measures

	AUD patient without dual diagnoses		AUD patient with dual diagnoses	
	Men (n = 58)	Women (n = 16)	Men (n = 125)	Women (n = 46)
DSM 5 severity criteria	8.40 ±1.45	6.50 ± 2.12	9.09 ± 1.77	9.08 ± 2.78
MMSE	15.25 ± 4.74	14.68 ± 3.98	15.56 ± 3.99	15.45 ± 2.63
WAIS	29.80 ± 17.18	32.68±20.35	35.47 ± 14.50	41.98 ± 14.53
SCL-90-R somatization	0.44 ± 0.45	0.50 ± 0.54	0.74 ± 0.67	0.85 ± 0.68
SCL-90-R obsessive compulsive	0.66 ± 0.55	0.58 ± 0.43	1.13 ± 0.72	1.23 ± 0.81
SCL-90-R interpersonal sensitivity	0.44 ± 0.44	0.45 ± 0.54	0.75 ± 0.64	0.90 ± 0.65
SCL-90-R depression	0.56 ± 0.46	0.59 ± 0.56*	0.95 ± 0.63	1.29 ± 0.83*
SCL-90-R anxiety	0.43 ± 0.47	0.54 ± 0.52	0.89 ± 0.64	0.91 ± 0.66
SCL-90-R hostility	0.28 ± 0.40	0.36 ± 0.38	0.63 ± 0.66	0.66 ± 0.77
SCL-90-R phobic anxiety	0.21 ± 0.28	0.23 ± 0.25	0.42 ± 0.51	0.38 ± 0.46
SCL-90-R paranoid ideation	0.52 ± 0.48	0.68 ± 0.68	0.86 ± 0.64	1.07 ± 0.79
SCL-90-R psychoticism	0.38 ± 0.40	0.45 ± 0.47	0.70 ± 0.66	0.89 ± 0.75
SCL-90-R GSI	0.48 ± 0.36	0.52 ± 0.42	0.84 ± 0.53	0.96 ±0.58
SADQ physical withdrawal	3.89 ± 3.27	2.87 ± 3.36	4.83 ± 3.26	5.35 ± 3.40
SADQ affective withdrawal	1.86 ± 2.01	2.81 ± 3.82	3.78 ± 3.37	5.00 ± 4.16
SADQ withdrawal relief drinking	3.62 ± 4.29	2.19 ± 3.85	5.75 ± 4.41	5.24 ± 5.03
SADQ alcohol consumption	4.29 ± 2.31	3.94 ± 2.46	5.60 ± 3.38	4.89 ± 3.34
SADQ rapidity of reinstatement	3.24 ± 2.92	2.63 ± 2.83	5.03 ± 3.46	5.59 ± 3.80
SADQ total	16.93 ± 11.23	14.44 ± 9.58	14.44 ± 9.58	26.04 ± 15.95

SCL-90-R: symptom check list 90-R.

Table 3
SCL-90-R primary symptom dimensions and SADQ dependence levels (mean ± SD). # $p < 0.05$ Severe *vs* moderate/mild; § $p < 0.05$ moderate *vs* mild

SCL-90-R	Total SADQ n = 245	SADQ Mild dependence (Score range 0-15) n = 93	SADQ Moderate dependence (Score range 16-30) n = 88	SADQ Severe dependence (Score > 30) n = 64	F(df)	*p*
Somatization	0.68 ± 0.64	0.49 ± 0.48	0.81 ± 0.70§	0.76 ± 0.68	6.479(2,244)	= 0.002
Obsessive compulsive	1.00 ± 0.72	0.78 ± 0.62	1.10 ± 0.77§	1.18 ± 0.73	7.316(2,244)	= 0.001
Interpersonal sensitivity	0.68 ± 0.61	0.50 ± 0.49	0.75 ± 0.66§	0.86 ± 0.65	7.693(2,244)	= 0.001
Depression	0.90 ± 0.68	0.73 ± 0.65	0.97 ± 0.72	1.06 ± 0.62	5.431(2,244)	= 0.005
Anxiety	0.76 ± 63	0.52 ± 0.53	0.86 ± 66§	0.97 ± 0.64	12.007(2,244)	< 0.001
Hostility	0.54 ± 0.63	0.41 ± 0.55	0.65 ± 0.70§	0.55 ± 0.63	3.445(2,244)	= 0.033
Phobic anxiety	0.35 ± 0.45	0.23 ± 0.35	0.35 ± 0.39	0.52 ± 0.58#	8.414(2,244)	< 0.001
Paranoid ideation	0.81 ± 0.67	0.68 ± 0.61	0.83 ± 0.67	0.96 ± 0.72	3.682(2,244)	= 0.027
Psychoticism	0.65 ± 0.64	0.50 ± 0.57	0.71 ± 0.62	0.78 ± 0.72	4.485(2,244)	= 0.012
GSI	0.76 ± 0.53	0.58 ± 0.46	0.84 ± 0.56§	0.91 ± 0.53	9.748(2,244)	< 0.001

SADQ: severity of alcohol dependence questionnaire; SCL-90-R: symptom check list 90-R.

Psychiatric examination and SADQ scores

ANOVA considering AUD people with dual diagnosis *vs* AUD people without dual diagnosis and the SADQ total score as dependent variable shows that AUD patients with dual diagnosis had significantly ($F(1,244) = 23.101$; $p < 0.001$) higher mean scores of total SADQ (25.30 ± 14.25) compared to AUD people without dual diagnosis (16.39 ± 10.88 respectively).

Table 4
SCL- 90-R Scores and Psychiatric Examination (mean ± SD)

SCL-90-R	Psychiatric examination		F	*p*
	Non-psychiatric AUD patients n = 74	Psychiatric AUD patients n = 171		
Somatization	0.46 ± 0.47	0.77 ± 0.67	13.599	< 0.001
Obsessive compulsive	0.65 ± 0.52	1.15 ± 0.75	28.758	< 0.001
Interpersonal sensitivity	0.45 ± 0.46	0.79 ± 0.64	17.212	< 0.001
Depression	0.57 ± 0.48	1.04 ± 0.70	27.720	< 0.001
Anxiety	0.45 ± 0.48	0.90 ± 0.65	27.815	< 0.001
Hostility	0.30 ± 0.40	0.64 ± 0.69	15.855	< 0.001
Phobic anxiety	0.21 ± 0.27	0.41 ± 0.49	9.935	= 0.002
Paranoid ideation	0.55 ± 0.53	0.92 ± 0.69	16.011	< 0.001
Psychoticism	0.40 ± 0.41	0.75 ± 0.69	16.877	< 0.001
GSI	0.49 ± 0.37	0.88 ± 0.54	30.975	< 0.001

SCL-90-R: symptom check list 90-R.

The emerging finding from the SADQ scales and the psychiatric evaluation clearly demonstrates that AUD people with dual diagnosis describe themselves affected by a more severe alcohol dependence than AUD people without a dual diagnosis.

Comparable results were found in the SADQ subscales: patients with dual diagnosis referred to higher levels of physical withdrawal (4.97 ± 3.29 *vs* 3.68 ± 3.29), affective withdrawal (4.11 ± 3.63 *vs* 2.07 ± 2.51), withdrawal relief drinking (5.61 ± 4.58 *vs* 3.31 ± 4.23), alcohol consumption (5.41 ± 3.38 *vs* 4.22 ± 2.33), and rapidity of reinstatement (5.18 ± 3.55 *vs* 3.11 ± 2.89) compared to AUD patients without dual diagnosis (ps < 0.05).

SADQ/SCL-90-R and drinking parameters (TLFB/LDH)

Figure 1 shows the relationships between the SCL-90-R, the SADQ and the drinking parameters measured by TLFB. Indeed, correlations reveal that the total score of SADQ positively correlates in all AUD patients with the alcoholic units totally consumed (r = 0.301; p ≤ 0.001) and the daily alcoholic units consumed in the last month (r = 0.284; p ≤ 0.001) when measured by TLFB. No correlations were found with the drinking parameters evaluated by LDH.

Relatively to the SADQ subscales *(Figure 2)* the correlations demonstrate that the Withdrawal Relief Drinking and Alcohol Consumption subscales were significantly and positively associated with the alcoholic units totally consumed and the alcoholic units consumed daily in the last month. No relationship was found between total and daily alcoholic units and Affective Withdrawal and Rapidity of Reinstatement subscales. Significant negative correlations were observed between SADQ total scores, physical withdrawal, alcohol consumption and the age of onset of alcohol problems (see plots of *Figure 2*). No relationship was found between SADQ total scores/SADQ subscales with the years of at-risk drinking.

Quite interestingly, no correlations were found between SCL-90-R and the drinking parameters of the TLFB/LDH (alcohol unit/daily, alcohol unit/monthly, age of alcohol onset and years of at risk drinking). Furthermore, no evidence was found between psychiatric examination and the drinking parameters of the TLFB/LDH.

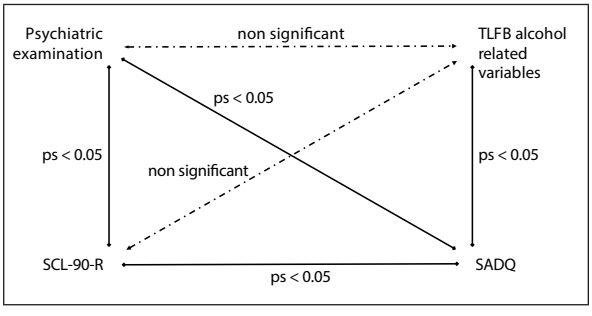

Figure 1
Picture illustrating the connections and statistical significance between SCL-90-R, SADQ, TLFB alcohol related variables and psychiatric examination.

SCL-90-R and SADQ subscales

Table 5 indicates the correlation between the symptoms' scales of SCL-90-R and the SADQ subscales. Data shows that affective withdrawal, physical withdrawal and rapidity of reinstatement subscales of SADQ were significantly and positively associated with the GSI of the SCL-90-R. No relationship was found between SADQ alcohol consumption and withdrawal relief drinking subscales and GSI.

DISCUSSION

In the present study, we evaluated the relationship between the AUD severity and the presence of psychiatric comorbidity. Serious AUD patients with dual diagnosis are more at-risk of relapse and abandonment of treatment. The psychometric tools used to assess the magnitude of addiction are mainly self-reported interviews,

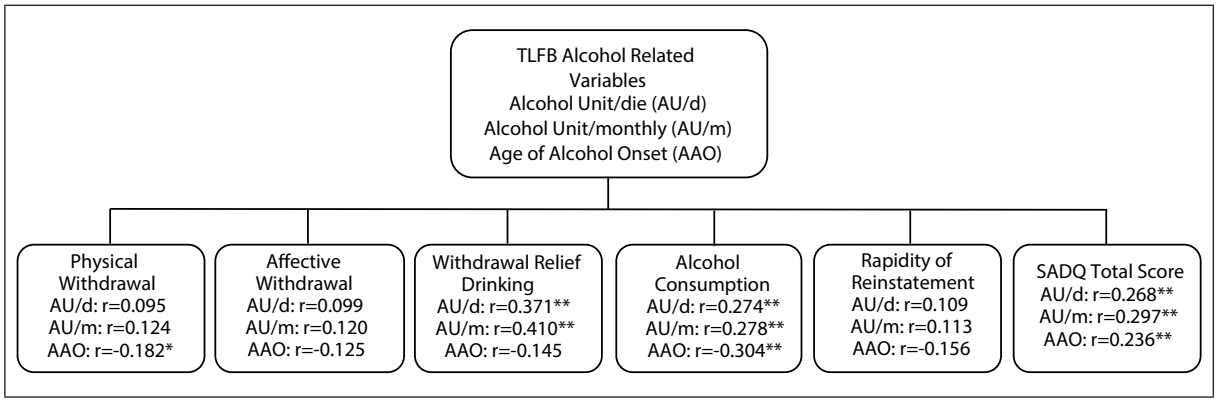

Figure 2
The figure shows the relationship between TLFB alcohol drinking variables and SADQ subscales.
** = p < 0.01; * = p < 0.05

Table 5
The table shows the correlation between SCL-90-R and SADQ by Pearson's analysis. Asterisks indicates correlation at 0.05 (*) and 0.01 (**)

	SADQ physical withdrawal	SADQ affective withdrawal	SADQ withdrawal relief drinking	SADQ alcohol consumption	SADQ rapidity of reinstatement	SADQ total score
SCL-90-R Somatization	0.204**	0.170**	0.131*	0.187**	0.210**	0.229**
SCL-90-R Obsessive compulsive	0.238**	0.274**	0.141*	0.130*	0.281**	0.270**
SCL-90-R Interpersonal sensitivity	0.183**	0.279**	0.157*	0.133*	0.234**	0.253**
SCL-90-R Depression	0.171**	0.241**	0.131*	0.085	0.222**	0.218**
SCL-90-R Anxiety	0.243**	0.285**	0.232**	0.136*	0.315**	0.314**
SCL-90-R Hostility	0.091	0.073	0.069	0.031	0.160*	0.108
SCL-90-R Phobic anxiety	0.210**	0.232**	0.198**	0.179**	0.230**	0.271**
SCL-90-R Paranoid ideation	0.141*	0.191**	0.116	0.105	0.159*	0.182**
SCL-90-R Psychoticism	0.160*	0.272**	0.103	0.085	0.180**	0.203**
SCL-90-R GSI	0.234**	0.277**	0.177**	0.156*	0.283**	0.288**

SADQ: severity of alcohol dependence questionnaire; SCL-90-R: symptom check list 90-R

with the exception of the severity scale of DSM-5 and of the anamnestic instruments based on the frequency and the quantities of alcohol consumption, which are instead detected by the clinician. In the present investigation, we found that there are no differences between AUD people with dual diagnosis and AUD people without dual diagnosis based on the amount of alcohol drunk and on the severity highlighted by DSM-5. Indeed, our patients were all heavy drinkers, however, is that despite the dual and non-dual AUD patients do not show differences in the alcohol parameters or even in the observation of the clinician, dual AUD patients report a higher gravity of SADQ dependence.

As highlighted in the results section, we evaluated the presence of a psychiatric disorder either through a self-report tool, the SCL-90-R, or through a psychiatric examination and in both cases AUD patients describe themselves as more severe at SADQ. We used the two methods because the SCL-90-R, despite being used in other studies previously conducted [56, 57], is a screening questionnaire that identifies the presence of psychological distress, while obviously, the psychiatric interview conducted on the criteria of the DSM-5 allows to the clinician to be able to make an affordable diagnosis.

Although self-report instruments may offer a rapid method to collect information, their use also reveals certain disadvantages [64]. One is that they are vulnerable to the consequences of social desirability biases. Patients tend to present themselves in a favorable way, especially when they are asked to make judgments about attitudes and traits that are negatively valued [64]. Another self-report instruments' limit is that they necessarily rely on information that is consciously accessible to the person. This problem, known as the introspective restriction, has a significant impact on the information reliability obtained using self-report instruments [65]. Based on these biases, to investigate the association between alcohol addiction and psychiatric associated diseases, we used other tools as the DSM-5 criteria by a specialist examination, to further assess psychiatric associated disorders and LDH and TLFB to assess alcohol consumption. These latest semi-struc-

tured tools have the highest quality to assess alcohol consumption using several memory aids to enhance recall in which the clinicians have a facilitator role [46, 66]. Obviously, information on alcohol drinking behavior obtained using TLFB and LDH are not a specific measure of dependence severity, but they certainly offer crucial information on the nature of patient alcohol behavioral relationship [67].

In particular, we found that, by using DSM-5 criteria, AUD people with a positive psychiatrist diagnosis, as shown by psychiatrist examination, had higher SADQ subscales mean scores compared with AUD patients negative to psychopathology. Intriguingly, when analyzing the alcohol consumption measured by the clinicians (TLFB and LDH), no correlations were found between SCL-90-R and alcohol drinking, as emerged by TLFB and LDH, and no differences were found in drinking habits between patients with or without psychiatric associated disorders assessed by psychiatric examination because the values of alcohol consumption are in AUD people with or without dual diagnosis comparable. Data analyzing SADQ and alcoholic units totally consumed and the daily alcoholic units consumed in the last month by TLFB disclosed significant correlations.

Investigating the different dimensions of the dependence levels by SADQ we found that the dimensions most closely related to the physical size of addiction (physical withdrawal, withdrawal relief drinking and alcohol consumption) correlate with the quantities of alcohol consumed. However, when we aimed to evaluate the relationship between the SADQ subscales and the SCL-90-R scales correlations with the affective withdrawal, physical withdrawal and rapidity of reinstatement scales were revealed. Finally, the association between the psychiatric examination and the SADQ subscales clearly demonstrates that AUD patients with dual diagnosis describe themselves as more affected in all dimensions.

To further investigate the relationship between psychiatry, the severity of dependence and alcohol variables, we considered how the five SADQ subscales (physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption, and rapidity of reinstatement) were related to SCL-90-R and alcohol drinking variables. We found that alcohol drinking behavioral variables were significantly and positively associated with physical withdrawal and alcohol consumption SADQ subscales and the total SADQ score whereas no relationships were found with affective withdrawal, withdrawal relief drinking and rapidity of reinstatement SADQ subscales. By contrast, affective withdrawal, physical withdrawal and relief rapidity of reinstatement SADQ subscales correlated with SCL-90-R GSI while no relationship was found between alcohol consumption and withdrawal relief drinking SADQ subscales and SCL-90-R GSI.

These findings clearly show that *i)* the GSI of SCL-90-R correlates mainly with the affective behavior subscales of SADQ and less with the physical aspects of SADQ subscales; *ii)* intriguingly, the alcoholic units consumed by AUD people are mainly linked with the physical aspects of SADQ subscales and less with the affective behavior subscales; *iii)* SADQ, although is one of the most widely used questionnaires and recommended by the guidelines, suffers a bias due to the patient's psychiatric conditions. The SADQ specifically captures the perception of the severity of addiction that in patients with dual diagnosis such perception is emphasized and considered more disabling and suffering. However, it should be noted that AUD patients with a dual diagnosis perceiving a greater amount of stress due to their psychopathology feel more dramatically the compulsive phase of dependence, while the SADQ self-responses differs from the measures obtained by the specialist examination where the operator discloses the data on consumption without considering the emotional part related to consumption.

Although many environmental, social, genetic, physiological and neurobiological factors have been shown to contribute to the gender difference in response to alcohol induced damage [68, 69], our study did not disclose gross sex differences in behavioral responses. Nonetheless, the subject of drinking abuse in women is quite significant since women are more sensitive compared to men to the harm induced by ethanol [70, 71] and because women who drink during gestation may stimulate a variety of damaging effects to the fetus named Fetal Alcohol Spectrum Disorders (FASD) [42, 70-82 as also shown in 73, 78, 83-86].

CONCLUSION

In conclusion, the strength of the present study is that by analyzing 245 AUD patients with or without a dual diagnosis, those with dual diagnosis appear to emphasize the emotional aspects of their addiction based on the SADQ results. Psychiatric comorbidity is a crucial issue among patients suffering AUD because increases the risk of relapse [87, 88] making more arduous the therapeutic intervention [89-97]. Our data suggest that an overestimated self-perception of addiction for alcohol, as measured by SADQ, may represent a useful prognostic index to relapse but only for patients with dual diagnosis. A careful analysis of the SADQ affective subscales could reveal in AUD people with a dual diagnosis a disrupted addiction self-perception, information that could be used as a warning signal for treating not only dependence per se but, particularly, the psychopathological associated diseases to properly address pharmacological intervention [98, 99].

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Conflict of interest statement

Authors do declare that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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REFERENCES

1. Coriale G, Bilotta E, Leone L, Cosimi F, Porrari R, De Rosa F, et al. Avoidance coping strategies, alexithymia and alcohol abuse: A mediation analysis. Addict Behav. 2012;37:1224-9. doi:10.1016/j.addbeh.2012.05.018
2. Grant B, Stinson F, Dawson D, Chou S, Dufour M, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the national epidemiologic survey on alcohol and relatedconditions. Alcohol Res Heal. 2004;29:807-16. doi:10.1001/archpsyc.61.8.807
3. Ledda R, Battagliese G, Attilia F, Rotondo C, Pisciotta F, Gencarelli S, et al. Drop-out, relapse and abstinence in a cohort of alcoholic people under detoxification. Physiol Behav. 2019;198:67-75. doi:10.1016/j.physbeh.2018.10.009
4. Iannitelli A, Castra R, Antenucci M. Doppia diagnosi o comorbidità? Definizioni e osservazioni cliniche. Ann Ist Super Sanità. 2002;38:233-9.
5. Ciafrè S, Carito V, Ferraguti G, Greco A, Chaldakov GN, Fiore M. How Alcohol drinking affects our genes: an epigenetic point of view. Biochem Cell Biol. Press n.d. doi:10.1139/bcb-2018-0248
6. Grant BF, Stinson FS, Dawson DA, Chou SP, Ruan WJ, Pickering RP. Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States. Arch Gen Psychiatry. 2004;61:361-8. doi:10.1001/archpsyc.61.4.361
7. Helzer JE, Pryzbeck TR. The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. J Stud Alcohol. 1988;49:219-24. doi:10.15288/jsa.1988.49.219
8. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51:8-19. doi:10.1001/archpsyc.1994.03950010008002
9. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997;54:313-21. doi:10.1001/archpsyc.1997.01830160031005.
10. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990;264:2511-8. doi:10.1001/jama.1990.03450190043026
11. Rich SD, Riley LJ. Neurodevelopmental Disorder Associated with Prenatal Alcohol Exposure: Consumer Protection and the Industry's Duty to Warn. Cham: Springer; 2016. p. 39-47. doi:10.1007/978-3-319-20866-4_3
12. Stewart SH. Alcoholics in acute medical settings have increased risk for other drug, mood, and personality disorders. Int J Psychiatry Med. 2007;37:59-67. doi:10.2190/E075-04TK-2N6J-1RH5.
13. Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science. 1987;236:410-6. doi:10.1126/science.2882604
14. Gulec Oyekcin D, Gurgen A. Is cloninger type 1 and type 2 alcoholism differ in terms of emotion regulation? Eur Psychiatry. 2017;41:S863-4. doi:10.1016/J.EURPSY.2017.01.1727
15. Driessen M, Veltrup C, Wetterling T, John U, Dilling H. Axis I and axis II comorbidity in alcohol dependence and the two types of alcoholism. Alcohol Clin Exp Res. 1998;22:77-86. doi:10.1097/00000374-199802000-00009
16. Echeburúa E, De Medina BR, Aizpiri J. Alcoholism and personality disorders: an exploratory study. Alcohol Alcohol. 2005;40:323-6. doi:10.1093/alcalc/agh158
17. Ipser JC, Wilson D, Akindipe TO, Sager C, Stein DJ. Pharmacotherapy for anxiety and comorbid alcohol use disorders. In: Ipser JC (Ed). Cochrane Database Syst. Rev., Vol. 1. Chichester, UK: John Wiley & Sons, Ltd; 2015. p. CD007505. doi:10.1002/14651858.CD007505.pub2
18. Karpyak VM, Biernacka JM, Geske JR, Abulseoud OA, Brunner MD, Chauhan M, et al. Gender-specific effects of comorbid depression and anxiety on the propensity to drink in negative emotional states. Addiction. 2016;111:1366-75. doi:10.1111/add.13386
19. Swendsen JD, Merikangas KR. The comorbidity of depression and substance use disorders. Clin Psychol Rev. 2000;20:173-89. doi:10.1016/S0272-7358(99)00026-4
20. Tragesser SL, Trull TJ, Sher KJ, Park A. Drinking motives as mediators in the relation between personality disorder symptoms and alcohol use disorder. J Pers Disord. 2008;22:525-37. doi:10.1521/pedi.2008.22.5.525
21. Verheul R. Co-morbidity of personality disorders in individuals with substance use disorders. Eur Psychiatry. 2001;16:274-82. doi:10.1016/S0924-9338(01)00578-8
22. Stewart SH. Alcoholics in acute medical settings have increased risk for other drug, mood, and personality disorders. Int J Psychiatry Med. 2007;37:59-67. doi:10.2190/E075-04TK-2N6J-1RH5
23. Ciafrè S, Carito V, Tirassa P, Ferraguti G, Attilia ML, Ciolli P, et al. Ethanol consumption and innate neuroimmunity. Biomed Rev. 2018;28:49-61. doi:10.147848/bmw.v28.4451
24. Ciafrè S, Fiore M, Ceccanti M, Messina MP, Tirassa P, Carito V. Role of neuropeptide tyrosine (NPY) in ethanol addiction. Biomed Rev. 2017;27:27-40. doi:10.147848/bmw.v27.2110
25. Di Sclafani V, Finn P, Fein G. Psychiatric comorbidity in long-term abstinent alcoholic individuals. Alcohol Clin Exp Res. 2007;31:795-803. doi:10.1111/j.1530-0277.2007.00361.x
26. Bischof G, Rumpf H-J, Meyer C, Hapke U, John U. Influence of psychiatric comorbidity in alcohol-dependent subjects in a representative population survey on treatment utilization and natural recovery. Addiction. 2005;100:405-13. doi:10.1111/j.1360-0443.2005.01008.x
27. Greenfield SF, Weiss RD, Muenz LR, Vagge LM, Kelly JF, Bello LR, et al. The effect of depression on return to drinking: a prospective study. Arch Gen Psychiatry. 1998;55:259-65. doi:10.1001/archpsyc.55.3.259
28. Morley KC, Baillie A, Sannibale C, Teesson M, Haber PS. Integrated care for comorbid alcohol dependence and anxiety and/or depressive disorder: study protocol for an assessor-blind, randomized controlled trial. Addict Sci Clin Pract. 2013;8:19. doi:10.1186/1940-0640-8-19
29. Booth PG. Maintained controlled drinking following severe alcohol dependence--a case study. Br J Addict. 1990;85:315-22; discussion 323-8. doi:10.1111/j.1360-0443.1990.tb00641.x
30. Langenbucher J, Sulesund D, Chung T, Morgenstern J. Illness severity and self-efficacy as course predictors of DSM-IV alcohol dependence in a multisite clinical sample. Addict Behav. 1996;21:543-53. doi:10.1016/0306-4603(95)00085-2
31. Quartini A, Pacitti F, Bersani G, Iannitelli A. From adolescent neurogenesis to schizophrenia: opportunities,

challenges and promising interventions. Biomed Rev. 2018;28:62. doi:10.14748/bmr.v28.4452
32. Derogatis L. SCL-90-R: symptom checklist-90-R : administration, scoring & procedures manual. 3rd ed. Minneapolis Minn: National Computer Systems Inc.; 1994.
33. Stockwell T, Murphy D, Hodgson R. The severity of alcohol dependence questionnaire: its use, reliability and validity. Br J Addict. 1983;78:145-55. doi:10.1111/j.1360-0443.1983.tb05502.x
34. Ceccanti M, Sasso GF, Nocente R, Balducci G, Prastaro A, Ticchi C, et al. Hypertension in early alcohol withdrawal in chronic alcoholics. Alcohol Alcohol. 2006;41:5-10. doi:10.1093/alcalc/agh221
35. Ewusi-Mensah I, Saunders JB, Johnson RD, Williams R. Alcohol dependence and psychopathology in alcoholic liver disease. Addiction.1986;81:231-5. doi:10.1111/j.1360-0443.1986.tb00321.x
36. Pradeep RJ, Dhilip AM, Mysore A. Do SADQ and AUDIT identify independent impacts of alcohol abuse - clinical and biochemical markers respectively? Indian J Psychiatry. 2015;57:278-83. doi:10.4103/0019-5545.166629
37. Drummond DC. The relationship between alcohol dependence and alcohol-related problems in a clinical population. Br J Addict. 1990;85:357-66. doi:10.1111/j.1360-0443.1990.tb00652.x
38. Stockwell T, Hodgson R, Edwards G, Taylor C, Rankin H. The development of a questionnaire to measure severity of alcohol dependence. Br J Addict Alcohol Other Drugs. 1979;74:79-87.
39. Ceccanti M, Hamilton D, Coriale G, Carito V, Aloe L, Chaldakov G, et al. Spatial learning in men undergoing alcohol detoxification. Physiol Behav. 2015;149:324-30. doi:10.1016/J.PHYSBEH.2015.06.034
40. Ceccanti M, Coriale G, Hamilton DA, Carito V, Coccurello R, Scalese B, et al. Virtual Morris task responses in individuals in an abstinence phase from alcohol. Can J Physiol Pharmacol. 2018;96:128-36. doi:10.1139/cjpp-2017-0013
41. National Institute on Alcohol Abuse and Alcoholism. Alcohol facts and statistics fact sheet. n.d.
42. Mangrum LF, Spence RT, Steinley-Bumgarner MD. Gender differences in substance-abuse treatment clients with co-occurring psychiatric and substance-use disorders. Br Treat Cris Interv. 2006;6:255-67. doi:10.1093/brief-treatment/mhl006
43. Frem Y, Torrens M, Domingo-Salvany A, Gilchrist G. Gender differences in lifetime psychiatric and substance use disorders among people who use substances in Barcelona, Spain. Adv Dual Diagn. 2017;10:45-56. doi:10.1108/ADD-01-2017-0002
44. Ferraguti G, Ciolli P, Carito V, Battagliese G, Mancinelli R, Ciafrè S, et al. Ethylglucuronide in the urine as a marker of alcohol consumption during pregnancy: Comparison with four alcohol screening questionnaires. Toxicol Lett. 2017;275:49-56. doi:10.1016/j.toxlet.2017.04.016
45. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596
46. Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. J Stud Alcohol. 1982;43:1157-70. doi:10.15288/jsa.1982.43.1157
47. Jacob T, Seilhamer RA, Bargeil K, Howell DN. Reliability of lifetime drinking history among alcohol dependent men. Psychol Addict Behav. 2006;20:333-7. doi:10.1037/0893-164X.20.3.333
48. Koenig LB, Jacob T, Haber JR. Validity of the lifetime drinking history: a comparison of retrospective and prospective quantity-frequency measures. J Stud Alcohol Drugs. 2009;70:296-303. doi:10.15288/jsad.2009.70.296
49. Sobell LC, Ellingstad TP, Sobell MB. Natural recovery from alcohol and drug problems: methodological review of the research with suggestions for future directions. Addiction. 2000;95:749-64.
50. Sobell MB, Sobell LC. Controlled drinking after 25 years: how important was the great debate? Addiction. 1995;90:1149-53; discussion 1157-77.
51. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98. doi:10.1016/0022-3956(75)90026-6
52. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. JAMA J Am Med Assoc. 1993;269:2386. doi:10.1001/jama.1993.03500180078038
53. Wechsler D. Manual for the Wechsler adult intelligence scale-revised (WAIS-R). San Antonio: TX Psychol Corp; 1981.
54. Derogatis LR. SCL-90-R: symptom checklist-90-R: administration, scoring & procedures manual. 3rd ed. Minneapolis: National Computer Systems; 1994.
55. Moussas G, Fanouraki I, Pachi A, Asomatou A, Drylli O, Paschalakis G, et al. Comorbid psychopathology and alcohol use patterns among methadone maintenance treatment patients. J Addict. 2015;2015:1-10. doi:10.1155/2015/197652
56. Derogatis LR, Cleary PA. Confirmation of the dimensional structure of the scl-90: A study in construct validation. J Clin Psychol. 1977;33:981-9. doi:10.1002/1097-4679(197710)33:4<981::AID-JCLP2270330412>3.0.CO;2-0
57. Prunas A, Sarno I, Preti E, Madeddu F, Perugini M. Psychometric properties of the Italian version of the SCL-90-R: a study on a large community sample. Eur Psychiatry. 2012;27:591-7. doi:10.1016/j.eurpsy.2010.12.006
58. Sarno I, Preti E, Prunas A, Madeddu F. SCL-90-R Symptom checklist-90-R Adattamento italiano. Firenze: Giunti, Organizzazioni Speciali; 2011.
59. Stockwell T, Bolt L, Milner I, Russell G, Bolderston H, Pugh P. Home detoxification from alcohol: its safety and efficacy in comparison with inpatient care. Alcohol Alcohol. 1991;26:645-50.
60. Stockwell T, Bolt L, Milner I, Pugh P, Young I. Home detoxification for problem drinkers: acceptability to clients, relatives, general practitioners and outcome after 60 days. Addiction. 1990;85:61-70. doi:10.1111/j.1360-0443.1990.tb00624.x
61. Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. Br Med J. 1976;1:1058-61. doi:10.1136/bmj.1.6017.1058
62. Raistrick D, Dunbar G, Davidson R. Development of a questionnaire to measure alcohol dependence. Br J Addict. 1983;78:89-95.
63. Doyle SR, Donovan DM. A validation study of the alcohol dependence scale. Stud Alcohol Drugs. 2009;70:689-99.
64. Okada M, Oltmanns TF. Comparison of three self-report measures of personality pathology. J Psychopathol Behav Assess. 2009;31:358-67. doi:10.1007/s10862-009-9130-8
65. Greenwald AG, Pickrell JE, Farnham SD. Implicit partisanship: taking sides for no reason. J Pers Soc Psychol. 2002;83:367-379. doi:10.1037/0022-3514.83.2.367
66. Sobell LC, Sobell MB. Timeline follow-back. In: Lit-

ten RZ, Allen JP (Eds). Measuring alcohol consumption. Totowa, NJ: Humana Press; 1992. p. 41-72. doi:10.1007/978-1-4612-0357-5_3
67. Witkiewitz K, Horn BP. Reductions in healthcare costs following alcohol treatment: moving toward low-risk drinking end points in alcohol clinical trials. Alcohol Clin Exp Res. 2016;40:1415-7. doi:10.1111/acer.13092
68. Koyejo OM, Kliewer W, Gbiri CAO, Svikis DS. Sex differences in alcohol-related problems among a sample of HIV-positive Nigerians. Int Perspect Psychol Res Pract Consult. 2018;7:231-9. doi:10.1037/ipp0000096
69. Holmila M, Raitasalo K. Gender differences in drinking: why do they still exist? Addiction. 2005;100:1763-9. doi:10.1111/j.1360-0443.2005.01249.x
70. Mancinelli R, Vitali M, Ceccanti M. Women, alcohol and the environment: an update and perspectives in neuroscience. Funct Neurol. 2009;24:77-81.
71. Mancinelli R, Binetti R, Ceccanti M. Woman, alcohol and environment: Emerging risks for health. Neurosci Biobehav Rev. 2007;31:246-53. doi:10.1016/j.neubiorev.2006.06.017
72. Coriale G, Fiorentino D, Di Lauro F, Marchitelli R, Scalese B, Fiore M, et al. Fetal Alcohol Spectrum Disorder (FASD): neurobehavioral profile, indications for diagnosis and treatment. Riv Psichiatr. 2018;48:359-69. doi:10.1708/1356.15062
73. Ceccanti M, De Nicolò S, Mancinelli R, Chaldakov G, Carito V, Ceccanti M, et al. NGF and BDNF long-term variations in the thyroid, testis and adrenal glands of a mouse model of fetal alcohol spectrum disorders. Ann Ist Super Sanità. 2013;49:383-90. doi:10.4415/ANN_13_04_11
74. Ceccanti M, Coccurello R, Carito V, Ciafrè S, Ferraguti G, Giacovazzo G, et al. Paternal alcohol exposure in mice alters brain NGF and BDNF and increases ethanol-elicited preference in male offspring. Addict Biol. 2016;21:776-87. doi:10.1111/adb.12255
75. Tarani L, Micangeli G, Rasio D, Ottombrino S, Liberati N, Angelis D De, et al. Clinical and genetic approach to the dysmorphic child. Biomed Rev 2018;29:37-46. doi:10.14748/bmr.v29.5848.
76. Carito V, Parlapiano G, Rasio D, Paparella R, Paolucci V, Ferraguti G, et al. Fetal alcohol spectrum disorders in pediatrics. FASD and the pediatrician. Biomed Rev. 2018;29:27-35. doi:10.14748/bmr.v29.5847
77. Carito V, Ceccanti M, Ferraguti G, Coccurello R, Ciafrè S, Tirassa P, et al. NGF and BDNF Alterations by Prenatal Alcohol Exposure. Curr Neuropharmacol. 2019;17:308-17. doi:10.2174/1570159X15666170825101308
78. De Nicolò S, Carito V, Fiore M, Laviola G. Aberrant Behavioral and Neurobiologic Profiles in Rodents Exposed to Ethanol or Red Wine Early in Development. Curr Dev Disord Reports 2014;1:173-80. doi:10.1007/s40474-014-0023-5
79. Ferraguti G, Merlino L, Battagliese G, Piccioni MG, Barbaro G, Carito V, et al. Fetus morphology changes by second-trimester ultrasound in pregnant women drinking alcohol. Addict Biol 2019. doi:10.1111/adb.12724
80. Ceccanti M, Fiorentino D, Coriale G, Kalberg WO, Buckley D, Hoyme HE, et al. Maternal risk factors for fetal alcohol spectrum disorders in a province in Italy. Drug Alcohol Depend. 2014;145:201-8. doi:10.1016/j.drugalcdep.2014.10.017
81. Kodituwakku P, Coriale G, Fiorentino D, Aragon AS, Kalberg WO, Buckley D, et al. Neurobehavioral Characteristics of children with fetal alcohol spectrum disorders in communities from Italy: preliminary results. Alcohol Clin Exp Res. 2006;30:1551-61. doi:10.1111/j.1530-0277.2006.00187.x
82. Coriale G, Fiorentino D, Kodituwakku PW, Tarani L, Parlapiano G, Scalese B, et al. Identification of Children With Prenatal Alcohol Exposure. Curr Dev Disord Reports. 2014;1:141-8. doi:10.1007/s40474-014-0018-2
83. Ceccanti M, Mancinelli R, Tirassa P, Laviola G, Rossi S, Romeo M, et al. Early exposure to ethanol or red wine and long-lasting effects in aged mice. A study on nerve growth factor, brain-derived neurotrophic factor, hepatocyte growth factor, and vascular endothelial growth factor. Neurobiol Aging. 2012;33:359-67. doi:10.1016/j.neurobiolaging.2010.03.005
84. Angelucci F, Fiore M, Cozzari C, Aloe L. Prenatal ethanol effects on NGF level, NPY and ChAT immunoreactivity in mouse entorhinal cortex: a preliminary study. Neurotoxicol Teratol. 1999;21:415-25. doi:10.1016/S0892-0362(99)00005-7
85. Fiore M, Mancinelli R, Aloe L, Laviola G, Sornelli F, Vitali M, et al. Hepatocyte growth factor, vascular endothelial growth factor, glial cell-derived neurotrophic factor and nerve growth factor are differentially affected by early chronic ethanol or red wine intake. Toxicol Lett. 2009;188:208-13. doi:10.1016/j.toxlet.2009.04.013
86. Fiore M, Laviola G, Aloe L, di Fausto V, Mancinelli R, Ceccanti M. Early exposure to ethanol but not red wine at the same alcohol concentration induces behavioral and brain neurotrophin alterations in young and adult mice. Neurotoxicology. 2009;30:59-71. doi:10.1016/j.neuro.2008.11.009
87. Bradizza CM, Stasiewicz PR, Paas ND. Relapse to alcohol and drug use among individuals diagnosed with co-occurring mental health and substance use disorders: A review. Clin Psychol Rev. 2006;26:162-78. doi:10.1016/j.cpr.2005.11.005
88. Smith JP, Randall CL. Anxiety and alcohol use disorders: comorbidity and treatment considerations. Alcohol Res. 2012;34:414-31.
89. Ceccanti M, Iannitelli A, Fiore M. Italian Guidelines for the treatment of alcohol dependence. Riv Psichiatr. 2018;53:105-6. doi:10.1708/2925.29410
90. Daley DC, Moss H. Dual disorders : counseling clients with chemical dependency and mental illness. Hazelden; 2002.
91. Sterling S, Chi F, Hinman A. Integrating care for people with co-occurring alcohol and other drug, medical, and mental health conditions. Alcohol Res Health. 2011;33:338-49.
92. Vitali M, Sorbo F, Mistretta M, Coriale G, Messina MP, Alessandrini G, et al. Drafting a dual diagnosis program: a tailored intervention for patients with complex clinical needs. Riv Psichiatr. 2018;53:149-53. doi:10.1708/2925.29417
93. Coriale G, Fiorentino D, De Rosa F, Solombrino S, Scalese B, Ciccarelli R, et al. Treatment of alcohol use disorder from a psychological point of view. Riv Psichiatr. 2018;53:141-8. doi:10.1708/2925.29416
94. Coriale G, Fiorentino D, Porrari R, Battagliese G, Capriglione I, Cereatti F, et al. Diagnosis of alcohol use disorder from a psychological point of view. Riv Psichiatr. 2018;53:128-40. doi:10.1708/2925.29415
95. Vitali M, Sorbo F, Mistretta M, Scalese B, Porrari R, Galli D, et al. Dual diagnosis: an intriguing and actual nosographic issue too long neglected. Riv Psichiatr 2018;53:154-9. doi:10.1708/2925.29418.
96. Attilia F, Perciballi R, Rotondo C, Capriglione I, Iannuzzi S, Attilia ML, et al. Pharmacological treatment of alcohol use disorder. Scientific evidence. Riv Psichiatr. 2018;53:123-7. doi:10.1708/2925.29414

97. Attilia F, Perciballi R, Rotondo C, Capriglione I, Iannuzzi S, Attilia ML, et al. Alcohol withdrawal syndrome: diagnostic and therapeutic methods. Riv Psichiatr. 2018;53:118-22. doi:10.1708/2925.29413
98. Kelly TM, Daley DC. Integrated treatment of substance use and psychiatric disorders. Soc Work Public Health. 2013;28:388-406. doi:10.1080/19371918.2013.774673
99. Orford J. [Commentary] Joining the queue of dissenters. Addiction. 2008;103:706-7. doi:10.1111/j.1360-0443.2007.02128.x

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Detection of tick-borne pathogens in ticks collected in the suburban area of Monte Romano, Lazio Region, Central Italy

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Abstract

Background. A study on tick species characterization and tick borne pathogens detection was performed by a survey conducted during 2012 and 2013 in the Viterbo province (Lazio Region, Central Italy). Seven sites were selected for the study investigation, including two farms and a military zone.

Methods. A total of 255 ticks, *Rhipicephalus (Boophilus) annulatus* (n = 215), *Rhipicephalus bursa* (n = 28), and *Hyalomma marginatum* (n = 12) were screened individually by molecular methods for the tick borne bacterial agents: *Borrelia burgdorferi* sensu lato group, *Bartonella* spp., *Coxiella burnetii, Ehrlichia* spp., *Francisella* spp., and *Rickettsia* spp.

Results and conclusion. Overall, 182 ticks (71%) were infected with at least one pathogen; among these co-infections were found in 94 ticks. Tick borne pathogens identified were *C. burnetii, B. burgdorferi* s.l., *Bartonella* spp., *Rickettsia* spp., *Francisella* spp., and *Ehrlichia* spp. In *R. bursa* and *H. marginatum*, the presence of *B. burgdorferi* s.l. was positively correlated with that of *C. burnetii*, *Rickettsia* spp., and *Bartonella* spp. and their coinfection probabilities were 29.8%, 22.7% and 11.7%, respectively; the probability of coinfection for *Francisella* spp. and *Rickettsia spp.* and for *Francisella* spp. and *Bartonella* spp. was 14.9% and 17.9%, respectively. In *R. (Boophilus) annulatus*, the probability of coinfection between *C. burnetii* and *B. burgdorferi* s.l. was 11.3%, while those between *C. burnetii* and *Bartonella* spp. and between *B. burgdorferi* s.l. and *Bartonella* spp. were 0.8%. Further studies are needed in order to assess the risk associated with these unusual tick-borne pathogens in Central Italy.

Key words

- ticks
- *Borrelia burgdorferi* sensu lato
- *Bartonella* spp.
- *Ehrlichia* spp.
- *Coxiella burnetii*
- *Francisella* spp.
- *Rickettsia* spp.
- co-infection
- Italy

INTRODUCTION

Ticks can transmit a great variety of pathogenic agents to animals and humans. Different factors such as global warming, dynamics of ticks, human population density, animal fauna composition in urban and peri-urban environments, or socio-demographic elements (urban, suburban, and rural) may influence and modulate the interactions of the vectors with hosts and pathogens. All mentioned aspects expose susceptible hosts to infections with tick-borne pathogens' [1, 2].

Among pathogens of veterinary and medical importance transmitted by hard ticks, we can include *Borrelia burgdorferi* s.l. complex (Lyme disease), *Rickettsia* spp. (rickettsiosis, including Mediterranean spotted fever), and *Ehrlichia* spp. However, *Bartonella* spp. (cat starch disease), *Francisella* spp. (tularemia) and *Coxiella burnetii* (Q fever) have also been detected in these arthropods but so far, they are only suspected for the disease transmission [3]. Urban areas with recreational zones and peri-urban habitats with their natural sites can produce a particular gradient of adaptation involving wildlife, ticks and related pathogens defining a complex ecological system [4, 5].

This ecological modification became of particular im-

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portance because humans and pets can encounter potentially infected ticks from outskirt environment [2]. In Italy, the prevalence of human tick-borne diseases is realistically underestimated because the surveillance system is fragmented and not well supported. As far as ticks and tick-borne pathogens are concerned, very limited studies have been performed in Central Italy, and only seroepidemiological surveys have been described in healthy and professional people for infection with *B. burgdorferi* and the tick-borne encephalitis [6-9].

To better understand the circulation of tick bacterial zoonosis in Lazio Region (Central Italy), and after several reports about the high density of ticks and tick-bites from soldiers operating in a military shooting area within the municipality of Monte Romano (province of Viterbo, Lazio Region, Central Italy), we planned to investigate the presence of tick borne bacterial agents in tick collections. In relation to potential risk factors for tick-borne infections, arthropods were collected in seven representative sites of the suburban environment of Monte Romano municipality, including two farms and the military area [10].

MATERIALS AND METHODS

Study site and tick collection

This study was carried out in the suburban area of Monte Romano (42°16'05"N 11°53'55"E) in the Viterbo Province (Lazio Region), with typical Mediterranean climate, flora and fauna well characterized [11, 12]. Seven sites of this area were chosen for the tick-borne pathogens investigation, including two farms and a military zone *(Figure 1)*. The study was conducted from June to September 2012 and from March to October 2013, and ticks were obtained by dragging or directly picked from cattle. Ticks were identified morphologically at species level [10].

Pathogens detection by molecular analyses

From a total of 518 ticks collected in our previous study [10], 255 samples were available for molecular analyses. Genomic DNA was extracted from each homogenized tick, using Dneasy blood and tissue kit (Qiagen, Hilden, Germany) according to manufacturing protocol.

Molecular detection of *Rickettsia* spp. and *Ehrlichia* spp. was performed by classical PCR amplification, as previously described [13, 14]. PCR products were resolved by electrophoresis on a 1.5% agarose gel, and stained with ethidium bromide.

The real time PCR was employed to identify *Borrelia burgdorferi* sensu lato group, *Bartonella* spp., *Coxiella burnetii* and *Francisella* spp. All real time PCRs were performed into glass capillary tubes (Roche Diagnostics GmbH, Mannheim, Germany) and carried out in a LightCycler instrument (Roche Diagnostics), with primers/probes and protocols as previously described [15-18].

Statistical analysis

Molecular results for all pathogens screened were used as the binary response variables (pathogen detected/not detected by the PCR) for the statistical analyses. The presence of each pathogen was evaluated based on several characteristics of the collected ticks land cover type, season in which the ticks were collected, collection site and state of maturity of the tick (nymph or adult). The association was evaluated through a multivariable regression analysis. In particular, first logis-

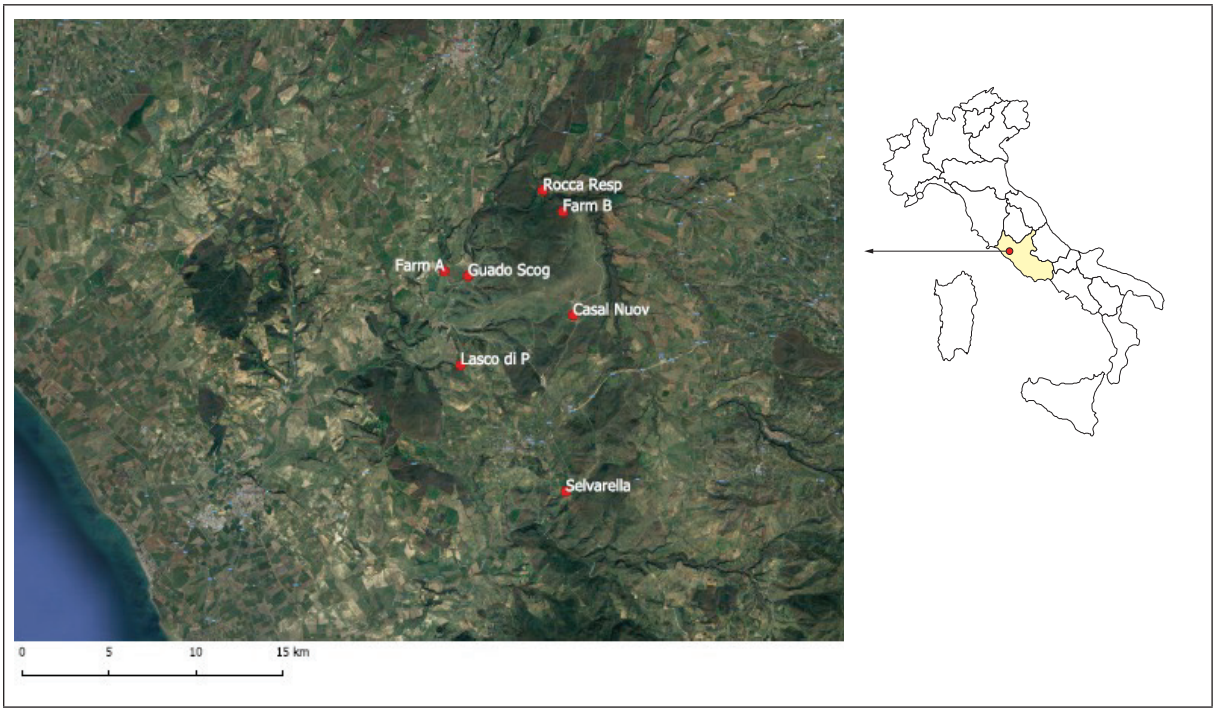

Figure 1
Tick collection sites, suburban area of Monte Romano, Lazio Region, Central Italy

tic regressions were carried out and evaluated within a frequentist framework to get some insight on what could be appropriate value for the parameters and to test significance of the covariate parameters. Then a Bayesian model was determined based on the parameter estimate obtained from the frequentist models. The multi-response approach was used to model response variables simultaneously. A multi-response hierarchical logistic regression model with conditional autoregressive (CAR) spatial random effects was carried out [19]. For each pathogen, PCR results for the other pathogens were included in the model as covariates. Neighborhoods were defined based on the distance between the area centroids. Errors at the individual level were modeled as multivariate normal random variables to estimate correlations among pathogens. The other terms in the equation were estimated as univariate normal random variables. We fitted a model for *R. (Boophilus) annulatus* and a model including *R. bursa* and *H. marginatum*. These two species were analyzed together due to the small numbers and because of previous analysis, in which the two tick species were analyzed separately yielded similar estimates for *R. bursa* and *H. marginatum*. Model parameters were estimated by drawing 10 000 samples from their joint posterior distributions using the Markov Chain Monte Carlo (MCMC) algorithm implemented in WinBugs [20, 21].

RESULTS

Tick species and tick-borne pathogens detection

The species composition of the 255 ticks were morphologically identified as follows: *Rhipicephalus (Boophilus) annulatus* (n = 215; 84%), *Rhipicephalus bursa* (n = 28; 11%), and *Hyalomma marginatum* (n = 12; 5%). All *R. bursa* and *H. marginatum* were collected by dragging while *R. (Boophilus) annulatus* were picked from animals.

From the totality of ticks examined by PCR methods, 182 (71%) samples were positive for tick-borne pathogen DNAs. As shown in *Table 1*, pathogens were found in all *H. marginatum* (12/12), in 69% of *R. (Boophilus) annulatus* (148/215), and in 79% of *R. bursa* (22/28).

In particular, *C. burnetii, B. burgdorferi* s.l.., *Bartonella* spp., *Rickettsia* spp., *Francisella* spp., and *Ehrlichia* spp. were detected in 83, 79, 48, 47, 32 and 27 ticks, respectively.

The prevalence of infection in *R. (Boophilus) annulatus*, *R. bursa* and *H. marginatum* species were reported in *Table 1*.

Co-infection analysis

Concerning the 182 positive ticks, 48% (88/182) showed one infectious agent, whereas 32% (59/182), 17% (30/182) and 3% (5/182) were co-infected with two, three and four pathogens, respectively *(Table 2)*.

The most frequent infection due to only one agent was observed with *C. burnetii* (16%), *Rickettsia* spp. (11%), and *B. burgdorferi* sl. (8%). The recurrent double and triple infection involved *C. burnetii / B. burgdorferi* sl. (8%) and *Bartonella spp. / C. burnetii / B. burgdorferi* sl. (5%), respectively. Only few cases of co-infections with four pathogens were detected *(Table 2)*.

A high proportion of multiple infections was found in *R. bursa* and *H. marginatum (Figure 2)*, with the exception of the coinfection between *C. burnetii* and *Bartonella spp.* which was more frequent in *R. (Boophilus) annulatus (see Table 3)*.

As shown in *Table 3*, in *R. bursa* and *H. marginatum*, *B. burgdorferi* s.l. was positively correlated with *C. burnetii* (ρ: 0.502), *Rickettsia* spp. (ρ: 0.323), and *Bartonella* spp. (ρ: 0.240).

Their joint probabilities ranged between 29.8% for *C. burnetii and* 11.7% for *Bartonella* spp and were significantly higher than the product of the corresponding marginal probabilities.

Similarly, *Francisella* spp. was positively correlated with *Rickettsia* spp. (ρ: 0.467) and with *Bartonella* spp. (ρ: 0.307) with joint probabilities respectively of 17.9% and 14.9%. Also in this case, the joint probabilities were significantly higher than the product of the corresponding marginal probabilities.

Table 1
Prevalence of pathogens detected in ticks

		Pathogens n. (%)					
Tick species (n.)	**Positive ticks n. (%)**	***Rickettsia* spp**	***Ehrlichia* spp**	***C. burnetii***	***Francisella* spp.**	***Bartonella* spp.**	***B. burgdorferi* s.l.**
H. marginatum (12)	12 (100)	8(66)	2 (16)	4 (33)	8 (66)	3 (25)	6 (50)
R. (Boophilus) annulatus (215)	148 (69)	36(16)	17 (7)	70 (32)	18 (8)	40 (18)	58 (26)
R. bursa (28)	22 (79)	3(10)	8 (28)	9 (32)	6 (21)	5 (17)	15 (53)
Total (255)	182	47	27	83	32	48	79
Prevalence *R. (Boophilus) annulatus*		0.178	0.089	0.329	0.089	0.186	0.265
(95% CI)		(0.131; 0.231)	(0.057; 0.132)	(0.269; 0.391)	(0.060; 0.126)	(0.143; 0.236)	(0.213; 0.324)
Prevalence *R. bursa* and *H. marginatum*		0.270	0.274	0.316	0.367	0.174	0.524
(95% CI)		(0.002; 0.411)	(0.002; 0.415)	(0.001; 0.454)	(0.001; 0.505)	(0.001; 0.287)	(0.001; 0.659)

Table 2
Bacterial pathogen infections and co-infections in ticks

	Sample		Pathogen	
	n.	(%)	n.	(%)
Bartonella spp.	9	(5)	47	(15)
C. burnetii	29	(16)	27	(9)
Ehrlichia spp.	8	(4)	83	(26)
Rickettsia spp.	21	(11)	32	(10)
Francisella spp.	6	(3)	48	(15)
B. burgdorferi s.l.	15	(8)	79	(25)
Bartonella spp.+*C. burnetii*	6	(3)		
Bartonella spp.+ *Ehrlichia* spp.	2	(1)		
Bartonella spp + *Rickettsia* spp.	0	(0)		
Bartonella spp. +*B. burgdorferi s.l.*	7	(4)		
Bartonella spp.+*Francisella* spp.	3	(2)		
C. burnetii + *Ehrlichia* spp.	3	(2)		
C. burnetii + *Rickettsia* spp.	7	(4)		
C. burnetii+ *B. burgdorferi s.l.*	14	(8)		
C. burnetii + *Francisella* spp.	1	(0)		
Ehrlichia spp.+*Rickettsia* spp.	2	(1)		
Ehrlichia spp.+ *B. burgdorferi s.l.*	4	(2)		
Ehrlichia spp.+ *Francisella* spp.	0	(0)		
Rickettsia spp.+ *B. burgdorferi s.l*	4	(2)		
Rickettsia spp.+ *Francisella* spp.	2	(1)		
B. burgdorferi s.l. + *Francisella* spp.	4	(2)		
Bartonella spp. + *C. burnetii* + *Ehrlichia* spp.	0	(0)		
Bartonella spp .+ *C. burnetii* + *Rickettsia* spp.	0	(0)		
Bartonella spp. + *C. burnetii* + *B. burgdorferi s.l.*	9	(5)		
Bartonella spp. + *C. burnetii* + *Francisella* spp.	2	(1)		
Bartonella spp.+ *Ehrlichia* spp. + *Rickettsia* spp.	0	(0)		
Bartonella spp.+ *Ehrlichia* spp. + *B. burgdorferi s.l.*	2	(1)		
Bartonella spp.+ *Ehrlichia* spp. + *Francisella* spp.	0	(0)		
Bartonella spp.+ *Rickettsia* spp. + *B. burgdorferi s.l.*	0	(0)		
Bartonella spp.+ *Rickettsia* spp. + *Francisella* spp.	1	(0)		
Bartonella spp. + *B. burgdorferi s.l.* + *Francisella* spp.	4	(2)		
C. burnetii + *Ehrlichia* spp. + *Rickettsia* spp.	0	(0)		
C. burnetii + *Ehrlichia* spp. + *B. burgdorferi s.l.*	3	(2)		
C. burnetii + *Ehrlichia* spp. + *Francisella* spp.	0	(0)		
C. burnetii + *Rickettsia* spp. + *B. burgdorferi s.l.*	2	(1)		
C. burnetii + *Rickettsia* spp. + *Francisella* spp.	1	(0)		
C. burnetii + *B. burgdorferi s.l.* + *Francisella* spp.	2	(1)		
Ehrlichia spp. + *Rickettsia* spp. + *B. burgdorferi s.l.*	0	(0)		
Ehrlichia spp. + *Rickettsia* spp. + *Francisella* spp.	0	(0)		
Ehrlichia spp. + *B. burgdorferi s.l.* + *Francisella* spp.	1	(0)		
Rickettsia spp. + *B. burgdorferi s.l.* + *Francisella* spp.	3	(2)		
Bartonella spp. + *C. burnetii* + *Ehrlichia* spp. + *B. burgdorferi s.l.*	1	(0)		
Bartonella spp.+ *Rickettsia* spp. + *B. burgdorferi s.l.* + *Francisella* spp.	1	(0)		
Bartonella spp. + *C. burnetii* + *Rickettsia* spp.+ *B. burgdorferi s.l.*	1	(0)		
Rickettsia spp. + *C. burnetii* + *B. burgdorferi s.l.* +*Francisella* spp.	1	(0)		
Rickettsia spp. + *Ehrlichia* spp. + *C. burnetii* + *B. burgdorferi s.l.*	1	(0)		
Negative	73	(29)		

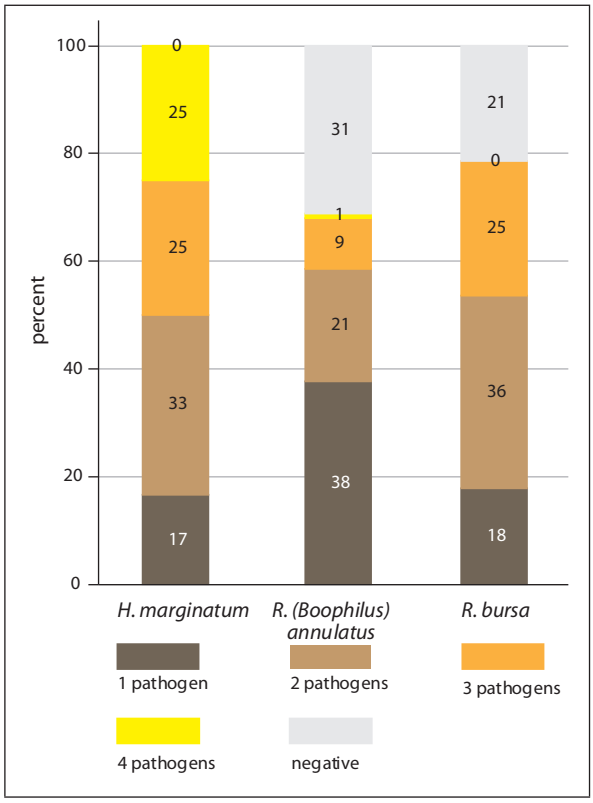

Figure 2
Infections and co-infections in tick species.

B. burgdorferi s.l. and *Francisella* spp. had a probability of coinfection of 17.6% but their correlation was of small magnitude (ρ: 0.086). In the same way, *Ehrlichia* spp. and *C. burnetii* had a prevalence of coinfection of 11.8% (p = 0.171) and a positive correlation of 0.118, whereas, *Ehrlichia* spp. and *Bartonella* spp. had a prevalence of coinfection of 0.8% (p = 0.091) and a small negative correlation of -0.043.

In *R. (Boophilus) annulatus*, *C. burnetii, B. burgdorferi* s.l. and *Bartonella* spp. were positively correlated. The probability of coinfection between *C. burnetii* and *B. burgdorferi* s.l. was 11.3% (p = 0.014) and those between *C. burnetii* and *Bartonella* and between *B. burgdorferi* s.l. and *Bartonella* were 0.8%. These were significantly higher than the product of their marginal probabilities (*C. burnetii* and *Bartonella*: p = 0.035; *B. burgdorferi* s.l. and *Bartonella*: p < 0.001). *B. burgdorferi* s.l. and *Francisella* spp. (ρ: 0.239), *Bartonella* spp. and *Francisella* spp. (ρ: 0.496) and *Ehrlichia* spp. and *B. burgdorferi* s.l. (ρ: 0.358) had a probability of coinfection of about 0.3%, and their joint probabilities were significantly higher than the product of their marginal probabilities with p values of 0.037, 0.007 and 0.085, respectively.

DISCUSSION AND CONCLUSION

Tick-borne diseases represent an increasing threat worldwide for human and animal health. Several aspects contributing to the global changes of our planet directly influence the spread of the vector borne diseases. Arthropods and microbes are revealing a remarkable adaptation to the globalization, migration, wildlife modifications, deforestation, new socio-demographic factors, climate changes and global warming [2]. Gardens, public parks and green areas between urban and peri-urban zones potentially expand tick populations and act as suitable places for the exposure of humans and animals, including pets, to tick bites, favoring the diffusion of zoonotic pathogens [4, 5, 12]. In these sites, there is a preponderance of generalist tick species capable to adapt to different host vertebrate species such as wildlife, rodents, birds or companion animals. The potential transmission of tick-borne agents to humans and the maintenance of the vector reservoir are related to the interaction between ticks and hosts [22-24].

This investigation, started after several tick-bite reports from soldiers of the military area, was focused on the presence of tick-borne bacterial agents in tick species collected in selected suburban environments, including the military shooting range. We screened ticks with the aim to improve and recognize the potential risk transmission of these pathogens. *R. (Boophilus) annulatus* was the most abundant collected species and being closely associated with the cattle on which it feeds during its life cycle [22], it has been almost exclusively picked up on these animals. *R. bursa* rarely bites humans and is generally found in environments like bushy glades and lawns. As expected, these ticks were collected from June to August, while *H. marginatum*, that could be very common in this Region, was found in early summer according to the wide range of the phenology of the species [22-24]. Besides all pathogens recognized, we found interesting the coinfection results acquired in around half of the positive ticks. In fact, the direct and the simultaneous blood transmission of more pathogens from a single tick may influence the disease progression in term of correct diagnosis and treatment.

In this study, *C. burnetii* / *B. burgdorferi* sl. / *Bartonella* spp. coinfection were positively correlated in *R. (Boophilus) annulatus*. All these microbial agents and diseases are unusual in Lazio Region and generally in Central Italy. Lyme disease is present in North Italy while Q fever is a notifiable disease but with marginal impact in the public health of our Country, and the risk is significantly associated with direct occupational exposure [25-27]. Bartonellae are emerging pathogens distributed worldwide and strictly related to mammalian hosts, vectors and favorable environment [28]. Roaming animals, pets and ticks may act as reservoir in the urban area, and their potential role in the maintenance of the bacterium may be important, notably due to the intracellular persistence of the pathogen [28]. Even if the tick species reported in this study are not considered in letterature as main vectors of the pathogens here investigated, they are known to be able to participate to their circulation. *H. marginatum* is a tick species known to participate to the circulation of Q fever in Italy, according to other studies, reporting the isolation of *C. burnetii* in this species [22, 29, 30]. In Sicily, *H. marginatum* resulted infected with *Rickettsia* spp. (n = 3/67; 4%). *R. bursa* is a vector and reservoir for *C. burnetii* in Bulgaria, Spain and in Crimea, where

Table 3
Probabilities of coinfection for *R. (Boophilus) annulatus* and *R. bursa* and *H. marginatum*

	R. (Boophilus) annulatus					
	***Rickettsia* Spp.**	***Ehrlichia* Spp.**	***C. burnetii***	***B. burgdorferi* s.l.**	***Bartonella* spp.**	***Francisella* spp.**
Rickettsia spp.		0.005 (0.001; 0.012) P = 0.996	0.033 (0.018; 0.055) P = 0.998	0.022 (0.010; 0.039) P = 0.999	0.004 (0.001; 0.011) P = 1.000	0.018 (0.007; 0.033) P = 0.390
Ehrlichia spp.	0.005 (0.001; 0.012) P = 0.996		0.009 (0.004; 0.019) P = 1.000	0.035 (0.017; 0.063) P = 0.085	0.009 (0.003; 0.019) P = 0.962	0.004 (0.001; 0.011) P = 0.933
C. burnetii	0.033 (0.018; 0.055) P = 0.998	0.009 (0.004; 0.019) P = 1.000		0.113 (0.079; 0.152) P = 0.014	0.078 (0.052; 0.110) P = 0.035	0.015 (0.007; 0.027) P = 0.997
B. burgdorferi s.l.	0.022 (0.010; 0.039) P = 0.999	0.035 (0.017; 0.063) P = 0.085	0.113 (0.079; 0.152) P = 0.014		0.082 (0.055; 0.114) P < 0.001	0.034 (0.019; 0.053) P = 0.037
Bartonella spp.	0.004 (0.001; 0.011) P = 1.000	0.009 (0.003; 0.019) P = 0.962	0.078 (0.052; 0.110) P = 0.035	0.082 (0.055; 0.114) P < 0.001		0.030 (0.015; 0.052) P = 0.007
Francisella spp.	0.018 (0.007; 0.033) P = 0.390	0.004 (0.001; 0.011) P = 0.933	0.015 (0.007; 0.027) P = 0.997	0.034 (0.019; 0.053) P = 0.037	0.030 (0.015; 0.052) P = 0.007	

	R. bursa* and *H. marginatum					
	***Rickettsia* Spp.**	***Ehrlichia* Spp.**	***C. burnetii***	***B. burgdorferi* s.l.**	***Bartonella* spp.**	***Francisella* spp.**
Rickettsia spp.		0.059 (0.016; 0.135) P = 0.741	0.077 (0.027; 0.160) P = 0.665	0.227 (0.110; 0.370) P = 0.035	0.027 (0.007; 0.067) P = 0.930	0.149 (0.068; 0.260) P = 0.074
Ehrlichia spp.	0.059 (0.016; 0.135) P = 0.741		0.118 (0.045; 0.223) P = 0.171	0.072 (0.023; 0.161) P = 0.972	0.080 (0.025; 0.159) P = 0.091	0.008 (0.001; 0.028) P = 1.000
C. burnetii	0.077 (0.027; 0.160) P = 0.665	0.118 (0.045; 0.223) P = 0.171		0.298 (0.166; 0.447) P = 0.005	0.014 (0.002; 0.040) P = 0.998	0.059 (0.019; 0.128) P = 0.977
B. burgdorferi s.l.	0.227 (0.110; 0.370) P = 0.035	0.072 (0.023; 0.161) P = 0.972	0.298 (0.166; 0.447) P = 0.005		0.117 (0.058; 0.205) P = 0.070	0.176 (0.090; 0.290) P = 0.661
Bartonella spp.	0.027 0.007; 0.067) P = 0.930	0.080 (0.025; 0.159) P = 0.091	0.014 (0.002; 0.040) P = 0.998	0.117 (0.058; 0.205) P = 0.070		0.179 (0.079; 0.305) P < 0.001
Francisella spp.	0.149 (0.068; 0.260) P = 0.074	0.008 (0.001; 0.028) P = 1.000	0.059 (0.019; 0.128) P = 0.977	0.176 (0.090; 0.290) P = 0.661	0.179 (0.079; 0.305) P < 0.001	

P = P (pathogen1) P (pathogen2) ≤ P (pathogen1, pathogen2); (95% CI) are reported in brackets.

is able to maintain the circulation of this infectious agent [22-24]. Recently, the presence of *C. burnetii* (n = 2/83; 20%) and *Bartonella sp*. (n = 1/22; 4%) has been recently detected in this species for the first time in Sardinia [30]. *R. annulatus*, reported as the main vector of haemoparasites, had not been reported before in the transmission of these infections. However, this arthropod may act as secondary vector in the maintenance of rickettsiae and coxiellae, considering that *R. annulatus* was found positive to *C. burnetii* (n = 2/83; 2%) in Sardinia, confirming a previous study carried out in Senegal (n = 1/5; 20%) [30, 31]. Another similar case was found in Israel where a *R. annulatus* tick picked-up from a Mesopotamian fallow deer resulted positive for *R. sibirica mongolitimonae* [32].

In conclusion, this study provides new information on the circulation of ticks and tick borne pathogens in Lazio Region (Central Italy). The aim of our study was the direct detection of pathogens in tick samples and potentially characterize the molecular prevalence of active infection(s), differing to serological studies that revealing past exposure or a not active infection.

The recognition of uncommon and potentially pathogenic agents in ticks from urban and suburban areas, may implement the surveillance screening of tick borne diseases. Further studies are required to determine the role of arthropod-vectors as carriers of these bacteria in the Mediterranean ecosystem.

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REFERENCES

1. Randolph SE. Tick-borne disease systems emerge from the shadows: the beauty lies in molecular detail, the message in epidemiology. Parasitology. 2009;136:1403-13. doi: 10.1017/S0031182009005782
2. Kilpatrick AM, Randolph SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. Lancet. 2012;380:1946-55. doi: 10.1016/S0140-6736(12)61151-9
3. Socolovschi C, Mediannikov O, Raoult D, Parola P. Update on tick-borne bacterial diseases in Europe. Parasite. 2009;16:259-73. doi: 10.1051/parasite/2009164259
4. Di Luca M, Toma L, Bianchi R, Quarchioni E, Marini L, Mancini F, Ciervo A, Khoury C. Seasonal dynamics of tick species in an urban park of Rome. Ticks Tick Borne Dis. 2013;4:513-7. doi: 10.1016/j.ttbdis.2013.06.008
5. Mancini F, Di Luca M, Toma L, Vescio F, Bianchi R, Khoury C, Marini L, Rezza G, Ciervo A. Prevalence of tick-borne pathogens in an urban park in Rome, Italy. Ann Agric Environ Med. 2014;21:725-9. doi: 10.5604/12321966.1129922
6. Verani P, Balducci M, Lopes MC, Alemanno A, Saccà G. Survey for antibodies against arthropod-borne viruses in man and animals in Italy. Serologic status of human beings in a central Italian region (Fondi province). Am J Trop Med Hyg. 1967;16:203-10.
7. Santino I, Cammarata E, Franco S, Galdiero F, Oliva B, Sessa R, Cipriani P, Tempera G, Del Piano M. Multicentric study of seroprevalence of *Borrelia burgdorferi* and *Anaplasma phagocytophila* in high-risk groups in regions of central and southern Italy. Int J Immunopathol Pharmacol. 2004;17:219-23.
8. Tomao P, Ciceroni L, D'Ovidio MC, De Rosa M, Vonesch N, Iavicoli S, Signorini S, Ciarrocchi S, Ciufolini MG, Fiorentini C, Papaleo B. Prevalence and incidence of antibodies to *Borrelia burgdorferi* and to tick-borne encephalitis virus in agricultural and forestry workers from Tuscany, Italy. Eur J Clin Microbiol Infect Dis. 2005;24:457-63 DOI 10.1007/s10096-005-1348-0
9. Di Renzi S, Martini A, Binazzi A, Marinaccio A, Vonesch N, D'Amico W, Moro T, Fiorentini C, Ciufolini MG, Visca P, Tomao P. Risk of acquiring tick-borne infections in forestry workers from Lazio, Italy. Eur J Clin Microbiol Infect Dis. 2010;29:1579-81. DOI 10.1007/s10096-010-1028-6
10. Toma L, Di Luca M, Mancini F, Severini F, Mariano C, Nicolai G, Laghezza Masci V, Ciervo A, Fausto AM, Cacciò SM. Molecular characterization of *Babesia* and *Theileria* species in ticks collected in the outskirt of Monte Romano, Lazio Region, Central Italy. Ann Ist Super Sanità. 2017;53:30-4. doi: 10.4415/ANN_17_01_07
11. Blasi C. L'Ambiente nella Tuscia laziale. Aree protette e di interesse naturalistico della provincia di Viterbo. In: *Lineamenti della vegetazione dell'Alto Lazio*. Viterbo: Università della Tuscia di Viterbo; 1992.
12. Celletti S, Papi R. Fauna vertebrata terrestre della provincia di Viterbo. In: *Seconda Relazione sullo Stato dell'Ambiente*. Viterbo: Provincia di Viterbo Assessorato Ambiente e Pianificazione del Territorio; 2003.
13. Regnery RL, Spruill CL, Plikaytis BD. Genotypic identification of rickettsiae and estimation of intraspecies sequence divergence for portions of two rickettsial genes. J Bacteriol. 1991;173:1576-89.
14. Parola P, Roux V, Camicas JL, Baradji I, Brouqui P, Raout D. Detection of Ehrlichiae in African ticks by polymerase chain reaction. Trans R Soc Trop Med Hyg. 2000;94:707-8.
15. Pietila¨ J, He Q, Oksi J, Viljanen MK. Rapid differentiation of *Borrelia garinii* from *Borrelia afzelii* and *Borrelia burgdorferi* sensu stricto by LightCycler fluorescence melting curve analysis of a PCR product of the *rec*A gene. J Clin Microbiol. 2000;38:2756-9.
16. Ciervo A, Ciceroni L. Rapid detection and differentiation of *Bartonella* spp. by a single-run real-time PCR. Mol Cell Probes. 2004;18:307-12. doi: 10.1016/j.mcp.2004.04.004
17. Klee SR, Tyczka J, Ellerbrok H, Franz T, Linke S, Baljer G, Appel B. Highly sensitive real-time PCR for specific detection and quantification of *Coxiella burnetii*. BMC Microbiol. 2006;6:2. doi: 10.1186/1471-2180-6-2
18. Byström M, Böcher S, Magnusson A, Prag J, Johansson A. Tularemia in Denmark: identification of a *Francisella tularensis* subsp. *holarctica* strain by real-time PCR and high-resolution typing by multiple-locus variable-number tandem repeat analysis. J Clin Microbiol. 2005;43:5355-8. doi:1 0.1128/JCM.43.10.5355-5358.2005
19. Besag J, Kooperberg C. On conditional and intrinsic autoregression. Biometrika. 1995:733-46.
20. Spiegelhalter D J, Thomas A, Best NG. WinBUGS Version 1.2 User Manual. MRC Biostatistics Unit; 1999.
21. Thomas A. BUGS: a statistical modelling package. RTA/BCS Modular Languages Newsletter. 1994;2:36-8.
22. Manilla G. Acari Ixodida. Fauna d'Italia. 36. Bologna: Calderini; 1986.
23. Iori A, Di Giulio A, De Felici S. Zecche d'Italia, parte III. In: Cringoli G (Ed). Mappe parassitologiche (6) (Zecche). Napoli: 2005.
24. Randolph SE, Rogers DJ. Ecology of tick-borne disease and the role of climate. In: Ergonul, O, Whitehouse C (Eds), Crimean-Congo hemorrhagic fever. A global perspective. The Netherlands: Springer; 2003.
25. Mantelli B, Pecchioli E, Hauffe HC, Rosa R, Rizzoli A. Prevalence of *Borrelia burgdorferi* s.l. and *Anaplasma phagocytophilum* in the wood tick Ixodes ricinus in the Province of Trento, Italy. Eur J Clin Microbiol Infect Dis.

2006;25:737-9. doi: 10.1007/s10096-006-0208-x

26. Piccolin G, Benedetti G, Doglioni C, Lorenzato C, Mancuso S, Papa N, Pitton L, Ramon MC, Zasio C, Bertiato G. A study of the presence of *B. burgdorferi, Anaplasma* (previously *Ehrlichia*) *phagocytophilum*, *Rickettsia*, and *Babesia* in *Ixodes ricinus* collected within the territory of Belluno, Italy. Vector Borne Zoonotic Dis. 2006;6:24-31. doi: 10.1089/vbz.2006.6.24
27. European Centre for Disease Prevention and Control. *Technical report. Risk assessment on Q fever*. Solna, Svezia: ECDC; 2010: Available from: http://ecdc.europa.eu/en/publications.Publications1005_TER_Risk_Assessment_Qfever.pdf.
28. Breitschwerdt E. Bartonellosis: one-health perspectives for an emerging infectious disease. ILAR J. 2014;55:4658. doi: 10.1093/ilar/ilu015
29. Rocchigiani G, Ebani V, Nardoni S, Bertelloni F, Bascherini A, Leoni A, Mancianti A, Poli A. Molecular survey on the occurrence of arthropod-borne pathogens in wild brown hares (*Lepus europaeus*) from Central Italy. Infect Genet Evol. 2018;59:142-7. doi: 10.1016/j.meegid.2018.02.005
30. Chisu V, Foxi C, Mannu R, Satta G, Masala G. A five-year survey of tick species and identification of tick-borne bacteria in Sardinia, Italy. Ticks and Tick-borne Dis. 2018;9:678-81. doi: 10.1016/j.ttbdis.2018.02.008
31. Mediannikov O, Fenollar F, Socolovschi C, Diatta G, Bassene H, Molez JF, Sokhna C, Trape JF, Raolut D. *Coxiella burnetii* in Humans and Ticks in Rural Senegal. PLoS Negl Trop Dis. 2010;4(4):e654. doi: 10.1371/journal.pntd.0000654
32. Waner T, Keysary A, Eremeeva ME, Beth Din A, Mumcuoglu KY, King R, Atiya-Nasagi Y. *Rickettsia africae* and Candidatus *Rickettsia barbariae* in Ticks in Israel. Am J Trop Med Hyg. 2014:90;920-2. doi: 10.4269/ajtmh.13-0697

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Are touch screen technologies more effective than traditional educational methods in children with autism spectrum disorders? A pilot study

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Abstract
Applied Computer technologies can address the needs of individuals with autism spectrum disorders (ASD). Data on the efficacy of assistive technology in ASD is limited, and its effectiveness in supporting and facilitating skill acquisition in this specific population must be still demonstrated. 63 Italian ASD subjects underwent learning activities administered by cardboards or a touch screen support. The support preference was evaluated in a choice trial, and quantitative analysis was performed on items regarding communication and challenging behaviours. Touch devices are attractive especially for males without intellectual disability and a lower communication and cooperation behaviours with the use of touch screen compared with paper support was shown depending on activities. Overall, our data do not confirm the hypothesis that touch screen presentation improves activity completion and behavioural performance for each individual with ASD. Data discourage an indiscriminate use of these devices and suggest analysing with more attention the core ingredients that should shape digital devices when used for people on ASD.

Key words
- autism spectrum disorders
- assistive technology
- touch screen
- structured learning

INTRODUCTION

Individuals with autism spectrum disorders (ASD) present special needs to sustain daily life and skill acquisition that often include external stimulus prompts to initiate, maintain, or terminate a behaviour. In particular, several studies emphasized the preference of this population towards visual stimuli, particularly those delivered via electronic screen [1, 2].

This attitude is supposed to be at the basis of the better use and learning from visual instructions of people with ASD [3-6]. However, some data are in contrast with the hypothesis that individuals with ASD are visual learners [7-9].

In the context of assistive technology, many types of computing systems are becoming more and more important in clinical and educational practice. In particular, enthusiasm towards tools that appear more appealing for users with ASD has led to a large diffusion of computer assistive technology (CAT) in different settings (laboratory, school, home), with the aim of improving language, cognitive, socio-emotional, adaptive as well as academic skills, and potentially allowing the sharing of intervention strategy across all child life environments [10-15]. Notwithstanding such interest, careful evaluation of the effects of these new technologies compared to traditional methods is still required [12, 16-18].

In first studies aimed at evaluating efficacy and validity of CAT for the habilitation of ASD people, researchers reported a positive effect of CAT, with an increase of pair to pair interaction and skill in communication, and a decrease in repetitive and challenging behaviours [19, 20]. Further studies confirmed such a positive effect, with particular relevance of the role of CAT in increasing access to educational programs and decreasing maladaptive behaviours [21-23]. CAT is indeed considered a useful medium to provide learning goals as it offers standard, automatic and predictable instructions, avoiding in vivo social behaviour that might overburden people with ASD [10, 24]. The automation is also an advantage for the trainer in the case of activities and tasks which need high level of repetition [25, 26], and potentially reduces need of individual support at school and/or at work [27].

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Structured intervention packages for ASD such as Treatment and Education of Autistic and related Communication Handicapped Children (TEACCH) [28] and Applied Behaviour Analysis (ABA) [29] place a heavy emphasis on structure and repetition, and on establishing a background environment that children do not find overwhelming. Furthermore, TEACCH and ABA principles involve adapting the behaviour and skill level to suit the subject's personal unique needs. In this framework, CAT appears a useful medium to provide individualized learning goals. Indeed, computer technology allows a wide quantitative and qualitative storage and analysis of data, resulting in an increased availability of examples (figures, words, video, colours and layouts) that educators can introduce in individual programs, and the tracking of each user's progress with the opportunity to modify the difficulty levels as a result [30]. Finally, a large part of the literature on the use of technology by people on the autism spectrum has pointed out its value as augmentative device to support interaction and communication [31]. Rather than "digital bubble", WEB navigation and the development of online dedicated forum appear to be tools useful to advocate, support, and emancipate people on autism empowering them towards social world [32, 33]. However, despite the apparent positive value of the online interaction opportunity, additional studies in this area are necessary to empirically confirm the efficacy and efficiency of the intervention with digital technology taking into account intervention specificity and its implementation by digital device [12, 25, 34].

Among the computer assistive technology, the use of multi-touch screen devices is growing. Despite this, few studies aim to verify if touch screen technology may provide a new way to deliver intervention to young children or to those with severe intellectual disabilities. Overall, studies showed positive effects of the use of multi-touch on challenging behaviour [22] and on active participation to learning programs [35, 36], as well on pair interaction and collaboration [31, 37, 38]. However, a recent review that analysed 34 studies stressed that research on the use of touch screen technology was focused on very basic use of the devices and was carried out on a limited sample of subjects. Furthermore, it was performed especially in school or home setting [39].

The present study aims to explore if multi-touch screen technology is actually friendly and able to improve compliance during ambulatory education activities with respect to traditional support. The study analysed the preference towards either little card-boards (PA, paper activities) or a multi-touch screen support (TA, touch activities) in a sample of subjects representing the ASD population usually attending local health ambulatory units. Furthermore, activity completion, behavioural performance, and communicative exchange of ASD subjects were assessed in order to evaluate the compliance of individual with ASD undergoing activities provided by means of PA or TA support.

METHODS

Participants

The study was carried out in the Center for Autism and Asperger Syndrome (CASA, ASL CN1, Mondovi, Italy), an ASD specialized outpatient service of the Italian public health system. All the subjects that were resident of Mondovì and were followed by CASA for habilitation intervention in the period 2012-2013 were assessed for enrolment. Exclusion criteria were genetic syndromes or motor disability at clinical examination. In that period, the total of resident patients in the health district amounted to 170, 61 (36%) were followed only for diagnosis or assessment. Among the 109 patients followed by CASA for habilitative intervention, 63 gave the consent to video-recording and data use for research. *Table 1* describes the final sample that included 63 subjects, 55 males (87.3%) and 8 females (12.7%), in the age range 4-32 years. Participants were grouped by means of their school attendance that in Italy is compulsory from 6 to 16 years of age. This number of subjects allows to evaluate small to medium size differences (Cohen $d_z = 0.36$) in a paired t-test with two-sided alpha = 0.05 and power = 0.80.

All the participants had an ASD diagnosis based on DSM-IV and ICD-10 criteria. The clinical diagnosis was supported by at least one standard assessment tool: specifically, the younger subjects (n. 30) had been evaluated with ADOS (Autism Diagnostic Observation Schedule) [40] while the older ones had been evaluated with other tools such as CARS (Childhood Autism Rating Scale) [41]), GARS (Gilliam Autism Rate Scale) [42] and ABC (Autism Behaviour Checklist) [43]. All diagnoses fulfilled the criteria for DSM-5 autistic spectrum disorders. Intelligence quotient was measured by WISC or WAIS (Wechsler, 1974, 1981, 1991), respectively for verbal children and verbal adolescents /adults (n = 46, 73.0%). Intelligence quotient was measured by Leiter (Roid & Miller, 1997) for the non-verbal subjects (n = 17, 27.0%). Adaptive behaviour was assessed by clinical evaluation, that was confirmed by Vineland Adaptive Behaviour Scale [44] where available (n = 43, 68.3%). Based on IQ and adaptive behaviour, subjects were classified in the categories of intellectual disability (ID) according to DSM-5 criteria. The family education level (measured as the higher attained level between parents) was also recorded.

As use of technology is currently allowed in health service for habilitation programs, review by an ethics committee was not mandatory for this kind of study (observational study). However, as stated above, we informed and asked for consent all subjects followed for habilitative intervention, and enrolled only those that accepted to participate.

MATERIALS AND SETTING

The study took place in the CASA center, in two comparable sized ambulatory rooms (about 3m x 4m), each room assigned to a treatment (PA or TA protocol). Both rooms were stimuli free, and furnished with only two chairs and one table. The TA protocol was administered individually by a multi-touch tabletop. The touch-table used in the study was part of CASA provision since 2010. It was suitable for compulsory schoolers/adolescents/adult children, while it was inappropriate for children under 5, due to the table height (25") and to the very large screen (47"). Indeed, to be comfortable in

Table 1
Description of the subjects participating to the study

	TOT		Diagnosis				Intellectual disability		
			AD	NOS	AS	n.a.	No	Mild	Severe
	n	%[a]	%[b]	%[b]	%[b]	%[b]	%[b]	%[b]	%[b]
Sex									
Male	55	87.3	54.6	32.7	7.3	5.5	16.4	49.1	34.5
Female	8	12.7	25.0	50.0	0.0	25.0	0.0	50.0	50.0
Age range									
PS	9	14.3	66.7	33.3	0.0	0.0	0.0	88.9	11.1
CS	34	54.0	44.1	41.2	5.9	8.8	11.8	52.9	35.3
NCS	9	14.3	55.6	33.3	11.1	0.0	33.3	11.1	55.6
AU	11	17.5	54.5	18.2	9.1	18.2	18.2	36.4	45.4
Diagnosis									
AD	32	50.8					3.1	43.8	53.1
NOS	22	34.9					22.7	59.1	18.2
AS	4	6.3					75.0	25.0	0.0
n.a.	5	7.9					0.0	60.0	40.0
Intellectual disability									
No	9	14.3	11.1	55.6	33.3	0.0			
Mild	31	49.2	45.2	41.9	3.2	9.7			
Severe	23	36.5	73.9	17.4	0.0	8.7			
Family educational level									
Elementary/Middle	19	30.2	52.6	36.8	5.3	5.3	10.5	47.4	42.1
High	31	49.2	48.4	32.3	6.5	12.9	12.9	54.8	32.3
University	13	20.6	53.8	38.5	7.7	0.0	23.1	38.5	38.5

Age range: PS = preschoolers (4-6 years), CS = compulsory education schoolers (7-15 years), NCS = non-compulsory education schoolers (16-18 years), AU = adults (19-32 years).
Diagnosis: AD = autistic disorder, NOS = pervasive developmental disorder not otherwise specified, AS = Asperger syndrome, n.a. = ICD10 F84 subcategory not available.
[a]Percentage computed on the total of subjects (n = 63).
[b]Percentage computed on the subjects belonging to the category indicated in the corresponding row heading.

looking at a screen the subject should sit at a distance where the screen fills 30° of subject's horizontal field of view. Since children under 5 must sit at a maximum distance of about 1.3 ft to be able to perform activities on the touch screen, the resulting optimal screen size should be under 20". Therefore, we used a 17" multi-touch screen in subjects younger than 5yrs. Although all the enrolled subjects were familiar with computers and/or touch devices (such as tablet, IPad, IPod, touch-screen phone), no one of them had previously seen and used the multi-touch tabletop.

Autism specialized operators administered the PA protocol by set of cardboards specifically made for this study using ARASAAC (Portal Aragonés de la Comunicación Aumentativa y Alternativa, http://arasaac.org/index.php) pictograms and uppercase letters. The operators supervised and assisted both TA and PA procedures and provided specific helps when necessary (see procedure description).

Both PA and TA protocol included four activities: (1) visual discrimination (VD), (2) classification (CL), (3) word-picture pairing (WPP), and (4) picture-picture pairing (PPP) (see *Table 2A* for a detailed description). Activities included in the protocol were chosen based on two main considerations: the activities are those usually delivered during ambulatory intervention; they can be implemented on touch screen support. Indeed, they are structured and almost self-explaining, they require and utilize only visual (CL, PPP) or visual and auditory sensory channels (VD, WPP), and they can be organized according to different level of complexity, thus preventing the occurrence of challenging behaviours due to boredom and/or annoyance possibly linked to the skill intensity demand. Four levels of complexity tailored on subject's age and IQ were defined for each activity: a) *low* (administered to n = 21 subjects), b) *medium-low* (administered to n = 21 subjects), c) *medium-high* (administered to n = 10 subjects) and d) *high* (administered to n = 11 subjects). Complexity levels and sample distribution according to complexity level, ID and age range are described in *Table 2A* and *2B*.

Procedures

Activities were presented to all subjects in the following order: VD, CL, WPP, and PPP. VD, CL, and WPP were delivered on both PA and TA, while PPP was pre-

Table 2A
Classification and description of activities included in the PA and TA protocols

Task	Description	Complexity level
VISUAL DISCRIMINATION (VD)	Verbal prompt: touch and give images corresponding to the operator request.	The four levels differ for number and size of objects that must be discriminated (the smaller the object, the more difficult the level)
CLASSIFICATION (CL)	One half of the picture cards lie on the table and the subject must associate each card with the image presented by the operator. Number and type of categories differ throughout trials.	Low level – two classification categories, in each category proposed pictures are equal. *Basal* trial: pictures are very different each others; *Intermediate* trial: pictures are different in colour; *Advanced* trial: pictures represent very similar objects.
		Medium-low level – three classification categories based on the geometric shape. Colour works as disruptive stimulus. *Basal*, *Intermediate*, and *Advanced* trials employ increasingly similar shapes.
		Medium-high level - three classification categories. *Basal* trial: home objects classification; *Intermediate* trial: food classification; *Advanced* trial: animals classification.
		High level – Classification of abstract categories. *Basal* trial: pictures and emotions; *Intermediate* and *Advanced* trials: abstract concept images.
WORD-PICTURE pairing (WPP)	Verbal prompt: touch the image corresponding to the operator request. The complexity of verbal prompt differs through the trials. ("Dog", "Touch the dog"; "Touch the barking animal"; "Touch the animal that gives a hearty welcome to its owner").	Images are increasingly similar to each other.
PICTURE-PICTURE pairing (PPP)	The subject must overlap images that are equal. The number of and similarity between images that must be paired increases through the trials.	Images are increasingly similar to each other.

PA: paper activities; TA: touch activities

Table 2B
Frequency of subjects according to the complexity level of the activity, ID and age range

		Age range				
Complexity level	**ID**	**PS 4-6 years**	**CS 7-15 years**	**NCS 16-18 years**	**AU 19-32 years**	**Tot**
Low	No	0	0	0	0	0
	Mild	9	0	0	0	9
	Severe	0	11	0	1	12
	Tot	*9*	*11*	*0*	*1*	*21*
Medium-low	No	0	0	0	0	0
	Mild	0	16	0	0	16
	Severe	0	1	4	0	5
	Tot	*0*	*17*	*4*	*0*	*21*
Medium-high	No	0	2	0	0	2
	Mild	0	2	1	0	3
	Severe	0	0	1	4	5
	Tot	*0*	*4*	*2*	*4*	*10*
High	No	0	2	3	2	7
	Mild	0	0	0	4	4
	Severe	0	0	0	0	0
	Tot	*0*	*2*	*3*	*6*	*11*
TOT		***9***	***34***	***9***	***11***	***63***

PS = preschoolers; CS = compulsory education schoolers; NCS = non-compulsory education schoolers; AU = adults

sented only on the activity support (either PA or TA) chosen by the subjects. Before starting each trial, the operator displayed to the subject how to perform the specific activity. The visual and auditory prompts foreseen for VD and WPP activities were supplied during PA modality by the operators, and during TA by a synthetic voice. During both activities, protocol permitted the following prompts: proximal indication, display of

the task, and physical guidance. At the end of each activity, visual (smile emoticon) and/or auditory stimulus (synthetic voice) were provided to the subject on the TA, while on the PA the visual and auditory reinforcements were provided by the operator.

Treatment sessions were recorded by a video recording system and then the videos were analysed and scored by two operators. Frequencies of the following behaviours were collected *(see Table 3)*: Uncooperativeness, number of non-collaborative behaviour episodes (Uncoop); Stereotypies, number of stereotyped, repetitive or sensory behaviours (Stereo); Helps, number of helps (i.e. pointing at the correct answer, modelling, physical guidance, verbal help) needed to accomplish the activity (Help); and Communication ability, number of spontaneous communication acts (Ca). Behavioural quantitative scoring was performed by means of a preset scoring form by each operator. Time needed to complete the activity (Duration) was also recorded, using a chronometer.

Design

The study followed a crossover design. Each subject performed the first three activities (1st: VD, 2nd: CL, and 3rd: WPP, same sequence for all subjects) both on PA and TA supports. To control for learning effects, both sequences of treatment administration were considered (PA followed by TA, PA-TA; TA followed by PA, TA-PA). Each subject was randomly assigned either to PA-TA or to TA-PA sequence. The whole group of subjects was thus partitioned in two subgroups, namely the subgroup of subjects randomly assigned to the sequence PA-TA (n = 33, 53.4%) and those assigned to TA-PA (n = 30, 46.6%). The two subgroups did not differ with respect to sex, diagnosis, presence/degree of mental retardation and complexity level of the task (data not shown).

Statistical analysis

Quantitative variables are synthesized by mean and standard error of the mean (SE), median and range (minimum, maximum), while categorical variables by absolute and percentage frequencies.

The binomial test was used to evaluate if the proportion of subjects choosing TA support in performing the PPP activity was significantly different from the chance level (0.50, i.e. 50%), in the overall group of subjects and within each subgroup based on sex, autism diagnosis, intellectual disability, and order of support administration. A logistic regression analysis was also performed to determine which factor(s) among sex, age class, autism diagnosis, intellectual disability, and order of support administration was/were independently associated to the choice of TA support for the picture-picture pairing activity.

As for the behaviours collected through the scoring form during the card-based and the computer-based activities, the Intraclass Correlation Coefficient (ICC) was used to measure the interrater reliability between the operators that collected data. Coefficient up to 0.20 was interpreted as slight/poor agreement, from 0.21 to 0.4 as fair agreement, from 0.41 to 0.6 as moderate agreement, from 0.61 to 0.8 as substantial/strong agreement, and from 0.81 to 1.0 as almost perfect agreement (Landis & Koch, 1977). The ICC between the two operators was always high (strong to perfect) when considering stereotyped behaviours, duration of the activity, helps needed and communication ability, while it was lower (moderate to substantial) when evaluating the uncooperativeness *(Figure 1, panels A-C)*. Due to the overall good level of concordance, data from the two operators were averaged for each behaviour in each activity, and the averages were used in the following analyses.

Differences in the behaviours collected during the card- and the computer-based activities were analysed by multivariate analysis of variance (MANOVA) followed by Student paired t test. Specifically, in order to assess the effect of activity support on the overall behaviour within each activity we used a MANOVA model including activity support (PA *vs* TA) as within-subject factor and the whole set of variables (Uncooperativeness, Duration of the activity, Stereotypies, Helps needed, Communication ability) collected within the specific activity (VD, CL, WPP) as multivariate outcome. Secondly, at the aim of assessing the effect of activity support on the specific behaviour across all the activities performed we applied a different MANOVA model, including activity support (PA *vs* TA) as within-subject factor and the specific behavioural score collected in the different activities (VD, CL, WPP) as multivariate outcome. When a significant effect of activity support was found, the paired t test was performed to compare PA *vs* TA separately within each activity and for each dependent variable; Bonferroni's correction was applied to control for multiple testing (15 comparisons, pairwise alpha = 0.0033). Cohen's d (or d_z in case of paired t test) was computed as a measure of the observed effect size (values for d or d_z around 0.20 can be roughly interpreted as a small effect, around 0.50 as a medium effect, and around 0.80 as a large effect). MANOVAs were also repeated including sex, age (pre-schoolers, 4-6 years; CS = compulsory education schoolers, 7-15 years; NCS =

Table 3
Behavior's category and examples

Category	Example
Uncooperativeness (Uncoop): number of non-collaborative behaviour episodes	Go away from the task Push away the object Problem behavior Adult intervention
Stereotypies (Stereo): number of stereotyped, repetitive or sensory behaviours	Stereotypies that interfere with the task execution Stereotypies that don't interfere with the task execution Sensory interest Repetitive behaviors
Helps needed (Help): number of helps needed to accomplish the task	Helps allowed: Pointing at the correct answer, modelling, physical guidance, verbal help
Communication ability (Ca): number of spontaneous communications	Ask for help Make questions Share Comment

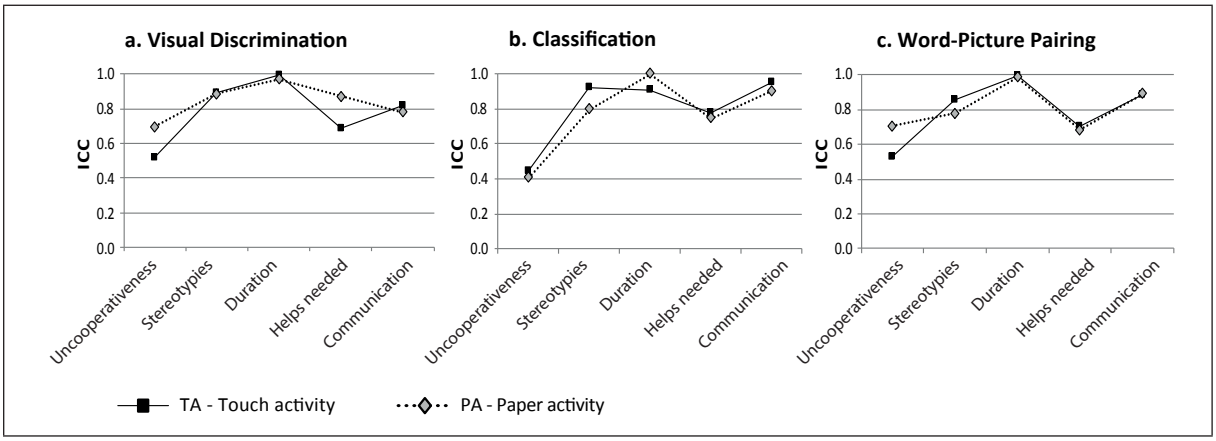

Figure 1
Intraclass correlation coefficient (ICC) between operators on the behaviours collected during visual discrimination, classification, and word-picture pairing activities (Panels a-c)

non-compulsory education schoolers, 16-18 years; AU = adults, 19-32 years), autism diagnosis (AD = autistic disorder, NOS = pervasive developmental disorder not otherwise specified), and intellectual disability (no, mild, severe), as between-subject factors, to assess the interaction of such characteristics with activity support, on subjects' behaviour during the activities.

For all statistical tests p values < 0.05 were considered statistically significant. Differences whose significance level was 0.05 < p < 0.10 were mentioned if they were coherent and in agreement with other statistically significant results.

RESULTS

Support preference (TA vs PA)

Table 4 describes the results from binomial test performed on the preference of support for the PPP activity. Overall, subjects showed a preference towards

Table 4
Preference between PA and TA support in the Picture-Picture pairing activity, according to sex, age range, administration turn, intellectual disability, and ASD categories. Binomial test is reported

Group		PA		TA		Binomial test p (two tails)
		n	%	n	%	
OVERALL	63	24	38.10	**39**	**61.90**	**0.0769**
Sex						
Male	55	19	34.55	**36**	**65.45**	**0.0300**
Female	8	5	62.50	3	37.50	0.7266
Age range						
PS	9	6	66.67	3	33.33	0.5078
CS	34	14	41.18	20	58.82	0.3915
NCS	9	1	11.11	**8**	**88.89**	**0.0391**
AU	11	3	27.27	8	72.73	0.2266
Administration turn						
PA-TA	33	13	39.39	20	60.61	0.2962
TA-PA	30	11	36.67	19	63.33	0.2005
Intellectual disability						
No	9	0	0.00	**9**	**100.0**	**0.0039**
Mild	31	16	51.61	15	48.39	1.0000
Severe	23	8	34.78	15	65.22	0.2100
Diagnosis						
AD	32	15	46.88	17	53.13	0.8601
NOS	22	6	27.27	**16**	**72.73**	**0.0525**

PA = paper activity; TA = touch activity
Age range: PS = preschoolers (4-6 years), CS = compulsory education schoolers (7-15 years), NCS = non-compulsory education schoolers (16-18 years), AU = adults (19-32 years).
Diagnosis: AD = autistic disorder, NOS = pervasive developmental disorder not otherwise specified.

Table 5
Logistic regression analysis on Picture-Picture pairing activity

Independent factors	OR	95% CI		p
		lower	upper	
Sex				
Males	1			
Females	0.18	0.03	1.07	0.059
Diagnosis				
AD	1			
NOS	3.17	0.87	11.55	0.081

OR = odd ratio; CI = confidence interval; p = level of statistical significance
Diagnosis: AD = autistic disorder, NOS = pervasive developmental disorder not otherwise specified.

TA support (61.9% *vs* 38.1%, p = 0.077), significant in males (65.5% *vs* 35.5%, p = 0.030), in compulsory education schoolers (88.9% *vs* 11.1%, p = 0.039) and in subject ts with typical intellectual functioning (100% *vs* 0%, p = 0.004). PDD-NOS subjects too show a preference towards TA support that just felt short of statistical significance (72.7% *vs* 27.3%, p = 0.052). In parallel, the remaining subgroups of subjects did not show a significant preference towards either PA or TA support. Interestingly, the sequence of treatment administration did not affect the preference towards TA support, chosen by 60.6% of the TA-PA subjects and by 63.3% of the PA-TA subjects (p > 0.20 for both).

The logistic regression, performed to determine which factors were independently associated to the preference towards TA support in the PPP activity, confirmed the role of sex and autism diagnosis in affecting TA preference, even if the corresponding p-levels just missed statistical significance (p = 0.059 and 0.081, respectively) *(Table 5)*.

Behavioural response

The MANOVA performed within each activity showed a significant effect of the support on the overall subject's behaviour in the CL and WPP activities, while no effect was observed in the VD activity. The MANOVA performed on each behaviour across activities pointed out significant increase due to TA support in non-collaborative acts (Uncooperativeness), Duration, Helps needed, and a decrease in Communication ability, while Stereotypies do not appear to be significantly affected by the support. Specifically, based on paired t test results, TA support appeared to significantly increase non-collaborative acts (Cohen's d_z = 0.42) and Helps needed (Cohen's d_z = 0.83) during CL activity, and Duration (Cohen's d_z = 1.12) during WPP activity (for statistical details, see *Table 6*).

The effect of activity support was not significantly affected by sex, age, autism diagnosis and intellectual disability.

DISCUSSION

Our study contributes to the evaluation of touch-screen technology as teaching support during cognitive-behavioural intervention for persons with ASD. We enrolled a large number of subjects representative of the population usually attending Italian ASD specialized local health units, that included both sexes, and belonged to the main ASD sub-categories as defined by DSM-IV, and to different levels of intellectual impairment. Finally, we used a crossover design to compensate the lack of a control group, and though this may still impair generalization of the results, it appears to improve the methodological approach in this research field.

The evaluation of multi-touch screen technology, including tabletop, should necessarily take into account the value of this device in supporting educational ac-

Table 6
Results of multivariate (MANOVA, first line and first column) and univariate (t test, body of the table) analyses on behaviors observed during activities provided on PA or TA support (overall group)

			VD			CL			WPP		
			PA	TA	Effect size	PA	TA	Effect size	PA	TA	Effect size
			mean ± SD	mean ± SD	d_z	mean ± SD	mean ± SD	d_z	mean ± SD	mean ± SD	d_z
	MANOVA										
	across activities	*across behaviors*	*W(1,61) = 0.8790*	*p = 0.1834*		***W(1,61) = 0.5179***	***p < 0.0001***		***W(1,61) = 0.3063***	***p < 0.0001***	
Uncooperativeness	***W(1,61) = 0.8358***	***p = 0.0137***	0.19 ±0.70 *t(62) = 0.0887*	0.20 ± 0.70[a] *p = 0.9296*	*0.01*	**0.29 ± 0.70** ***t(61) = 3.3281***	**0.75 ±1.20a** ***p = 0.0015****	***0.42***	0.26 ±0.72 *t(61) = 0.8763*	0.35 ± 0.92[a] *p = 0.3843*	*0.11*
Stereotypies	*W(1,61) = 0.9667*	*p = 0.5689*	2.17 ± 5.21 *t(62) = 0.4387*	2.35 ± 6.21 *p = 0.6624*	*0.06*	4.83 ± 9.43 *t(61) = 0.0758*	4.89 ± 11.25 *p = 0.9399*	*0.01*	2.13 ± 3.81 *t(61) = 1.2965*	3.05 ±6.74 *p = 0.1997*	*0.16*
Duration	***W(1,61) = 0.4185***	***p < 0.0001***	64.52 ± 36.33 *t(62) = 0.1357*	65.21 ± 41.55 *p = 0.8925*	*0.02*	187.5 ± 63.58 *t(61) = 1.8320*	208.8 ± 104.4 *p = 0.0718*	*0.23*	**61.26 ± 18.08** *t(61) = 9.0780*	**102.5 ± 37.06** ***p < 0.0001****	***1.15***
Helps needed	***W(1,61) = 0.5690***	***p < 0.0001***	1.75 ± 2.95 *t(62) = 0.9795*	2.05 ±2.92 p = 0.3311	*0.12*	**2.02 ± 3.52** ***t(61) = 6.5444***	**4.87 ± 5.41** ***p < 0.0001****	***0.83***	1.62 ± 2.56 *t(61) = 1.2921*	2.14 ± 3.51 *p = 0.2012*	*0.16*
Communication ability	***W(1,61) = 0.8762***	***p = 0.0489***	1.69 ± 2.11 *t(62) = 2.2901*	1.02 ± 1.48 *p = 0.0254*	*0.29*	6.23 ± 10.86 *t(61) = 1.5855*	4.23 ± 6.23 *p = 0.1180*	*0.20*	2.60 ± 4.39 *t(61) = 0.2663*	2.45 ± 3.63 *p = 0.7909*	*0.03*

VD = visual discrimination; CL = classification; WPP = word-picture pairing. PA = paper activity; TA = touch activity. Duration= total duration of the task from assignment up to completion. SD = standard deviation; MANOVA = multivariate analysis of variance; W = Wilks' lambda; t = t test statistics; p = significance level; * p < 0.05 and ** p < 0.01, with Bonferroni's correction. For more detail, see the Methods section.

tivities by a low-cost, shareable (home, school, ambulatory), and adaptable intervention strategy that may also be able to reduce stigma among peers. However, this advantage from a social and 'economic' point of view should parallel the advantage at the individual level in supporting activities and reducing challenging behaviours that are widely reported to affect completion of learning trials.

The use of technology for children on ASD is supported by the idea that these children have a natural affinity for technologies that can support learning and social interactions [6, 15, 45, 46]. In our study, when the subjects had to choose PA or TA to perform the picture-picture pairing activity, more than 60% of them chose TA, but the preference was significantly evident only in high functioning male subjects, and, as a trend, in individuals with a PDD-NOS diagnosis.

One further point assessed in the present study is whether in a ASD population sample TA elicits aspects of behaviour that can be considered positive for and/or coherent with the accomplishment of the task. We used duration of the activity as a proxy of the ability to fulfil the task, and oppositional and avoiding behaviours and helps needed to carry on the activities as a measure of the level of cooperation elicited by the support during the activity session. Our results show that TA negatively affects duration of WPP activity that is almost twofold with respect to PA. A lower compliance with TA support was also suggested by the increase of uncooperative behaviours and helps needed to fulfil the task during CL activity. Finally, present data suggest that the use of PA and TA in delivering activities is not influential on the number of stereotypies emitted. However, demographic and diagnostic characteristics did not appear to influence behavioural response to TA. This suggests that individual dimensional traits (i.e.: temperament, motivation, etc.), rather than categorical, could be more important in moderating the behaviours elicited by the two activity supports. Recently, it has been emphasized that skills and environment for which technology-based intervention has the potential to serve as support, as well as preference of both users and professionals, have to be taken into consideration [47, 48].

Communication, and in particular spontaneous communication, represents a domain of behavioural impairment that needs to be empowered in the majority of people on ASD. Indeed, results from the present study do not definitely support the facilitative role of TA showing, in same case, a negative effect on spontaneous communication. However, the TA procedure used in the present study appears insufficient to elicit a different quality of learning compared to PA. It is possible that the tasks on which the TA *vs* PA relative efficacy was assessed here are intrinsically weak in eliciting spontaneous communication. TA technology could be advantageously used to support other learning strategies such as collaborative learning [38, 46, 49], or in different activities such as leisure or social interaction [12, 31, 37]. Some studies, performed on the use of multi-touch tabletop in session of augmentative alternative communication (AAC) learning [31] or multiplayer activities [38, 49-51], appear to demonstrate that increase in social interaction is one of the main goals attained from interactive session around the tabletop. Furthermore, the role of rewards or visual strategy applied appears relevant in terms of child engagement. A recent study compared "mand" acquisition (following Applied Behavioural Analysis techniques "mand" is an operant that describes the ability to ask for what you want), in three preschool-aged males with ASD, across three different displays in two iPad AAC applications. Interestingly, the study evidenced that AAC display and design elements may influence "mand" acquisition, as preschoolers did not performed equally across different AAC displays and configurations, but also that these elements should be chosen taking into consideration individual propensity and learning characteristics [52].

Implications

Although provisional and based on a short-term evaluation, our results show that multi-touch screen tabletop is attractive, but only for selected subsets of participants. In addition, results do not confirm the hypothesis that touch screen presentation improves activity completion and behavioural performance for each individual with ASD, discouraging an indiscriminate use of these devices. The individual variability in response to CAT technology, confirmed in our study, may account for the inconsistency among results published in the scientific literature, besides the heterogeneity among aims, protocols, and CAT applications.

An important limitation of our study is the cross-sectional design that does not allow assessing differences in learning progression between activities presented on TA *vs* PA supports. Prospective long-term studies are required in order to evaluate the long-lasting effects of multi-touch screen use on preference of the subjects and on changes in their behavioural outcomes during learning session.

Author contribution

FB participated in the design and implementation of the study, performed the measurement, and helped to draft the manuscript; AV participated in the design of the study and interpretation of the data, and drafted the manuscript; FC participated in the design of the study, conceived and performed the statistical analysis, participated in the interpretation of the data, and drafted the manuscript; GMA conceived and supervised the study, participated in the interpretation of the data, and helped to draft the manuscript. FC and GMA act as equivalent co-senior authors. All authors read and approved the final manuscript.

Compliance with ethical standard

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and

its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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REFERENCES

1. Cardon T, Azuma T. Visual attending preferences in children with autism spectrum disorders: A comparison between live and video presentation modes. Res Autism Spectr Disord. 2012;6(3):1061-7.
2. Ganz JB, Boles MB, Goodwyn FD, Flores MM. Efficacy of handheld electronic visual supports to enhance vocabulary in children with ASD. Focus Autism Other Dev Disabl. 2014;29(1):3-12.
3. Bernard-Opitz V, Sriram N, Nakhoda-Sapuan S. Enhancing social problem solving in children with autism and normal children through computer-assisted instruction. J Autism Dev Disord. 2001;31(4):377-84.
4. Gillespie A, Best C, O'Neill B. Cognitive function and assistive technology for cognition: A systematic review. J Int Neuropsychol Soc. 2012;18(01):1-19.
5. Konstantinidis EI, Hitoglou-Antoniadou M, Luneski A, Bamidis PD, Nikolaidou MM, editors. Using affective avatars and rich multimedia content for education of children with autism. Proceedings of the 2nd International Conference on PErvasive Technologies Related to Assistive Environments; 2009. ACM; 2009.
6. Mineo BA, Ziegler W, Gill S, Salkin D. Engagement with electronic screen media among students with autism spectrum disorders. J Autism Dev Disord. 2009;39(1):172-87.
7. Erdödi L, Lajiness-O'Neill R, Schmitt TA. Learning curve analyses in neurodevelopmental disorders: are children with autism spectrum disorder truly visual learners? J Autism Dev Disord. 2013;43(4):880-90.
8. Trembath D, Vivanti G, Iacono T, Dissanayake C. Accurate or assumed: Visual learning in children with ASD. J Autism Dev Disord. 2015;45(10):3276-87.
9. McCarthy JW, Benigno JP, Broach J, Boster JB, Wright BM. Identification and drawing of early concepts in children with autism spectrum disorder and children without disability. Augment Altern Commun. 2018;34(2):155-65.
10. Bolte S, Golan O, Goodwin MS, Zwaigenbaum L. What can innovative technologies do for Autism Spectrum Disorders? Autism: the international journal of research and practice. 2010;14(3):155-9.
11. Palmen A, Didden R, Lang R. A systematic review of behavioral intervention research on adaptive skill building in high-functioning young adults with autism spectrum disorder. Res Autism Spectr Disord. 2012;6(2):602-17.
12. Parsons S, Yuill N, Brosnan M, Good J. Innovative technologies for autism: critical reflections on digital bubbles. J Assist Technol. 2015;9(2):116-21.
13. Ramdoss S, Machalicek W, Rispoli M, Mulloy A, Lang R, O'Reilly M. Computer-based interventions to improve social and emotional skills in individuals with autism spectrum disorders: a systematic review. Dev Neurorehabil. 2012;15(2):119-35.
14. Virnes M, Kärnä E, Vellonen V. Review of research on children with Autism Spectrum Disorder and the use of technology. JSET. 2015;30(1):13-27.
15. Ledbetter-Cho K, O'Reilly M, Lang R, Watkins L, Lim N. Meta-analysis of Tablet-Mediated Interventions for Teaching Academic Skills to Individuals with Autism. J Autism Dev Disord. 2018;48(9):3021-36.
16. Fletcher-Watson S. A targeted review of computer-assisted learning for people with autism spectrum disorder: Towards a consistent methodology. Review J Autism Dev Disord. 2014;1(2):87-100.
17. McCleery JP. Comment on Technology-Based Intervention Research for Individuals on the Autism Spectrum. J Autism Dev Disord. 2015;45(12):3832-5.
18. Odom SL, Thompson JL, Hedges S, Boyd BA, Dykstra JR, Duda MA, et al. Technology-Aided Interventions and Instruction for Adolescents with Autism Spectrum Disorder. J Autism Dev Disord. 2015;45(12):3805-19.
19. Colby KM. The rationale for computer-based treatment of language difficulties in nonspeaking autistic children. J Autism Child Schizophr. 1973;3(3):254-60.
20. Panyan MV. Computer technology for autistic students. J Autism Dev Disord. 1984;14(4):375-82.
21. Murray D, Aspinall A. Getting IT: Using information technology to empower people with communication difficulties. Jessica Kingsley Publishers; 2006.
22. Neely L, Rispoli M, Camargo S, Davis H, Boles MB. The effect of instructional use of an iPad® on challenging behavior and academic engagement for two students with autism. Res Autism Spectr Disord. 2013;7(4):509-16.
23. Muharib RC, Wood CL, Haughney KL. Effects of functional communication training using GoTalk NowTM iPad® application on challenging behavior of children with autism spectrum disorder. JSET. 2018;34(2):71-9.
24. O'Neill SJ, Smyth S, Smeaton A; O'Connor NE. Assistive technology: Understanding the needs and experiences of individuals with autism spectrum disorder and/or intellectual disability in Ireland and the UK. Assistive Technology. 2019; doi: 10.1080/10400435.2018.1535526
25. Knight V, McKissick BR, Saunders A. A review of technology-based interventions to teach academic skills to students with autism spectrum disorder. J Autism Dev Disord. 2013;43(11):2628-48.
26. Shipley-Benamou R, Lutzker JR, Taubman M. Teaching daily living skills to children with autism through instructional video modeling. J Posit Behav Interv. 2002;4(3):166-77.
27. Gentry T, Kriner R, Sima A, McDonough J, Wehman P. Reducing the need for personal supports among workers with autism using an iPod touch as an assistive technology: Delayed randomized control trial. J Autism Dev Disord. 2015;45(3):669-84.
28. Mesibov GB, Shea V. The TEACCH program in the era of evidence-based practice. J Autism Dev Disord. 2010;40(5):570-9.
29. Howard JS, Sparkman CR, Cohen HG, Green G, Stanislaw H. A comparison of intensive behavior analytic and eclectic treatments for young children with autism. Research in developmental disabilities. 2005;26(4):359-83.
30. Boucenna S, Narzisi A, Tilmont E, Muratori F, Pioggia G, Cohen D, et al. Interactive technologies for autistic chil-

dren: A review. Cognitive Computation. 2014;6(4):722-40.
31. Chien ME, Jheng CM, Lin NM, Tang HH, Taele P, Tseng WS, et al. iCAN: A tablet-based pedagogical system for improving communication skills of children with autism. Int J Hum-Comput St. 2015;73:79-90.
32. Kapp SK, Gillespie-Lynch K, Sherman LE, Hutman T. Deficit, difference, or both? Autism and neurodiversity. Developmental psychology. 2013;49(1):59-71.
33. Nguyen T, Duong T, Phung D, Venkatesh S. Affective, Linguistic and Topic Patterns in Online Autism Communities. In: Benatallah B, Bestavros A, Manolopoulos Y, Vakali A, Zhang Y, editors. Web Information Systems Engineering – WISE 2014. Lecture Notes in Computer Science. 8787. Cham: Springer; 2014. p. 474-8.
34. Grynszpan O, Weiss PL, Perez-Diaz F, Gal E. Innovative technology-based interventions for autism spectrum disorders: a meta-analysis. Autism: the international journal of research and practice. 2014;18(4):346-61.
35. Lee A, Lang R, Davenport K, Moore M, Rispoli M, van der Meer L, et al. Comparison of therapist implemented and iPad-assisted interventions for children with autism. Dev Neurorehabil. 2015;18(2):97-103.
36. Yakubova G, Taber-Doughty T. Brief report: learning via the electronic interactive whiteboard for two students with autism and a student with moderate intellectual disability? J Autism Dev Disord. 2013;43(6):1465-72.
37. Gal E, Lamash L, Bauminger-Zviely N, Zancanaro M, Weiss PL. Using Multitouch collaboration technology to enhance social interaction of children with high-functioning autism. Phys Occup Ther Pediatr. 2016;36(1):46-58.
38. Giusti L, Zancanaro M, Gal E, Weiss PLT. Dimensions of collaboration on a tabletop interface for children with autism spectrum disorder. In: ACM (Ed). Proceedings of the SIGCHI Conference on Human Factors in Computing Systems, 2011. p. 3295-304.
39. Stephenson J, Limbrick L. A review of the use of touchscreen mobile devices by people with developmental disabilities. J Autism Dev Disord. 2015;45(12):3777-91.
40. Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, et al. Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. J Autism Dev Disord. 1989;19(2):185-212.
41. Schopler E, Reichler RJ, Rochen Renner BR. The Childhood Autism Rating Scale for diagnostic screening and classification of autism. New York: Irvington; 1986.
42. Gilliam JE. Gilliam Autism Rating Scale (GARS). Austin: Pro-Ed; 1995.
43. Krug D, Arick J, Almond P. Autism Behavior Checklist – ABC. In: Krug DA AJ, Almond P, editor. Autism Screening Instrument for Educational Planning- ASIEP-2. Austin, Texas: PRO-ED; 1993.
44. Sparrow SS, Balla DA, Cicchetti DV, Harrison PL, Doll EA. Vineland adaptive behavior scales. Circle Pines, MN: American Guidance Service; 1984.
45. Holt S, Yuill N. Facilitating other-awareness in low-functioning children with autism and typically-developing preschoolers using dual-control technology. J Autism Dev Disord. 2014;44(1):236-48.
46. Yuill N. Going along with or taking along with: a cooperation continuum in autism? Frontiers in Psychology. 2014;5:1266.
47. Fletcher-Watson S. Evidence-based technology design and commercialisation: Recommendations derived from research in education and autism. TechTrends. 2015;59(1):84-8.
48. Fletcher-Watson S, Petrou A, Scott-Barrett J, Dicks P, Graham C, O'Hare A, et al. A trial of an iPad™ intervention targeting social communication skills in children with autism. Autism: the international journal of research and practice. 2016;20:771-82.
49. Battocchi A, Ben-Sasson A, Esposito G, Eynat G, Pianesi F, Tomasini D, Venuti P, Weiss P L, Zancanaro M. Collaborative puzzle game: a tabletop interface for fostering collaborative skills in children with autism spectrum disorders. J Assist Technol. 2010;4(1):4-13.
50. Crowell C, Mora-Guiard, J, Pares, N. Structuring collaboration: Multi-user full-body interaction environments for children with autism spectrum disorder. Res Autism Spectr Disord. 2019;58:96-110.
51. Winoto P, Tang. T. Training joint attention skills and facilitating proactive interactions in children with Autism Spectrum Disorder: A loosely coupled collaborative tabletop-based application in a Chinese special education classroom. JECR. 2019;57(1):32-57.
52. Gevarter C, O'Reilly MF, Rojeski L, Sammarco N, Sigafoos J, Lancioni GE, et al. Comparing acquisition of AAC-Based mands in three young children with autism spectrum disorder using iPad® applications with different display and design elements. J Autism Dev Disord. 2014;44(10):2464-74.

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Night work and quality of life. A study on the health of nurses

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Abstract

Background. Job quality and evaluation of workers' health have both medical and social important implications. We studied health-related quality of life (HRQL) in nurses who perform their activity in night shifts.

Methods. A cross-sectional study was conducted between October and November 2014. Nurses who attended night shift in the Siena Teaching Hospital (Azienda Ospedaliera Universitaria Senese – AOUS) were sampled using EpiInfo software (confidence interval 95%) and investigated using the SF-36 Questionnaire. Our results were compared with the Italian general population (Apolone, 1997). A Descriptive analysis was conducted. Wilcoxon test, Pearson coefficient, t-test, Wilcoxon signed-rank test and logistic regression were used for the statistical investigation.

Results. 197 questionnaires were analyzed. Females were 71.7%; mean age was 39.2 years (DS 8.6); smokers were 37.8%. Males scores were higher than those of females in all dimensions of physical and mental health ($p < 0.05$). The time taken to reach the place of work appeared to influence the dimension of General Health (coeff. -0.17); we found a worsening of 0.17 points of this dimension for every minute spent in travel. Men and nurses with more working years had a better score in Physical Pain dimension. AOUS nurses scored significantly ($p < 0.05$) less compared with the correspondent Italian general population in General Health, Energy-fatigue, Social functioning, Physical functioning and Bodily pain.

Conclusions. There is a significant relationship between night work and HRQL of nurses. The health profile of AOUS nurses' ranks below the values of the Italian general population in various dimensions.

Key words
- night work
- quality of life
- nurse

INTRODUCTION

The progressive flexibility of working hours in all market sectors has significantly changed the organization of labour and people's lifestyles. In most industrialized countries, working shifts involve about one-third of the population and one fifth also works at night. According to Eurostat data, in 2012 people aged 15-74 normally employed in night shifts in Italy were 7.4% of the population, compared with a European average of 6.5% [1, 2]. Shift work is often a specific and necessary condition for the provision of health services, especially in hospitals, wards, emergency services and critical areas where it is the only way to ensure continuous service and care of patients. The influence of work on the quality of life is not limited to income but also has a role in identity-building and provides opportunities for social relations. Work occupies a large part of people's lives in terms of time while offering satisfaction, self-realization and psychological as well as economic recompense.

Quantity and quality of work can be measured by indicators, such as unemployment (including long-lasting unemployment) and part-time work. Qualification of work may be evaluated using indicators like income and benefits (incidence of low wages), balance between work and free time (based on the average of hours worked) and occupational safety (incidence of accidents) [1]. The impact of work on quality of life and on workers' health is important from a medical and social

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viewpoint, besides having implications for the economic and psycho-physical well-being of the population. In Latin countries in general, and in Italy in particular, few studies have been conducted on this topic.

Several studies reported negative effects of shift work and night shifts in particular on health [3]. Various aspects have been investigated but, to our knowledge, only a study has investigated whether the time taken to reach the place of work may affect perceived health [4]. Different shift durations, contractual agreements, cultural approaches and lifestyles of different countries all determine significant distinctions in the management of working hours and in the personal, family and social impact on workers' lives.

As previously reported in the literature, shift work may cause sleep disorders, worsen the quality of life of workers and can impact negatively on health [5-9]. The severity of the shift work disorders correlates with the number of night shifts per year, the length of working time and the increase in age [10]. These disorders are related to changes in circadian rhythms, including sleep/wake cycles and fast/feeding cycles [11], which can cause insomnia, obesity, metabolic syndrome, diabetes mellitus [9, 12-14], depression [15], alter physiological arousal and impaired cognitive processes [16]. The literature analysis seems to highlight that people who worked continuously have more psychosomatic symptoms and less psychological well-being than those who did the fractioned journey [4]. In this study, we evaluate whether our data are in accordance with previous studies and whether the time taken to reach work can influence the scores of the 8 scales of SF36.

This study provides an opportunity to shed light on a condition of occupational risk (night work), often underestimated and considered a necessary stage in the occupational career by nurses and health administrations. It investigates the quality of life of nursing staff on night shifts in an Italian teaching hospital. In particular, the aims are: i) to assess the differences between the quality of life of nurses working at night and the quality of life of the general population; ii) to study how some characteristics of the population studied can influence the perceived health.

MATERIALS AND METHODS

Setting

A cross-sectional study design, including an analytical component, was adopted on a sampled population of nurses regularly working night shifts at the Azienda Ospedaliera Universitaria Senese – AOUS (Siena Teaching Hospital).

The Short Form Questionnaire (SF36) with some extra questions useful to detect socio-demographic information was adopted. The data were collected between October and November 2014 after obtaining authorization from the hospital health administration. The hospital units enrolled in the study were identified by consulting the database of the hospital nursing services administration, used for personnel management. To have better estimates we considered all the staff working in the hospital on August 28, 2014. We only excluded nurses who never or just sporadically worked at night.

The number of nurses working in the hospital was 946, divided into 37 units; among them, 586 were involved in night shifts.

Sample

In order to correctly represent the phenomenon that we intended to analyze, we determined the necessary size of the study population. The number of nurses necessary was 193, calculated using EpiInfo software (confidence interval 95%) and the following formula [17]:

$n = [1-(1-a)\ 1/d] \times [N-(d-1/2)]$.

Where n was sample size, a desired confidence interval (95%), d the expected frequency of return of the questionnaire (65%) and N the total number of shift-working nurses.

Questionnaire and data collection

To evaluate the nurses' self-perceived health we used the Italian version of SF36. SF36 was designed in the United States in the mid-eighties. It was successfully translated and adapted culturally in 1991 to countries participating in the International Quality of Life Assessment (IQOLA) project. It is a generic questionnaire on quality of life, composed of 36 items and eight scales: PF, Physical functioning; RP, Role limitation due to physical health problems; BP, Bodily pain; GH, General health perception; VT, Vitality; SF, Social functioning; RE, Role limitation due to personal or emotional problems; MH, Mental health. This instrument was designed to provide an age and gender-specific profile, useful to understand the differences in the physical and emotional status of members of the population on the basis of a point score [18].

The point score of each scale ranges from 0 to 100: a better quality of life earns a higher score. The scales PF, RP, BP, SF and RE define health as absence of limitations or disabilities. In these scales, the maximum score of 100 is given for no limitations or disabilities. The scales GH, VT and MH are bipolar and measure a broader range of positive and negative states of health. In these scales, an intermediate score is earned by subjects who do not report any limitation or disability, whereas a score of 100 is earned by subjects who report excellent health [19].

Besides the information requested by SF36 we also collected the following data: i) marital status: unmarried/married, married/living together, separated/divorced; ii) age; iii) partner also doing shift work: yes/no; iv) children: number and age; v) smoker: yes/no; vi) commuter: yes/no; vii) time taken to travel to work; viii) total years of service; ix) years of service involving shift work; x) years of service with the current hospital unit.

To administer the questionnaire we contacted all the Nursing Coordinators of the units involved in the study, providing information on the aim of the research. Anonymity was guaranteed by law and the data was only to be used for statistical and scientific purposes. The printed questionnaires consisted of two pages: i) an informative note and a section for socio-demographic data (page 1); ii) the questionnaire (SF36), to be filled directed by the nurses, anonymously, (pages 2 and 3, printed on both sides of the paper).

The Nursing Coordinator was asked to deliver the questionnaires to the nurses and to instruct them. The questionnaires were returned at different times. Many visits were necessary to remind the nurses to fill them in, and to complete collection, in order to minimize the chance of missing data. The number of questionnaires was distributed in proportion to the number of nurses in each unit.

The frequency distribution of travelers was calculated according to time taken, which was organized into five classes: up to 29 minutes (class 1) 37.6%; 30-59 minutes (class 2) 23.8%; 60-89 minutes (class 3) 8.1%; 90-120 minutes (class 4) 1% and more than 120 minutes (class 5) 0.5%. About a third of the nurses (28.9%) did not answer this question.

Data management

Each questionnaire had a tracking code to ensure the anonymity of the respondent. The completed questionnaires were processed and the data stored in a single database containing the demographic aspects and the results of the eight SF36 scales that had been previously calculated. Points were assigned to the eight scales of SF36 using the program ProfiSalute, developed by the Health Services Management Laboratories of the University of Siena. The program enabled to: i) enter data; ii) calculate point scores by summing the replies to the questions of each scale (raw point score); iii) convert of raw point scores of the scales to scores between 0 and 100 (converted scores).

Data analysis

The values obtained for each of the eight scales were entered in the appropriate field. Percentages, means, minimum and maximum value, medians and standard deviations were calculated for descriptive graphs and tables.

All socio-demographic variables (age, marital status, partner on shift work, travelling time, overall years of service, years of shift work and years of work in the same unit) were analysed against the eight scales of SF36 (dependent variables). Outcomes variables in which was assessed normality, using frequency distribution analysis and the formal test of Shapiro-Wilk, were studied with multiple linear regression. The final models of these scales were obtained with the back forward elimination method after it was previously assessed the role of the covariates which highlighted statistical differences ($p < 0.05$) in a simple linear regression. The unpaired t-test was used for comparing means.

Not normally distributed dependent variables were studied with Spearman's rho correlation coefficient which investigated the strength of the relationship between the ordinal variables and the scores of the 8 scales; Mann-Whitney test was used to compare medians for dichotomous covariates.

The t-test was used also to compare means of scales, after Shapiro-Wilk test assessment, with mean reference of the Italian population. Wilcoxon test was used to compare medians of scales having a non-normal distribution with the reference median value of the Italian population.

The data provided by the questionnaires was organised and processed with software Stata® SE, version 12.1 (StataCorp, College Station, Texas, USA). Significance was set at $p < 0.05$.

RESULTS

The total number of questionnaires distributed was 257 and 211 (82.1%) were returned. The number from which the scores of the various scales could be calculated was 197 (76.7%). In the study population, the percentage of females was 71.7% and the mean age was 39.2 years (SD 8.6 years). Most were married or living with a partner (61%), 32% were single and 7% were separated or divorced; 40% of nurses had a shift-working partner; 52.8% had no children, 23.4% had one, 20.3% had two and 3.5% had three or more children; 37.8% were smokers. 46.4% of the studied population usually travelled to work by car, taking from a minimum of 5 minutes to a maximum of 200 minutes. General health perception deteriorated with increasing travelling time: for every additional 2 hours of travel, this parameter declined by -19.2 points ($p = 0.027$).

As shown in *Table 1a*, total years of service ranged from minimum of 2 years to a maximum of 41 years; 43% of the sample had 0-10 years working experience,16.2% of the sample had 11-15 years of service and18.3% had 16-20 years of work.

Years in shift work ranged 0-10 for 45% of the nurses and 11-20 for 36% of them. For years of service in the current unit: 30% of the sample had been working in

Table 1a
Service in the current unit, shift work, total years of service by years and number of nurses

	Years	N. nurses (%)
Total years of service	0-10	85 (43.1)
	11-15	32 (16.2)
	16-20	36 (18.3)
	21-25	15 (7.6)
	26-30	20 (10.2)
	31-40	8 (4.1)
	41+	1 (0.5)
Shift work	0-10	88 (44.7)
	11-20	70 (35.5)
	21-25	17 (8.6)
	26-30	13 (6.6)
	31-40	8 (4.1)
	40+	1 (0.5)
Service in the current unit	<5	59 (29.9)
	5-10	73 (37.1)
	11-15	31 (15.7)
	16-20	16 (8.1)
	21-25	11 (5.6)
	26-30	6 (3.1)
	31-40	1 (0.5)

Table 1b
Scales of SF36 by item, mean, SD, IC 95%, median, val. min, val. max scores (sample nurses Azienda Ospedaliera Universitaria Senese – AOUS)

Scales	Items	Mean	SD	IC 95%		Median	Val. min	Val. max
PF	10	87.36	14.7	85.2	89.42	90	30	100
RP	4	68.78	25.3	63.8	73.75	75	0	100
BP	2	67.59	21.5	64.57	70.61	72	22	100
GH*	5	61.42	18.7	58.78	64.05	62	15	100
VT*	4	54.39	17.4	51.93	56.84	55	5	100
SF*	2	61.65	21.1	58.68	64.61	62.5	0	100
EL	3	66.84	37.8	61.51	72.15	100	0	100
MH	5	65.11	16.4	62.79	67.42	64	8	100

PF, Physical functioning; RP, Role limitation due to physical health problems; BP, Bodily pain; GH, General health perception; VT, Vitality; SF, Social functioning; RE, Role limitation due to personal or emotional problems; MH, Mental health. * normally distribuited.

the same unit for <5 years and 37% for 5-10 years. The point scores for the eight scales of SF36 are shown in *Table 1b*.

The GH scale, at the crude analysis, showed to be significantly and negatively influenced by travelling time, overall years of services, years of shift works, years of work in the same unit and age *(Table 2)*. However, at the multivariate analysis, only travelling time (p = 0.012; coeff. = -0.17), years of services (p = 0.002, coeff. = -0.56), and gender (p = 0.002; coeff. = 11.05) resulted significantly associated. Males score was 11.05 times higher than women.

In the VT scale, (vitality) which describes the subjective perception of physical and mental health, the children number (p = 0.035; coeff. = 2.82), the overall years of service (p = 0.017; coeff. = -0.34), and gender (p <0.001; coeff. =11.11) were significantly associated at the multivariate analysis.

In the SF scale, related to the interference between physical and emotional problems and social functioning, the multivariate analysis highlights a significant association with years of shift work (p = 0.007; coeff. = -0.63), years of work in the same unit (p = 0.008; coeff. = 0.72), and gender (p <0.001; coeff. = 11.95).

The PF scale measures the capacity for heavy physical work such as running, lifting weights or sporting activity. Significant differences (Spearman e Mann-Whitney) were found with male nurses (p = 0.0002) and nurses whose partners did shift work (p = 0.0341): these subjects achieved higher scores than their counterparts (female nurses and nurses whose partners did not do shift work). Regarding this scale, nurses with longer working experience (p <0.001; rho = -0.40), with many years' experience of shift work (p <0.001; rho = -0.40), longer service in the same unit (p <0.001; rho = -0.31), and older ages (p <0.001; rho = -0.33) had lower point scores.

The RP scale measures the limitations or disabilities that may prevent a person from working or performing usual activities. Males scored significantly higher (median 75 for females and 100 for males), indicating significantly fewer work-related physical health problems (p = 0.012).

The BP scale measures pain interference with normal activities. The results showed significant values for the following variables: marital status (p = 0.0018), gender (p = 0.0008), number of children (p = 0.0017), years of service (p <0.001), years of shift work (p <0.001), years of service in the same unit (p = 0.0052) and age (p < 0.001).

The EL scale assesses the presence/absence of interference with working activity due to the emotional condition. In our study it is associated (p = 0.0138) with more years of service in the same unit.

The MH scale measures different components of emotional health relating to skills and well-being. Males seemed to enjoy better mental health than females (median 64 for females and 72 for males) (p = 0.0188).

The means of the GH, VT and SF scales, having a normal distribution, when compared with the corresponding means of the Italian population, showed significant differences *(Table3a)*. The medians of the scales, PF and BP, not normally distributed, were significantly different from the corresponding Italian medians *(Table 3b)*.

A further comparison was performed in the study population, stratifying by age groups, compared to the national population.

Figure 1 shows the values of the eight scales for subjects of the different age groups. In the group 25-34 years significant differences were found for the scales: BP (p <0.001), GH (p <0.001), VT (p <0.001), SF (p <0.001), MH (p = 0.001). In the age group 35-44 years, significant differences in the PF (p < 0.001), BP (p < 0.001), GH (p = 0.045), VT (p <0.0139) and SF(p < 0.001) scales emerged.

In the age group 45-54 years, all scales showed significant differences. In the age group 55-64 years significant differences were only found for GH (p = 0.0094), VT (p = 0.0047) and SF (p <0.001).

DISCUSSION

The aim of the present study was to investigate the relation between night work and health status of nurses. More specifically, we looked for a relationship between socio-demographic variables and nurses' health. The

Table 2
Coefficient, CI 95% and P-value of crude and adjusted analysis of the covariates with the scales General health perception, Vitality and Social functioning

Crude analysis	General health perception				Vitality				Social functioning			
	Coeff	IC 95%		P	Coeff	IC 95%		P	Coeff	IC 95%		P
Children number	-1.62	-4.39	1.15	0.25	0.96	-1.62	3.55	0.46	0.37	-2.76	3.50	0.82
Travelling time	-0.16	-0.29	-0.18	**0.027**	0.05	-0.79	0.17	0.48	0.08	-0.07	0.23	0.29
Overall years of services	-0.51	-0.79	-0.22	**0.001**	-0.27	-0.55	0.003	0.52	-0.19	-0.52	0.15	0.27
Years of shift work	-0.51	-0.81	-0.20	**0.001**	-0.28	-0.57	0.02	0.051	-0.23	-0.58	0.12	0.19
Years of work in same unit	-0.49	-0.84	-0.13	**0.007**	-0.27	-0.61	0.06	0.11	0.12	-0.28	0.53	0.60
Age	-0.44	-0.74	-0.14	**0.004**	-0.16	-0.44	0.13	0.29	-0.01	-0.36	0.34	0.96
Crude analysis	**General health perception**				**Vitality**				**Social functioning**			
	Mean	**IC 95%**		**P**	**Mean**	**IC 95%**		**P**	**Mean**	**IC 95%**		**P**
Gender	-10.0	-15.77	-4.25	**0.0007**	-10.7	-16.03	-5.45	**0.0001**	-11.1	-17.55	-4.72	**0.0008**

Adjusted analysis	General health perception						
	Initial model				Final model		
	Coeff	IC 95%		P	Coeff	IC 95%	P
Children number	0.85	-2.69	3.86	0.73	–	–	–
Travelling time	-0.18	-0.31	-0.04	**0.01**	-0.17	-0.30 0.04	**0.012**
Overall years of services	-0.61	-1.95	0.73	0.37	-0.56	-0.90 0.22	**0.002**
Years of shift work	0.08	-1.25	1.40	0.91	–	–	–
Years of work in same unit	-0.21	-0.78	0.36	0.47	–	–	–
Age	0.10	-0.71	0.90	0.81	–	–	–
Gender	10.73	3.52	17.94	**<0.01**	11.05	4.16 17.94	**0.002**
Adjusted analysis	**Vitality**						
	Initial model				**Final model**		
	Coeff	**IC 95%**		**P**	**Coeff**	**IC 95%**	**P**
Children number	3.44	0.47	6.41	**0.02**	2.82	0.20 5.44	**0.035**
Travelling time	0.40	-0.08	0.16	0.53	–	–	–
Overall years of services	-0.65	-1.86	0.57	0.29	-0.34	-0.62 -0.63	**0.017**
Years of shift work	0.31	-0.89	1.52	0.61	–	–	–
Years of work in same unit	-0.14	-0.66	0.37	0.59	–	–	–
Age	-0.03	-0.76	0.69	0.93	–	–	–
Gender	10.44	3.91	16.98	**<0.01**	11.11	5.85 16.37	<0.001
Adjusted analysis	**Social functioning**						
	Initial model				**Final model**		
	Coeff	**IC 95%**		**P**	**Coeff**	**IC 95%**	**P**
Children number	1.69	-1.85	5.23	0.35	–	–	–
Travelling time	0.08	-0.07	0.23	0.30	–	–	–
Overall years of services	0.04	-1.41	1.49	0.96	–	–	–
Years of shift work	-0.82	-2.25	0.61	0.26	-0.63	-1.08 -0.17	**0.007**
Years of work in same unit	0.60	-0.02	1.22	0.06	0.72	0.19 1.26	**0.008**
Age	0.19	-0.68	1.05	0.67	–	–	–
Gender	12.84	5.06	20.62	**<0.001**	11.95	5.57 18.33	**<0.001**

Table 3a
Health scales of SF36 showing normal distribution: comparison mean of Italian population and sample

Scales	Mean Italian population	Mean sample AOUS	P	IC 95%	
GH	65.22	61.42	0.0049	58.78	64.05
VT	61.89	54.39	0.0001	51.93	56.84
SF	77.43	61.65	0.0001	58.68	64.62

Table 3b
Health scales of SF36 showing non-normal distribution: comparison median of Italian population and sample

Scales	Median Italian population	Median sample AOUS	P
PF	95	90	0.0033
RP	100	75	N.S.
BP	84	72	0.0001
EL	100	100	N.S.
MH	68	64	N.S.

AOUS: Azienda Ospedaliera Universitaria Senese.

results confirm that the nurses in our sample enjoyed poorer health than the Italian general population.

The percentage of questionnaires returned was in line with similar studies [20, 21] and the composition of our sample was similar in regards to gender and age [2, 4, 20]. With regard to marital status, the percentage was similar to that found by Montesinos *et al.* [4] with a large majority of married or de facto married nurses (61%) whereas the percentage of single persons was greater in our sample, with 32% versus 21.3%. The percentage of separated/divorced persons in our sample (6.5%) was lower than in other studies [4, 21] and higher than in the study of Soric *et al.* about Croatian nurses [22]. Soric *et al.* also found that older and unmarried nurses have lower scores on the scales of social interactions [22]. Otherwise, in our sample, the Social functioning scale was influenced by gender, years of shift work, and years of work in the same unit, but not by age and marital status.

The study by Dargahi *et al.* [2] showed that married nurses who do night shifts can be at higher risk of family tensions than unmarried nurses. The mechanism is probably related to changes in family routine and amount of time spent together [23]. In our study, we did not specifically investigate the presence of family tensions, but in accord with other studies [4, 20, 21, 23, 24], we found that the number of children has an impact on the VT scale; for each extra child, the Vitality scale increased by 2.82 points. The percentage of childless nurses was 52.8%: although this percentage is high, it is still lower than the 70.2% reported by Shu-Yu Tai *et al.* among nurses working in night shifts. This result is noteworthy because it suggests that shift work and night shifts could be factors that do not encourage maternity and paternity [23].

To our knowledge, travelling to work was only considered in one previous study [4], which examined whether travel was continuous or whether it involved a change in the mean of transport. A continuous journey had a negative influence on psychological well-being. Our results pointed out that time taken in travelling to work was significantly associated with the GH scale. In commuters (namely, workers spending more than 2 hours in total between the outward and return journey [25, 26]) this scale worsens -19.6 points for every additional 2 hours of travelling time.

With respect to total years of service, more than 40% of our sample was composed of nurses with 0-10 years of working experience which is similar to the mean length of service of other researchers [4, 27].

The demographic and occupational characteristics of our sample were similar to those of other studies conducted on the health of nurses using SF36; this is a major indication of the validity of our results. The socio-demographic variables of our sample correlated with the scores of the SF36 scales and confirmed the results of other studies [4, 20, 28]. In a sample of Greek nurses, Tountas *et al.* showed that men scored significantly higher than women on all dimensions of SF36. The gender differences found by Tountas *et al.* are in accordance with our results except for RE. In their sample, the mean scores for the eight scales were much lower than the reference data of the US population and many populations of European countries. Their results showed a health profile that, although lower than European reference data, was nevertheless higher than the results obtained by our study in all scales of the SF36 except PF [20].

The GH scale showed significant relations with almost all the socio-demographic variables, as in the study by Tountas *et al.* [20]. We observed an interesting relation relation between years of working experience and BP, namely reduced pain perception with increasing years of working life. The same result was recorded by Tountas *et al.* [20]. Pain perception studies are controversial regarding the relationship between age and pain. The experience of pain is subjective, changes with age and involves both cognitive processes and experience [29, 30].

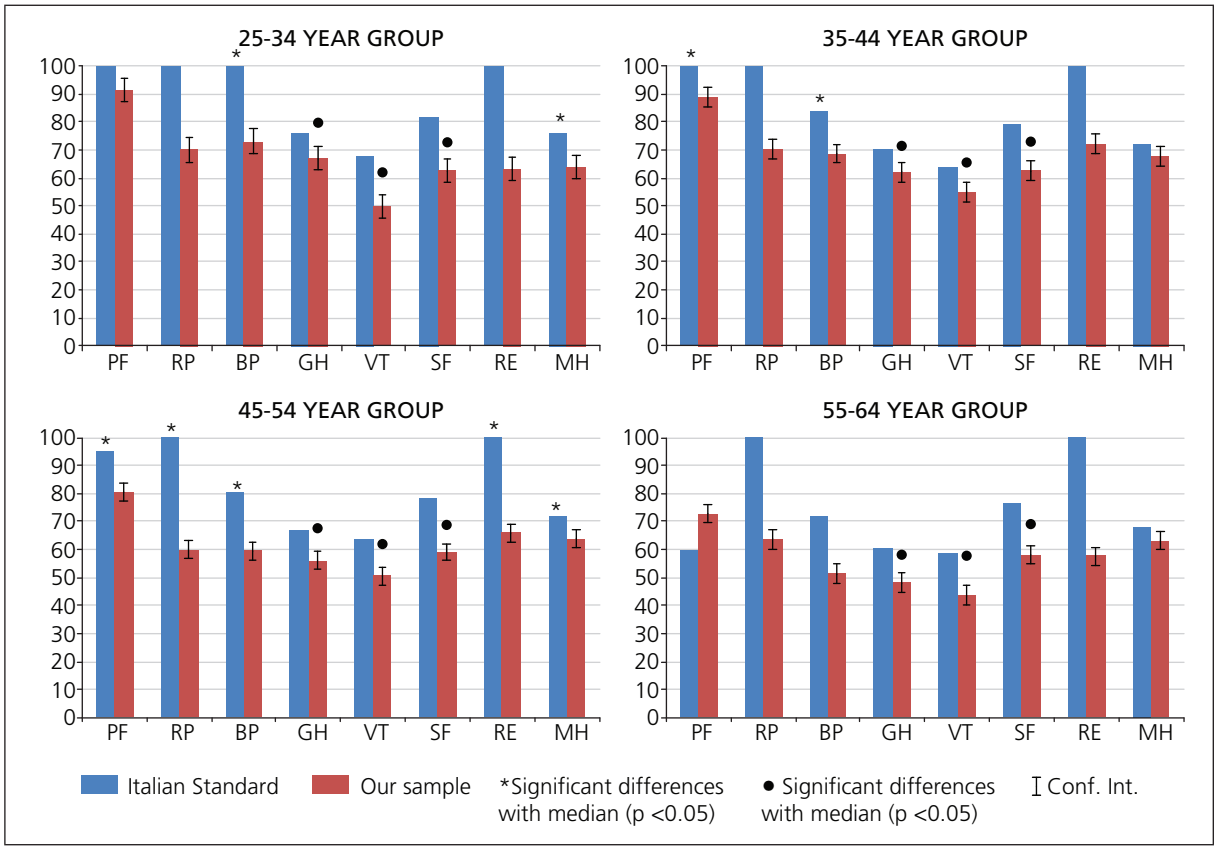

Figure 1
Comparison of our sample and Italian Standard stratified by age group.

The SF and VT scales, besides showing significant gender differences, were absolutely coherent with the results of other studies. Indeed, in a study involving nurses as well as administrative staff, doctors, technicians and auxiliary personnel, Tountas *et al.* concluded that nurses showed poorer health status in all SF36 scales than male nurses. Poor health and health-related quality of life reflect the difficulties they encounter on a daily basis and above all the difficulty of being a woman in a highly competitive and male-dominated field [20]. This hypothesis is also sustained by the lower score of nurses for SF.

The health profile of our sample was inferior to that of the Italian general population and also lower than it would be expected in a healthy population that undergoes medical check-ups of fitness for night work every two years.

The difference in female health profile in the scales RP, VT, SF, RE was also significant compared with the general population of Italy. These results are in line with the Italian study by Klersy *et al.* on dialysis centers that found results in line with means of the Italian population, except for a slightly lower score for SF [21].

Moreover, comparing the present results on health profile with those of Budge *et al.* [24], we notice that Siena nurses had lower health status than the New Zealand sample, although we also have to consider that means for the NZ population are higher than those of the Italian reference population.

We were unable to compare our results with those obtained by other studies on quality of life of nurses in Italy by means of questionnaires that assess health status. In fact, compared to the rich international literature on the negative effects of working at night, the literature for nurses is somewhat lacking. In addition, some studies have evaluated aspects that we did not investigate. For example, Kim *et al.* highlighted that working women involved in night shift work have lower Health-Related Quality of Life (HRQoL) profile compared to women working during the day [6].

As regards psychological disorders Tahghighi *et al.* did not find definitive evidence that shift work is associated with poorer psychological functioning in nurses. They highlight that the impact of shift work is dependent on several contextual and individual factor; also they suggest that more studies are needed in order to compare the psychological outcomes and resilience of nurse shift workers with no shift workers [31].

Giorgi *et al.* investigated any possible relationship between sleep disorders, burnout and job performance in a shift-work sample of nurses. They showed that female gender and personal burnout were significantly associated with impaired sleep quality. A significant negative association between patient-related burnout and job performance was found [32]. Puerta *et al.* reported that night shift nurses had significantly worse sleep quality (80.6% had bad perceived sleep quality) than nurses working mornings (41%) and evenings (44.4%) [7].

These results disagree with the findings of Palhares *et al.* where night shift work is not associated with impaired sleep quality when compared to other work shifts. They suggest that other factors, like age and lower education level, influence negatively sleep quality. In fact in the model adjusted for age, it was found that night-shift work is associated with severe worsening of sleep quality [33] in accordance with another study [34].

Also, Asaoka *et al.* investigated the effects on sleep in nurses working with rapid-rotation schedules. The results suggest that missing napping opportunities during night work, long night time working hours, and delay of circadian rhythms are associated with sleeping disorders [8].

LIMITS

The limits of our study include a reference population data ten years older than the study sample. This could have affected a correct interpretation of the results but still are the most updated data that we have available. Another limit is the higher than expected number of questionnaires that were not returned, that is almost 1/5 of the sample (18%). The reasons for this could be due to the laxity of the Nursing Coordinator in promoting participation. We noted that two of the units, both in the same surgical field and with the same number of nurses, returned very different percentages of questionnaires: 70% *versus* 20%. However, we also observed the same pattern in two other units with the same coordinator: 72% *versus* 46%. This suggests that the need to train the coordinator to make him understand the importance of his role in motivating the completion of the questionnaires.

Another limitation may be the absence of a control group to compare data with those of workers not working at night.

CONCLUSIONS

The study highlighted a possible relationship between night work and the health of nurses. We have found that commuting can adversely affect health; this variable seems to be underestimated and it is consistent with the only data we have found in the literature [4]. Therefore, further studies may be necessary to investigate this issue further.

Protection of the health of shift workers cannot be limited to the monetary compensation envisaged by collective labour contracts and health surveillance. It is absolutely necessary to redesign the organization of labour, recognizing the fundamental role of nurses in healthcare. In recent years, health authorities have attempted to save costs and improve efficiency as imposed by economic policies that emulate industrial models of productivity which have little, if anything, to do with health.

Nurses are trained to help improve the quality of life of patients, but their quality of life seems to be ignored. Quality of life is essential to improve quality of healthcare and has a direct influence on other aspects, such as health, absenteeism, accidents, productivity and loyalty to the organization [27]. The health profile of Siena University Hospital nurses showed lower scores than those of the general population of Italy, and these disadvantages are hardly compensated by additional pay for doing night shifts. The results of this study offer material for reflection on how to improve and promote the health of all healthcare professionals.

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Conflicts of interest

None to declare.

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REFERENCES

1. Eurostat Statistic Explained. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Main_Page.
2. Dargahi H. Radiology employees 'quality of work life in tehran university of medical sciences hospitals' radiology departments. Iran J Radiol. 2011;8(3):192-3.
3. Books C, Coody LC, Kauffman R, Abraham S. Night shift work and its health effects on nurses. Health Care Man. 2017;36(4):347-53.
4. Montesinos MJL. Psychosocial study about the consequences of work in hospital nurses as human resource management. Rev Lat-Am Enferm. 2013;21:61-70.
5. The National Institute for Occupational Safety and Health (NIOSH). Caruso C. Available from: www.cdc.gov/NIOSH/. 2012 (09/06/2015).
6. Kim W, Kim TH, Lee TH, Choi JW, Park EC. The impact of shift and night work on health related quality of life of working women: findings from the Korea Health Panel. Health Qual Life Outcomes. 2016;14(1):162.
7. Puerta Y, Garcia M, Heras E, Lopez-Herce J, Fernandez SN, Mencia S, et al. Sleep characteristics of the staff working in a pediatric intensive care unit based on a survey. Front Pediatr. 2017;5:288.
8. Asaoka S, Aritake S, Komada Y, Ozaki A, Odagiri Y, Inoue S, et al. Factors associated with shift work disorder in nurses working with rapid-rotation schedules in Japan: the nurses' sleep health project. Chronobiol Int. 2013;30(4):628-36.
9. Nena E, Katsaouni M, Steiropoulos P, Theodorou E, Constantinidis TC, Tripsianis G. Effect of shift work on sleep, health, and quality of life of health-care workers. Indian J Occup Environ Med. 2018;22(1):29-34.
10. Anbazhagan S, Ramesh N, Nisha C, Joseph B. Shift work disorder and related health problems among nurses working in a tertiary care hospital, Bangalore, South India. Indian J Occup Environ Med. 2016;20(1):35-8.

11. 11. Foster RG, Wulff K. The rhythm of rest and excess. Nat Neurosci. 2005;6(5):407-14.
12. Boivin DB, Tremblay GM, James FO. Working on atypical schedules. Sleep Med. 2007;8(6):578-89.
13. Guo Y, Liu Y, Huang X, Rong Y, He M, Wang Y, et al. The effects of shift work on sleeping quality, hypertension and diabetes in retired workers. PloS One. 2013;8(8):e71107.
14. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Nat Acad Sci USA. 2009;106(11):4453-8.
15. Scott AJ. Shift work and health. Prim care. 2000;27(4):1057-79.
16. Fisk AS, Tam SKE, Brown LA, Vyazovskiy VV, Bannerman DM, Peirson SN. Light and cognition. Roles for circadian rhythms, sleep, and arousal. Front Neurol. 2018;9:56.
17. Bottarelli B, Ostanello, F. Epidemiologia. Teoria ed esempi di medicina veterinaria. Milano: Ed. Agricole-New Business Media; 2011.
18. Quercioli C, Messina G, Barbini E, Carriero G, Fani M, Nante N. Importance of sociodemographic and morbidity aspects in measuring health-related quality of life: performances of three tools: comparison of three questionnaire scores. Eur J Health Econ. 2009;10(4):389-97.
19. Apolone G, Mosconi P, Ware J jr. Questionario sullo Stato di Salute SF-36 - Manuale d'uso e guida all'interpretazione dei risultati. Milano: Guerini e Associati Editore; 1997.
20. Tountas Y, Demakakos PT, Yfantopoulos Y, Aga J, Houliara L, Pavi E. The health related quality of life of the employees in the Greek hospitals: assessing how healthy are the health workers. Health Qual Life Outcomes. 2003;1:61.
21. Klersy C, Callegari A, Martinelli V, Vizzardi V, Navino C, Malberti F, et al. Burnout in health care providers of dialysis service in Northern Italy. A multicentre study. Nephrol Dial Transplant. 2007;22(8):2283-90.
22. Soric M, Golubic R, Milosevic M, Juras K, Mustajbegovic J. Shift work, quality of life and work ability among Croatian hospital nurses. Coll Antropol. 2013;37(2):379-84.
23. Shu-Yu Tai P-CL, Yao-Mei Chen, Hsin-Chia Hung, Chih-Hong Pan, Shung-Mei Pan, Chung-Yin Lee, Chia-Tsuan Huang, Ming-Tsang Wu. Effects of marital status and shift work on family function among registered nurses. Industrial Health. 2014;52(4):296-303.
24. Budge C, Carryer J, Wood S. Health correlates of autonomy, control and professional relationships in the nursing work environment. J Adv Nurs. 2003;42(3):260-8.
25. Italia - Regione Autonoma Friuli Venezia Giulia. Linee guida per l'applicazione negli ambienti di lavoro dellle norme a tutela della maternità. Dicembre 2009. Coordinamento SPSAL 25/2/10 – Illustrato e discusso Comitato Regionale di coordinamento 7/3/10.
26. Consiglio delle comunità europee. Bruxelles, 05.10.2000 COM(2000) 466 definitivo. Comunicazione della commissione sulle linee direttrici per la valutazione degli agenti chimici, fisici e biologici, nonchè dei processi industriali ritenuti pericolosi per la sicurezza o la salute delle lavoratrici gestanti, puerpere o in periodo di allattamento (direttiva 92/85/CEE del Consiglio).
27. Moradi T, Maghaminejad F, Azizi-Fini I. Quality of working life of nurses and its related factors. Nurs Midwif Studies. 2014;3(2): e19450.
28. Esquirol Y, Perret B, Ruidavets JB, Marquie JC, Dienne E, Niezborala M, et al. Shift work and cardiovascular risk factors: new knowledge from the past decade. Arch Cardiovasc Dis. 2011;104(12):636-68.
29. Raffaeli W, Montalti M, Nicolò E. L'infermieristica del dolore. Padova: Ed. Piccin; 2010.
30. Tiengo M. La percezione del dolore. ruolo della corteccia frontale. Ed. Springer-Verlag; 2001.
31. Tahghighi M, Rees CS, Brown JA, Breen LJ, Hegney D. What is the impact of shift work on the psychological functioning and resilience of nurses? An integrative review. J Adv Nurs. 2017;73(9):2065-83.
32. Giorgi F, Mattei A, Notarnicola I, Petrucci C, Lancia L. Can sleep quality and burnout affect the job performance of shift-work nurses? A hospital cross-sectional study. J Adv Nurs. 2018;74(3):698-708.
33. Palhares Vde C, Corrente JE, Matsubara BB. Association between sleep quality and quality of life in nursing professionals working rotating shifts. Rev Saude Publica. 2014;48(4):594-601.
34. Oliveira BHD YM, Cupertino APFB,, AL N. Relações entre padrão do sono, saúde percebida e variáveis socioeconômicas em uma amostra de idosos residentes na comunidade: Estudo PENSA. Cienc Saude Coletiva. 2010;15(3):851-60.

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ORIGINAL ARTICLES AND REVIEWS

Someone to rely on: the impact of social support on self-perceived health in Slovene elderly

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Abstract

Introduction. Aiming at highlighting the importance of social networking for health of elderly, the association between social support and self-perceived health (SPH) was assessed in Slovenia.

Methods. Data from three consecutive cross-sectional surveys on health behaviour in Slovenia (2008, 2012 and 2016), for 4599 elderly, aged 65-75 years, were pooled. Association between poor SPH (PSPH) and social support (taking into account also existence of extended personal social network (EPSN)), adjusted for confounders, was analysed by multiple logistic regression.

Results. The PSPH odds were statistically significantly higher in single/divorced/living in extramarital partnership/widowed, all without EPSN (OR = 2.99; p = 0.005), and single/divorced with EPSN (OR = 1.49; p = 0.053) in comparison to married with EPSN.

Conclusion. Irrespective of gender, socio-economic status or health-related factors, elderly with low level of social support were more likely to perceive their health as poor/very poor. Public health measures to reduce isolation of elderly should be included in the action plan in the frame of the Longevity strategy.

Key words

- social support
- self-perceived health
- cross-sectional study
- healthy aging

INTRODUCTION

Today, it is broadly accepted that human health is a multidimensional concept. Although not in the forefront of the biomedical model, social dimension is important dimension of health, since humans are social beings. Additionally, this dimension makes an important contribution to other dimensions of health. The level of social health, which refers to building relationships, that enhance well-being, can be expressed in terms of the size and/or quality of the individual's social network. It is the ability to interact effectively with other people and the social environment, to develop satisfying interpersonal relationships and to fulfil social roles. Primary components of social health include social role participation, social network quality, social integration and interpersonal communication [1-3].

Social networks represent the net of social relationships that each person maintains. They can have an intimate character, e.g. relationships within family or close friends, or more formal character, e.g. relationships in the workplace [4, 5]. The impact of social networks on patterns of morbidity and mortality has been the focus of interest for many researchers since the mid-1970s [4, 6-11]. The results of many studies suggest that without social networks, health in general declines [1, 8-11]. Social networks influence health through multiple pathways: behavioural, and material, psychological and physiological. Extensive social networks might increase the likelihood that individuals engage in health-promoting behaviours or refrain from health-damaging ones. Individuals with strong social networks experiencing health problems receive advice, service, or material help from others earlier and thus benefit from better medical and other care [1-14]. Social isolation has the most negative effect on health [15].

An extra quality in the social networking, in terms people in the network feel to have obligations one to another, is social support [16]. In theory, social support involves exchange of emotional support, and information and instrumental assistance [17], and is probably the central health-enhancing aspect of relationships [18]. In this concept, care, attention, and readiness to help other people in the network is included. Thus, it does not mean that someone's network necessarily provides a social support by itself – some of ties within a social network are supportive in terms of offering various sources of help and resources, and the others are not [19]. However, if the network is larger, there is a

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greater chance that at least some ties will be supportive.

Among the population groups in which the social dimension of health has an important role, are the elderly [20-22]. They have a high risk of social isolation because of the inevitable experience of loss of significant others and decrease in social activity [21]. Elderly more likely experience health problems, which increases their need for social support and companionship [15]. With the population aging, social isolation of the elderly becomes an important problem to tackle. Strategies for promoting healthy and active aging have become a major component of health policy in the developed countries [23].

So far, there have been only two studies in Slovenia in which the relationship between health and social networks of individuals was studied to the certain extent. The first study was the ecological study which explored the role of different social networks in providing support during illness, with special emphasis on changes in the provision of social support to the elderly. The results showed that in this population group, in comparison to other age groups, important source of social support, beside close family, represented extended family and neighbours [24]. The second study was focused on major determinants of poor self-rated health in elderly population in urban areas in Slovenia, Lithuania and UK. Living alone was significantly associated with poor self-rated health only in Slovenia [25]. However, none of these two studies provided sufficient information for planning of comprehensive health promotion activities in Slovenia.

In the present study we approached the task of highlighting the importance of social support for health of elderly more from a public health rather than sociological perspective. In July 2018, the Longevity strategy was adopted in Slovenia and action plans containing proposals of concrete solutions for the realisation of the guidelines are expected to follow. Because of the complexity of the topic, different sectors will be involved in the process – Ministry of Labour, Family, Social Affairs and Equal Opportunities, Ministry of Education, Science and Sport, Ministry of Health and Ministry of the Environment and Spatial Planning [26]. With the purpose to emphasize the importance of social support for healthy aging in the process of developing the action plan for Longevity strategy in Slovenia, the objective of the study was to assess the association of social support and self-perceived health (SPH) in Slovenian elderly.

METHODS

Study design

The study was designed as a pooled individual-level data study. Data were collected in three cross-sectional surveys on health behaviours in adult population aged 25-74 years, conducted in 2008, 2012 and 2016, based in the frame of the Countrywide Integrated Non-Communicable Disease Intervention (CINDI) programme [27] in Slovenia. The methodology of CINDI Health Monitor (CHM) survey (health interview survey) was used [28]. The CHM survey is based on a common core questionnaire. Questions are categorised as obligatory and optional and countries can add their local questions, based on the local situation and needs. After translation, the questionnaire was tested in local conditions [28]. A random representative sample of the population was provided by the national statistics office. The number of invited in 2008 was 15 963 while in 2012 and 2016 it was 16 000.

Study instrument

A self-administered postal questionnaire, based on the CHM Core Questionnaire [28] and slightly adapted for the needs of the population of Slovenia, was used as the instrument. In 2012 and 2016, an online questionnaire was also applied. To increase the response rate, media campaigns, incentives encouraging healthy behaviour, and up to two reminder letters, were used.

Observed outcome

In this study, SPH was assessed through the question: "How do you assess your present state of general health?" (1 = very good; 2 = good; 3 = fair; 4 = poor, 5 = very poor). As the observed outcome it was decided self-perceived health rated as poor or very poor. Consequently, a new variable, called "poor self-perceived health" (PSPH) was created (PSPH: 0 = no, 1 = yes).

Explanatory factor

In assessing social support of individuals, a new variable was created by cross-classification of two questions, asking about their marital status and extended personal social network (EPSN) (extended family and extra-familiar social network). Participants reported their marital status as 1 = single, 2 = married, 3 = extra-marital partnership, 4 = widowed or 5 = divorced. EPSN was assessed on the basis of question "How many friends do you have, which you can visit any time without an invitation?" in 2008 (1 = a lot, 2 = many, 3 = some, 4 = one, 5 = none) and "How many persons are close enough to you to rely on, when you have a serious personal problem?" in 2012 and 2016 (1 = none, 2=1-2, 3 = 3-5, 4= more than 5). Due to discrepancies in categories, the EPSN status was reduced only to existence of EPSN (EPSN: 0 = no, 1 = yes). EPSN = 0 covered those, who answered "none" in all 3 surveys and EPSN = 1 covered those, who selected any other answer ("a lot", "many", "some", "one" in 2008 and "1-2", "3-5", "more than 5" in 2012 and 2016). Afterwards, both marital status and EPSN were on the basis of results of preparatory analysis of our dataset and findings of previous research on marital status and health [29-32] combined into a complex variable, called "social support", with four categories (1 = married with EPSN, 2 = married without EPSN/widowed with EPSN/living in extramarital partnership with EPSN, 3 = single with EPSN/divorced with EPSN, 4 = single without EPSN/living in extramarital partnership without EPSN/widowed without EPSN/divorced without EPSN), for which it was assumed that the highest level of social support is provided within the first category, and the lowest within the last category.

Confounding factors

As potential confounders self-reported demographic and socio-economic data, data on stress and morbidity, as well as region of residency and year of the study

were included in the analysis. After harmonization of variables and their categories between all three cross-sectional studies following confounders were considered: gender (1 = female, 2 = male), educational level (1 = incomplete primary/primary, 2 = vocational, 3 = secondary, 4 = college, 5 = university/postgraduate), employment (1 = employed, 2 = retired), social class (1 = lower/labour, 2 = middle, 3=upper-middle/upper), admission to the hospital in the last year (1 = none, 2 = once, 3 = multiple times), health problems in the last 30 days - chest pain during physical activity, back pain, neck/shoulder pain, joint pain, coughing, legs swelling, allergies, constipation, headache, insomnia, feeling depressed, toothache and problems with urinating (1 = none, 2 =≥ 1), health status (number of diseases diagnosed by a physician) - hypertension, hypercholesterolemia, diabetes, myocardial infarction, angina pectoris, heart failure, cerebrovascular insult, spine illness, joint illness, chronic bronchitis, asthma, stomach ulcer, liver cirrhosis, depression and thyroid disorder (1 = none, 2 =≥ 1), perception of tension/stress/heavy pressure with at least minor difficulties in coping (1 = no, 2 = yes), region of residency (1 = Nova Gorica, 2 = Koper, 3 = Kranj, 4 = Ljubljana, 5 = Ravne na Koroškem, 6 = Novo mesto, 7 = Celje, 8 = Maribor, 9 = Murska Sobota) and year of the survey (1 = 2008, 2 = 2012, 3 = 2016).

Statistical analysis

The association between PSPH and social support as explanatory factor was assessed first by univariate analysis, using chi-square test. Afterwards it was adjusted for confounders by using binary multiple logistic regression analysis. Dummy variables were created for explanatory and confounding variables, applying the simple method (one group was assigned as the reference group). In all statistical tests, $p \leq 0.05$ was considered significant. SPSS for Windows Version 21.0 (SPSS Inc., Chicago, IL., USA) was used for analysis.

RESULTS

Description of the study group

There were 25 440 participants in the initial pooled data-base (2008: 7352, 2012: 9498, 2016: 8590), whose questionnaires were eligible for analysis (the response rate was 49.0% in 2008, 59.6% in 2012 and 54.9% in 2016). Among them 4599 participants were aged 65-74 years (2008: 1280, 2012: 1741, 2016: 1578) and were eligible for the present study. There was a slight predominance of women versus men (55.8% and 44.2%, respectively). Other study group characteristics are presented in the *Table 1*.

Results of univariate analysis

SPH was reported by 4524/4599 participants (98.4%), of which 3.8% reported very good SPH, 29.3% good SPH, 54.2% fair SPH, 10.7% poor SPH, and 2% reported very poor SPH. The prevalence of very good and good and fair SPH was higher in people with existing EPSN, whereas the prevalence of poor and very poor SPH was higher in those who were socially isolated *(Table 1)*.

After cross-matching of SPH with explanatory factor, 4417/4599 (96.0%) cases were included in the analysis *(Table 2)*. The prevalence of PSPH was increasing through the categories of social support variable and was three times as high in single or divorced or widowed or living in extramarital partnership, all without EPSN (33.3%), as in married with EPSN (11.2%). Prevalence of PSPH was 14.3% in married without EPSN or widowed with EPSN or living in extramarital partnership with EPSN and 15.4% in single with EPSN or divorced with EPSN. The differences were highly statistically significant ($p < 0.001$). The estimates of prevalence of PSPH according to different socio-economic and health-related characteristics are presented in the *Table 3*, along with the results of univariate statistical analysis.

Results of multiple logistic regression analysis

Complete data for multiple logistic regression analysis were available for 3328/4599 participants (72.4%). The results of the logistic regression model revealed a statistically significant association between PSPH and social support, also when this relationship was adjusted to several confounders. The OR for PSPH was increasing through the social support categories and was significant for single or divorced or living in extramarital partnership or widowed elderly, all without EPSN, and marginally significant for single or divorced elderly with EPSN, in comparison with married with EPSN. Detailed results are presented in the *Table 4*.

DISCUSSION

Major findings of the study

We investigated the association of social support and PSPH in the Slovenian elderly. The analysis revealed that, married elderly, who besides family also have EPSN, assess their health as very good, good or fair, while divorced or single or elderly living in extramarital partnership or widowed elderly, all without EPSN, rate their health as poor or very poor. It seems that single and divorced elderly with EPSN are also more likely to rate their health as poor in comparison with married with EPSN, but the difference is marginally significant. The difference was not statistically significant for married without EPSN, widowed with EPSN or elderly living in an extramarital partnership with EPSN compared to married with EPSN. The survey question in the present study was designed in a way which allowed us to identify those EPSNs, which are perceived by the participants as supportive. SPH was used as an outcome because it is one of the most commonly used measures of perceived overall health. It is easily available and reliable and it is also recommended to use for health monitoring by the European Union Commission and the WHO [33, 34].

Comparison of the results to the results of similar studies

The findings are consistent with previous studies that have proved the importance of social networks in determining SPH among older adults. Similar to our findings, White et al demonstrated adequate emotional support is associated with better self-reported health status in later life [35]. Elderly face a number of chal-

Table 1
Characteristics of participants taking part in the study of the impact of social support on self-perceived health in elderly aged 65-75; pooled individual level data from three cross-sectional studies in Slovenia 2008-2016

Characteristic	Category	N (%)
SPH	Very good	170 (3.8)
	Good	1326 (29.3)
	Fair	2454 (54.2)
	Poor	483 (10.7)
	Very poor	91 (2.0)
PSPH	Yes	574 (12.7)
	No	3950 (87.3)
Social support	Married with EPSN	2964 (66.2)
	Married without EPSN/widowed with EPSN/living in extramarital partnership with EPSN	1046 (23.4)
	Single with EPSN/divorced with EPSN	395 (8.8)
	Single without EPSN/living in extramarital partnership without EPSN/widowed without EPSN/divorced without EPSN	74 (1.7)
Gender	Men	2035 (44.2)
	Women	2564 (55.8)
Educational level	Incomplete primary/primary	1400 (30.8)
	Vocational	1018 (22.4)
	Secondary	1273 (28.0)
	College	439 (9.7)
	University/postgraduate	412 (9.1)
Employment	Employed	135 (3.0)
	Retired	4395 (97.0)
Social class	Lower/labour	1597 (38.0)
	Middle	2218 (52.8)
	Upper-middle/upper	389 (9.3)
Admission to hospital in the last year	No	3562 (81.0)
	Once	601 (13.7)
	Multiple times	233 (5.3)
Health problems in the last 30 days	None	657 (14.9)
	≥ 1	3755 (85.1)
Number of health problems*	None	761 (16.5)
	≥ 1	3583 (77.9)
Perception of stress with coping difficulties	No	3737 (86.4)
	Yes	586 (13.6)
Region	Nova Gorica	228 (5.0)
	Koper	331 (7.2)
	Kranj	501 (10.9)
	Ljubljana	1339 (29.1)
	Ravne	175 (3.8)
	Novo mesto	309 (6.7)
	Celje	690 (15.0)
	Maribor	734 (16.0)
	Murska Sobota	292 (6.3)
Year	2008	1280 (27.8)
	2012	1741 (37.9)
	2016	1578 (34.3)

SPH = self-perceived health; PSPH = poor self-perceived health; EPSN = extended personal social network (extended family + extra-familiar social network); * = confirmed by a physician.

Table 2
Estimates of prevalence of self-perceived health (SPH) within categories of social support in elderly aged 65-75; pooled individual level data from three cross-sectional studies in Slovenia 2008-2016

		SPH N (%)					
		Very good	Good	Fair	Poor	Very poor	Total
Social support	Married with EPSN	113 (3.9)	909 (31.1)	1574 (53.8)	289 (9.9)	40 (1.4)	2925 (100)
	Married without EPSN/widowed with EPSN/ living in extramarital partnership with EPSN	27 (2.6)	254 (24.7)	602 (58.4)	116 (11.3)	31 (3.0)	1030 (100)
	Single with EPSN/divorced with EPSN	27 (6.9)	123 (31.5)	180 (46.2)	52 (13.3)	8 (2.1)	390 (100)
	Single without EPSN/living in extramarital partnership without EPSN/widowed without EPSN/ divorced without EPSN	0 (0.0)	13 (18.1)	35 (48.6)	16 (22.2)	8 (11.1)	72 (100)
	Total	167	1299	2391	473	87	4417

EPSN = extended personal social network (extended family + extra-familiar social network).

lenges to remain socially connected. Life changes, such as retirement and loss of a spouse (widowhood), may lead to a loss of social roles and possible social isolation [15]. Marriage is one of the most fundamental and intimate ties among people. Grundy et al showed that those in long-term marriages had lower odds for chronic illness and lower mortality, which was especially true for older men [36]. Those who are not married, whether single, separated, widowed, or divorced, experience higher mortality rates than married people [13, 37]. A meta-analysis of studies of marital status and mortality in elderly age groups reported mortality risks for the widowed and never-married both about 10% higher than for the married [38]. Close friends are another important source of social support. But number of friends doesn't necessarily reflect the amount of support of an individual [13]. Our study incorporated close family as well as extended network of friends in the analysis, which are the most common sources of social support of individuals.

Limitations and strengths of the study

We are aware that the present study has some limitations. Firstly, CHMS is a cross-sectional dataset and any conclusions about causality drawn from the data are limited. A longitudinal data set would allow analyses of the relationship between social network and SPH over time. Secondly, because of collecting data through a self-administered self-assessment questionnaire, one may argue that the resulting data might be biased. However, these limitations present themselves in many surveys and the authors believe they did not affect the study findings to a greater extent [39, 40]. Next, because of the questionnaire changing over time, there were some issues with extracting the data on the same subjects from three different surveys. The wording in two questions assessing EPSN was quite different, but the context was very similar. In 2012 and 2016 the question is phrased in a way to address close family network and also extended family and friends' network. Since there is already a question about close family network in the questionnaire, we assumed participants were assessing their EPSNs here. The question should be rephrased in the future surveys. Next, we did not have any information on whether participants are living together with the people they identified as family members and this should be included in future research. Next, in assessing employment status, we removed those, who answered "unemployed", since adults in Slovenia aged 65 years and over are mostly retired, very few are still working, but there is no explanation, other than misunderstanding the question, why their status would be "unemployed". Next, some overlaps in participants across the surveys in three different years might be possible. However, only about 6% of adult population, aged 25-75 years, was invited to participate in each survey. The chance that the same person was included in all studies is therefore minute. Finally, one can argue that the possible interactions between different factors included in the multivariate model were not explored in details. However, a more detailed analysis was beyond the scope of this study.

On the other side the study has some important strengths. The most important is that to assess social support, a complex indicator was used. Considering both familiar and extended social ties, this is a special feature of the present study and it is what distinguishes it from other similar studies. Hence, present study contributes to understanding importance of social support on health in the later life in Slovenia, as well as in countries with similar socio-economic conditions and transition problems in the region. Additionally, in comparison to other two previously mentioned studies on the topic in Slovenia, the present study was performed on a large, nationally representative population-based data.

Importance of the study for public health

The results of the study are directly applicable in public health in Slovenia. First important information is that in the observed population the observed phenomenon was in the last decade rather stable. Next important information is that in the Novo mesto, Celje and Maribor regions the odds for perception of SPH as poor/very poor are significantly higher than in the reference region. This means there are additional risk factors

Table 3
Estimates of prevalence of poor self-perceived health (PSPH) within categories of social support and selected socio-economic and health-related factors in a study of the impact of social support on self-perceived health in elderly aged 65-75; pooled individual level data from three cross-sectional studies in Slovenia 2008-2016

Risk factor	Category	N_{PSPH}/N_{cat} (%)	p
Gender	Women	342/2524 (13.5)	0.050
	Men	232/2000 (11.6)	
Educational level	Incomplete primary/primary	280/1378 (20.3)	< 0.001
	Vocational	110/1004 (11.0)	
	Secondary	117/1249 (9.4)	
	College	40/433 (9.2)	
	University/postgraduate	16/406 (3.9)	
Employment	Employed	14/132 (10.6)	0.495
	Retired	545/4324 (12.6)	
Social class	Lower/labour	314/1578 (19.9)	< 0.001
	Middle	191/2180 (8.8)	
	Upper-middle/upper	12/383 (3.1)	
Admission to hospital in the last year	No	341/3509 (9.7)	< 0.001
	Once	111/590 (18.8)	
	Multiple times	90/230 (39.1)	
Health problems in the last 30 days	None	37/616 (6.0)	< 0.001
	≥ 1	505/3724 (13.6)	
Number of health problems*	None	48/712 (6.7)	< 0.001
	≥ 1	492/3560 (13.8)	
Perception of stress with coping difficulties	No	321/3684 (8.7)	< 0.001
	Yes	213/578 (36.9)	
Region	Nova Gorica	29/226 (12.8)	< 0.001
	Koper	33/329 (10.0)	
	Kranj	45/492 (9.1)	
	Ljubljana	122/1309 (9.3)	
	Ravne	23/174 (13.2)	
	Novo mesto	51/302 (16.9)	
	Celje	116/682 (17.0)	
	Maribor	108/720 (15.0)	
	Murska Sobota	47/290 (16.2)	
Year	2008	189/1267 (14.9)	0.009
	2012	216/1728 (12.5)	
	2016	169/1529 (11.1)	

EPSN = extended personal social network (extended family + extra-familiar social network); * = confirmed by a physician.

in these regions which need to be studied. Our findings also have important implications for clinical practice. Elderly who often feel under a lot of pressure and have difficulties in coping with stress represent a high risk group. Physicians, who often treat mental health problems like anxiety and depression with medications, should be aware of the importance of social health of their elderly patients. This holds for patients with chronic conditions, or patients being discharged from the hospital, as they have significantly higher odds of rating their health as poor in the present study. Finally, the findings of this study could be also important for health care personnel taking care of patients in need of palliative care [41].

Possibilities for future studying of the issue

Despite the important contribution of this study, more research is needed to specify the underlining characteristics of social networks affecting health in the elderly in Slovenia. Firstly, additional more in-depth analysis should be conducted in terms of stratified analysis to investigate the effect of each factor across the strata

Table 4
Results of multiple logistic regression analysis of the association between poor self-perceived health (PSPH) and social support in a study of the impact of social support on self-perceived health in elderly aged 65-75; pooled individual level data from three cross-sectional studies in Slovenia 2008-2016

Risk factor	Category	OR (95% CI for OR)	p
Social support	Married with EPSN	1.00	
	Married without EPSN/widowed with EPSN/living in extramarital partnership with EPSN	1.19 (0.89-1.58)	0.235
	Single with EPSN/divorced with EPSN	1.49 (0.99-2.22)	0.053
	Single without EPSN/living in extramarital partnership without EPSN/widowed without EPSN/divorced without EPSN	2.99 (1.39-6.43)	0.005
Gender	Women	1.00	
	Men	1.16 (0.90-1.50)	0.245
Educational level	University/postgraduate	1.00	
	Incomplete primary/primary	2.76 (1.25-6.08)	0.012
	Vocational	1.72 (0.78-3.79)	0.176
	Secondary	1.75 (0.81-3.76)	0.153
	College	2.00 (0.89-4.50)	0.096
Employment	Employed	1.00	
	Retired	1.32 (0.67-2.60)	0.422
Social class	Upper-middle/upper	1.00	
	Lower/labour	4.07 (1.85-8.94)	< 0.001
	Middle	2.10 (1.00-4.44)	0.052
Admission to hospital in the last year	No	1.00	
	Once	1.94 (1.44-2.61)	< 0.001
	Multiple times	6.05 (4.18-8.77)	< 0.001
Health problems in the last 30 days	None	1.00	
	≥1	1.87 (1.18-2.97)	0.008
Number of health problems*	None	1.00	
	≥1	1.65 (1.08-2.51)	0.020
Perception of stress with coping difficulties	No	1.00	
	Yes	4.84 (3.73-6.28)	< 0.001
Region	Kranj	1.00	
	Nova Gorica	1.38 (0.71-2.67)	0.343
	Koper	1.14 (0.61-2.12)	0.681
	Ljubljana	1.64 (0.82-3.28)	0.158
	Ravne	1.74 (0.96-3.16)	0.068
	Novo mesto	2.02 (1.23-3.31)	0.006
	Celje	2.06 (1.25-3.38)	0.004
	Maribor	2.02 (1.13-3.60)	0.017
	Murska Sobota	1.64 (0.82-3.28)	0.158
Year	2012	1.00	
	2008	1.25 (0.95-1.66)	0.115
	2016	1.18 (0.88-1.58)	0.278

EPSN = extended personal social network (extended family + extra-familiar social network); * = confirmed by a physician.

of each other factor, and in the case of existing interactions, it would be necessary to include those interaction effects in the multivariate model to test the possible interplay of selected variables with the variable "social support". Adding interaction terms to a simple additive regression model could greatly expand understanding of the relationships among variables, allow more hypotheses to be tested and, provide more effective information for policy makers as of the present work. Next, as previous studies have shown that both struc-

tural (number, density and diversity of social ties) and functional (quality of social ties – providing emotional, financial and informational support) dimension of social relations are linked to health [35], future research should focus on investigating the quality of existing social networks in the elderly in Slovenia and not just quantity of social ties. Special instruments should be used for this purpose, e.g. the Multidimensional Scale of Perceived Social Support (MSPSS) [42, 43]. Another important research area is the obstacles for the elderly for a satisfactory social activity and how to tackle them. Our study shows that 1.7% of elderly in Slovenia have no close ties among either relatives or nonrelatives. The reasons for social isolation must be determined and targeted with specific public health interventions. For future research and for studying trends, it is essential not to alter the questionnaires significantly, since it is not possible to compare results. Further studies are required to determine the causality of the association between social support and SPH.

CONCLUSIONS

Strong evidence regarding association between social support and SPH exist and our study contributes to the body of evidence. The present study confirms that social support in the elderly on an individual level is an important contributor to healthy aging. As the population in Slovenia is aging, this should be kept in mind when planning public health strategies and action plans to promote healthy aging. Unmarried elderly with no EPSN are especially at risk and tackling social isolation of the elderly with the identified risk factors should be high on the list of political priorities.

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Ethical approval

The research protocol was approved for the CINDI Health Monitor surveys by the Ethical Committee of the Republic of Slovenia.

Conflict of interest statement

The authors declare no conflicts of interest.

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REFERENCES

1. Hjelm JR. The dimensions of health: conceptual models. Sudbury, MA: Jones and Bartlett; 2010.
2. Hales D. An invitation to health. Belmont, CA: Wadsworth Cengage Learning; 2009.
3. Hahn EA, DeVellis RF, Bode RK, Garcia SF, Castel LD, Eisen SV. Measuring social health in the patient-reported outcomes measurement information system (PROMIS): item bank development and testing. Qual Life Res. 2010;19(7):1035-44. doi: 10.1007/s11136-010-9654-0
4. Seeman TE. Social ties and health: the benefits of social integration. Ann Epidemiol. 1996;6(5):442-51. doi: 10.1016/S1047-2797(96)00095-6
5. Bugental DB. Acquisition of the algorithms of social life: a domain-based approach. Psychol Bull. 2000;126(2):187-219. doi: 10.1037//0033-2909.126.2.187
6. Berkman LF. Social support, social networks, social cohesion and health. Soc Work Health Care. 2008;31(2):3-14. doi: 10.1300/J010v31n02_02
7. Helweg-Larsen M, Kjøller M, Thoning H. Do age and social relations moderate the relationship between self-rated health and mortality among adult Danes? Soc Sci Med. 2003;57(7):1237-47. doi: 10.1016/S0277-9536(02)00504-X
8. Nummela O, Sulander T, Karisto A, Uutela A. Self-rated health and social capital among aging people across the urban-rural dimension. Int J Behav Med. 2009;16(2):189-94. doi: 10.1007/s12529-008-9027-z
9. Kawachi I, Kennedy BP, Glass R. Social capital and self-rated health: a contextual analysis. Am J Public Health. 1999;89(8):1187-93. doi: 10.2105/AJPH.89.8.1187
10. Subramanian SV, Kim DJ, Kawachi I. Social trust and self-rated health in US communities: a multilevel analysis. J Urban Heal. 2002;79(Suppl. 1):S21-34. doi: 10.1093/jurban/79.suppl_1.S21
11. Waverijn G, Wolfe MK, Mohnen S, Rijken M, Spreeuwenberg P, Groenewegen P. A prospective analysis of the effect of neighborhood and individual social capital on changes in self-rated health of people with chronic illness. BMC Public Health. 2014;14:675. doi: 10.1186/1471-2458-14-675
12. Djomba JK, Zaletel-Kragelj L. A methodological approach to the analysis of egocentric social networks in public health research: a practical example. Zdr Varst. 2016;55(4):256-63. doi: 10.1515/sjph-2016-0035
13. Berkman LF. Assessing the physical health effects of social networks and social support. Annu Rev Public Health. 1984;5:513-32. doi: 10.1146/annurev.pu.05.050184.002213
14. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. Soc Sci Med. 2000;51(6):843-57. doi: 10.1016/S0277-9536(00)00065-4
15. Cornwell EY, Waite LJ. Social disconnectedness, perceived isolation, and health among older adults. J Health Soc Behav. 2009;50(1):31-48. doi: 10.1177/002214650905000103
16. Donev D, Pavlekovic G, Zaletel Kragelj L. Social networks and social support in health promotion programmes. In: Donev D, Pavlekovic G, Zaletel Kragelj L (Eds). Health promotion and disease prevention: a handbook for teachers, researchers, health professionals and decision makers: stability pact for South Eastern Europe. Lage: Hans Jacobs publishing company; 2007. pp. 125-36.
17. Ahrens W, Pigeot I (Eds). Handbook of epidemiology. New York: Springer-Verlag New York; 2005.
18. House JS. Work, stress and social support. Reading, MA: Addison-Wesley; 1981.
19. Fillit H, Rockwood K, Woodhouse KW. Brocklehurst's textbook of geriatric medicine and gerontology. Philadelphia: Saunders; 2010.
20. Barnes M, Blom A, Cox K, Lessof C. The social exclusion of older people: evidence from the first wave of the English Longitudinal Study of Ageing (ELSA): final report. London: Office of the Deputy Prime Minister; 2006.

21. Victor C, Scambler S, Bond J, Bowling A. Loneliness, social isolation and living alone in later life. Rev Clin Gerontol. 2000;10(4):407-17. doi: 10.1017/S0959259800104101
22. Berkman LF. The role of social relations in health promotion. Psychosom Med. 1995;57(3):245-54. doi: 10.1097/00006842-199505000-00006
23. Hawton A, Green C, Dickens AP, Richards SH, Taylor RS, Edwards R, et al. The impact of social isolation on the health status and health-related quality of life of older people. Qual Life Res. 2011;20(1):57-67. doi: 10.1007/s11136-010-9717-2
24. Pahor M, Hlebec V. Socialna omrežja in zdravje: spremembe v Sloveniji. Zdr Varst. 2006;45(4):175-185.
25. Stanojevic Jerkovic O, Sauliune S, Šumskas L, Birt CA, Kersnik J. Determinants of self-rated health in elderly populations in urban areas in Slovenia, Lithuania and UK: findings of the EURO-URHIS 2 survey. Eur J Public Health. 2017;27(Suppl. 2):74-9. doi: 10.1093/eurpub/ckv097
26. Government of the Republic of Slovenia. Longevity strategy in Slovenia. 2017. Available from: www.vlada.si/teme_in_projekti/strategija_dolgozive_druzbe/.
27. World Health Organization. Protocol and Guidelines: Countrywide Integrated Noncommunicable Diseases Intervention (CINDI) Programme. Copenhagen: WHO Regional Office for Europe; 1995.
28. Prättälä R, Helasoja V, Laaksonen M, Laatikainen T, Nikander P, Puska P. Cindi Health Monitor. Proposal for practical guidelines. Publications of the National Public Health Institute. Helsinki: WHO Regional Office for Europe; 2001.
29. Brown SL, Kawamura S. Relationship quality among cohabitors and marrieds in older adulthood. Soc Sci Res. 2010;39(5):777-86. doi:10.1016/j.ssresearch.2010.04.010
30. Noel-Miller CM. Partner caregiving in older cohabiting couples. J Gerontol B Psychol Sci Soc Sci. 2011;66B(3):341-53. doi:10.1093/geronb/gbr027
31. Robards J, Evandrou M, Falkingham J, Vlachantoni A. Marital status, health and mortality. Maturitas. 2012;73(4):295-9. doi:10.1016/j.maturitas.2012.08.007
32. Brown SL, Wright MR. Marriage, cohabitation, and divorce in later life. Innov Aging. 2017;1(2):1-11. doi:10.1093/geroni/igx015
33. Mackenbach JP, Van Den Bos J, Joung IMA, Van De Mheen H, Stronks K. The determinants of excellent health: different from the determinants of ill-health? Int J Epidemiol. 1994;23(6):1273-81. doi: 10.1093/ije/23.6.1273
34. Manderbacka K. Examining what self-rated health question is understood to mean by respondents. Scand J Public Health. 1998;26(2):145-53. doi: 10.1177/14034948980260020301
35. White AM, Philogene S, Fine, L, Sinha S. Social support and self-reported health status of older adults in the United States. Am J Public Health. 2009;99(10):1872-8. doi: 10.2105/AJPH.2008.146894
36. Grundy EMD, Tomassini C. Marital history, health and mortality among older men and women in England and Wales. BMC Public Health. 2010;10:554. doi:10.1186/1471-2458-10-554
37. Robards J, Evandrou M, Falkingham J, Vlachantoni A. Marital status, health, and mortality. Maturitas. 2012;73(4):295-9. doi: 10.1016/j.maturitas.2012.08.007
38. Manzoli L, Villari P, Pirone MG, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. Soc Sci Med. 2007;64(1):77-94. doi: 10.1016/j.socscimed.2006.08.031
39. Farkas J, Pahor M, Zaletel-Kragelj L. Self-rated health in different social classes of Slovenian adult population: nationwide cross-sectional study. Int J Public Health. 2011;56(1):45-54. doi: 10.1007/s00038-009-0103-1
40. Ranfl M, Zaletel-Kragelj L. Assessment of the association between dentate status and self-rated general health. Zdr Varst. 2017;56(2):131-9. doi: 10.1515/sjph-2017-0017
41. Klok L, Engels Y, Veldhoven C, Rotar Pavlic D. Early identification of patients in need of palliative care in Slovenian general practice. Zdr Varst. 2018;57(2):55-64. doi: 10.2478/sjph-2018-0008
42. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess. 1988;52:30-41.
43. De Maria M, Vellone E, Durante A, Biagioli V, Matarese M. Psychometric evaluation of the multidimensional scale of perceived social support (MSPSS) in people with chronic diseases. Ann Ist Super Sanita. 2018;54(4):308-15. doi: 10.4415/ANN_18_04_07

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Unproven stem cell therapies: is it my right to try?

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Abstract

Background. Nowadays one of the most critical aspects of innovative cell-based therapies is the unregulated industry, as it is becoming a *competitor* of the regulated system. Many private clinics, worldwide, advertise and offer cell-based interventions treatments directly to the consumer and this poses a risk to both vulnerable patients and health systems. Several countries have implemented Compassionate Use Programmes (CUP) that provide patients with medicines that have not yet completed the approval pathway, in the event that no reasonable alternative exists. Recently, in the public discourse, compassionate use has been increasingly associated with a patient's right to try. Thus, the aim of this study was to assess public knowledge of the clinical trials process with specific reference to innovative stem cell treatments, and trust in the institutions responsible for regulatory activities. We also asked people about their "right" to use unregulated therapies.

Methods. We developed an *ad hoc* questionnaire on three main areas of concern and administered it to 300 people in the patient waiting room at an Italian university hospital.

Results. Our findings suggest that people have a good knowledge of the clinical trials process and trust in healthcare institutions. Nonetheless, one person in two believes it is a right to use unregulated therapies.

Conclusions. We stress the need, in the age of cellular therapies, for a commitment to support vulnerable patients and to strengthen awareness among the public about the substantial boundary that differentiates *experimental therapies* from *unproven therapies*. There should not be a "right to try" something that is unsafe but rather approved treatments and in line with good clinical practice. The trend, which emerged on this issue from our study, is quite different, confirming the urgent need to improve health information so that it is as complete as possible.

Key words

- stem cells
- compassionate use trials
- trust
- medical tourism

INTRODUCTION

Worldwide, innovative cell-based therapies have represented a considerable challenge for regulatory systems over the last decade. Within this field characterized by a rapid technological advancement, the products of the discoveries of medicine and biology have become more and more "therapeutic options" advertised and offered by private producers directly to the consumer. Over the last two decades, a boom in for-profit clinics offering stem cell therapy directly to patients for a wide range of diseases has occurred and tragically, some patients died from dangerous injections of cells [1].

Within a regulated context, the responsibility for the assessment of safety of treatment pertains to regulatory agencies; outside this setting, patients do not have an adequate guarantee of protection. The European Committee for Advanced Therapies (CAT) has expressed its views on this matter in many documents, with particular "concern about a phenomenon known as stem-cell tourism in which severely ill patients travel to clinics around the world where unauthorized stem-cell-based treatments are offered in the absence of rigorous scientific and ethical requirements" [2]. The CAT has strongly encouraged the development of stem-cell-based medicinal products in approved and high-quality research programs [3].

The protection of patients from ineffective and risky therapies is an important issue that requires legal, ethics and public health considerations. Currently, most stem cell therapies are experimental and many scientists do

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not know exactly how they work and how safe they are. In turn, the clinical application of these products, which has only just begun, is raising numerous ethical questions that the International Society for Stem Cell Research (ISSCR) has recently examined in detail in the "Guidelines for Stem Cell Research and Clinical Translation" [4, 5]. Specifically, the transparency of the clinical data, the accurate and effective communication in the process of informed consent are crucial elements, especially in the early phase of trials with humans, when there should be particular care in avoiding overestimation of benefits or therapeutic misconceptions [5]. For example, people may not clearly understand the significance that a regimented experimentation process assumes for the safety and protection of health and may be confused about the readiness of a technology for clinical application.

In the era of biotechnologies and great attention of media to these new therapies, which often creates disproportionate hope among people, these considerations are highly relevant for their implications. Patients and their families, especially if they have a very serious health condition, are vulnerable and must be protected as such. For the first time, the Guidelines focus on the importance of the communication process to the public, recommending timely correction of every possible misleading public representation. Inaccurate portraits of stem cell research may have severe consequences, including misinforming policy debate, and premature clinical use of unapproved treatments [6, 7]. An integrated effort is needed involving diverse actors, such as researchers, institutions and specialists in scientific communication to safeguard the public from misinformation.

The right to health

Stem cell therapies have become a matter of controversy in public debate and in legal decisions. There have also been cases in which patients opposed the State for access to experimental therapies. In 2014, Italy was the subject of a highly controversial legal battle, Durisotto *vs* Italy, also known as the "Stamina case", about an alleged innovative stem-cell therapy. The controversial and broad debate that developed around this case focused on the acceptability of providing treatment not based on scientific evidence when a patient's request is advanced as a last hope of healing or relief from a condition of suffering. The stamina treatment, which had been administered to numerous patients starting in 2008 in public hospital, was based on the use of mesenchymal stem cells (MSCs) and intended for the treatment of neurodegenerative diseases. Unfortunately, as was then demonstrated, there was no study protocol upstream, with one exception which presented serious flaws and omissions involving a procedure which did not comply with any Good Manufacturing Practices (GMP) [7, 8].

On 6 May 2014, the European Court of Human Rights (ECHR) ruled on the patient's right to decide to resort to unproven treatments – stem cell therapies – in the absence of other therapeutic possibilities, in the wake of the Durisotto *vs* Italy case. Mr. Durisotto applied to the ECHR following the refusal by the Italian courts to authorize compassionate therapy (specifically, the "Stamina" method) to treat his daughter's degenerative cerebral illness. The European Court rejected the patient's claim. In particular, it declared the application inadmissible under Article 8 of the European Convention on Human Right (right to respect for private and family life) stating that "the interference in the right to respect for the private life, represented by the refusal to grant the request for medical therapy, could be considered as necessary in a democratic society". The prohibition on access to the therapy in question "pursued the legitimate aim of protecting health and was proportionate to that aim" [9].

If the protection of the right to health is attributed to the legislator, access to a new therapy has to be regulated by healthcare norms that define all the conditions of the procedure. In other words, healthcare authorities must decide on the scientific validity and on the appropriateness of the treatment.

In media discourse, the reference to *compassion*, *hope* and *right* are often invoked and associated with the request for access to innovative or experimental procedures. As we will see later, the definition "compassionate use", used today even within institutional and regulatory documents, can be easily misunderstood regarding its exact meaning [10, 11]. However, in no way does it indicate the possibility of accessing any treatment offered by anyone without prior sharing of the rationale within a broader scientific community. It does not mean that any attempt is admissible: a choice made on the emotional wave of *despair* and *hope* may not be the best choice and could even be detrimental to the dignity of the person's own life if, for example, it involves avoidable or disproportionate suffering.

The Right To Try (RTT) movement

In recent years, many US States, in the face of great pressure from public movements, patient advocacies and think tanks, have passed "Right to Try" laws, which give terminally ill patients access to experimental compounds that have passed phase I testing [12]. These laws provide that a patient who wants to try an experimental drug can contact the pharmaceutical company directly, cutting out the "filter" of the competent authority, the Food and Drug Administration (FDA). Those against the Right to Try (RTT) laws generally argue that they are not a boon for patient rights, but that they rather dismantle the safety system that protects people. Liberal access to unproven therapies could have a negative impact on individual patients in a state of vulnerability, by offering false hope that leads to increased suffering. In the US, supporters of the RTT have used emotionally charged stories in which someone is dying – a child or parent – to invoke access to an experimental drug that might offer salvation. If there is hope that the treatment might work, RTT supporters argue, the patient has the right to try to preserve his own life. However, patients in very serious condition might judge risks and potential benefits differently than scientists do and they might not sense the irrationality of their own hope.

It should be noted that RTT laws offer not a right to try, as suggested in the name, but rather a right to

ask for access in order to try. To acclaim and advocate a right to try suggests that regulated systems do not permit access to experimental treatments, whereas in many countries, these systems provide compassionate use or expanded access of experimental treatments by defining a threshold of scientific evidence and safety necessary to support such use or access. In this regard, it is useful to stress that there is a difference between *unproven therapies* and *unregulated therapies* and that the treatments administered through compassionate use or expanded access programmes are unproven (i.e. not yet proven) but regulated. Around this issue, a radical idea of care as free choice – with no interference whatsoever – to make decisions regarding one's body seems to be emerging. Some authors have referred to a "right to self-medication", by rooting this right in the value of *autonomy* [13].

This radical position reflects either a feeling of distrust in institutions that must protect the interests of patients or a more generic statement of freedom of choice. Perhaps for some it is a mixture of the two. The basic question is: to what extent should the law prevent people from taking risks they voluntarily accept. For some, protection at all costs is considered paternalistic, a stance that disregards the value of autonomy of the individual.

Regarding these issues, the position expressed by the ECHR in Durisotto *vs* Italy is very clear. It is useful here to point out three facts:

- the ECHR reiterated that it was not to the place of the international court to substitute itself for the competent domestic authorities in determining the level of acceptable risk for patients wishing to have access to compassionate therapy in the context of experimental treatment;
- the ECHR stated that "The interference in the right to respect for one's private life, represented by the refusal to grant the request for medical therapy, could be considered as necessary in a democratic society";
- the protection of the right to health, on the part of the legislator, is realized through the non-authorization of unsafe or harmful treatments.

Compassionate use program

Regulation no. 726 /2004 of the European Parliament and Council regulates "Compassionate use", which it defines in art. 83, part 2 as "making a medicinal product (…) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease (…) and who cannot be treated satisfactorily by an authorized medicinal product" [14]. In turn, the European Medicines Agency (EMA) defines "compassionate use" as a treatment option that allows the use of an unauthorized medicinal product, which is under development. In Europe, EMA provides recommendations and guidelines for compassionate use [15] and every member state sets its own rules. Currently, a wide disparity exists across European member states regarding the procedures of application [16, 17].

Italian law allows compassionate use in some circumstances in which specific criteria are met. DM 7/09/2017 on "Therapeutic use of a medicine subjected to clinical trials" regulates access to experimental pharmacological therapies for use outside a clinical trial, to patients suffering from serious, rare or life-threatening diseases when, according to the clinician, there are no other valid therapeutic alternatives [18].

Innovative therapies, by their nature, are experimental treatments which cannot be evidence-based or clinically indicated and may lack a demonstrable safety profile. As some authors have highlighted, the primary purpose of legislation on innovation, and on medical innovation in particular, must be to benefit the individual patient [19]. To conduct an open debate on how to guarantee "responsible innovation" at a time when innovation in cell therapy and regenerative medicine is moving into the clinical context is an issue of paramount importance. Equally important is the need to increase public awareness of the significance of the regulated process of clinical experimentation and trust in institutions responsible for the control, approval and evaluation of the risk-benefit profiles of innovative treatments. Against this backdrop, we have conducted a pilot survey on a sample of the Italian population to assess public knowledge of the clinical trials process with specific reference to innovative stem cell treatments. We also asked people about their "right" to use unregulated therapies, in order to get a picture of how people are potentially vulnerable to undergoing unproven therapies and to have some indication of what the right to try means for them.

MATERIALS AND METHODS

A bibliographic search in the PubMed database was conducted to verify the presence of international studies on attitudes among the public towards both the use of unregulated therapies and general knowledge of the clinical trial process. No questionnaires related precisely to our query was found. We chose to carry out a survey on a sample of the population using an *ad hoc* questionnaire developed through the methodology of an expert focus group. Five experts took part in the focus group: a bioethicist, a bio-statistician, a philosopher of science, an expert in health professions and a psychologist. The issues that emerged from the working group discussions were divided into three conceptual blocks representing three topics under investigation: 1) public information on the clinical trial process; 2) specific information on treatments based on stem cells; 3) general trust in the governing bodies and institutions responsible for the control and regulation of the clinical trial process. Based on the experts' suggestions, we formulated ten questions for each thematic area and then asked the focus group members to indicate through a vote the most effective ones. The resulting questionnaire used for the survey consisted of 16 questions (6 for the first block, 4 for the second and 6 for the third), with an introductory section consisting of five items for sample stratification (sex; age; level of education; work in the health sector or not; medical sector in which the patient was seeking care). The sample for the study was randomly recruited among people who were in the patient waiting room at the Campus Bio-Medico University Hospital in Rome, Italy. The

questionnaire was distributed to a total of 300 people including patients and "companions" (persons accompanying patients). The questionnaire was anonymous and the estimated compilation time was approximately 4 minutes. Participants could stop filling out the questionnaire at any time. The data extrapolated from the returned questionnaires was placed in an electronic database built specifically for collection. The data was verified and analysed through the statistical package SPSS v24 copyright. A first descriptive analysis was conducted for each individual item. Then we proceeded to make comparisons among the responses to the various items by using the chi-square test. Differences with P <0.05 were considered statistically significant. When answers to different questions are been examined, the frequency of the correct answers is compared with the sum of the frequencies of the wrong answers across the different questions. The significant results of the study are reported and discussed in the next section.

RESULTS

A total of 219 questionnaires were returned (73% of the total responded). The descriptive analysis showed that the sample is homogeneous as regards the stratification variables with the exception of the level of education (67.12% of the sample had completed high school but not studied beyond that) and the type of occupation (86% of the responders are not healthcare professionals) (*Table 1*). On the questions concerning knowledge of the clinical trial process, 77.63% of the sample showed that they knew what a clinical trial is, answering that it is a study authorized by the institutions responsible for public health policies. 74.43% correctly answered the question about whether an investigational drug can be administered to humans. 52.05% answered that the experimentation of a new drug or treatment lasts on average from 7 to 10 years. The data showed that those who correctly answer questions about the clinical trial process have much more confidence that regulation protects the interests of patients compared to those who have no knowledge of the trial processes (P <0.05). Only 33.33% of the sample knew the meaning of "compassionate use" of a drug and 52.51% responded that they did not know if such use is possible in Italy. To the question "Do you think it is a right of patients to use treatments not authorized by the institutions responsible for public health policies", 43.38% of the sample replied no, 41.55% yes and 15.07% did not know. 95.89% of the sample responded they had heard of stem cell-based treatments. Answers to the question about the possibility of using stem cell-based treatments in Italy were homogeneously distributed (36.99% yes; 29.22% no; 33.79% I do not know). When asked about the number of pathologies for which stem cell treatments have proven effective, 42.47% responded "I don't know", 22.83% responded "more than 100 pathologies" and 33.79% responded "a very small number of pathologies". 72.60% of the sample said they have heard of patients going abroad to undergo treatment with stem cells not authorized in Italy. The analysis showed no significant correlation between the opinion about the use of unregulated drugs and the medical sector in which the patient was seeking care. Answers regarding trust in the institutions responsible for regulatory activities were positive in reference to the following: Italian Medicine Agency (AIFA) 75.9%; Ministry of Health 71.3%; Italian National Institute of Health (Istituto Superiore di Sanità – ISS) 79.9%; World Health Organization (WHO) 89.5%; Ethics Committees 76.3%. In addition, a statistically significant correlation was found (P <0.05) between responses to the question on trust in institutions and the question of trust in the fact that regulation of the process protects the interests of patients (*Table 2*). Only 12 of the 16 items in the questionnaire are shown in the table. We decided to omit four questions related to the third block because they showed no significant correlation. We believe this is probably due to the complexity of the construct formulation.

Table1
Overview of the responders to the pilot survey on the public's knowledge about. perception of. and trust in the testing process of a new drug or treatment

Characteristics	
Total (N)	219
Sex (%)	
Female	50.68
Male	49.32
Age (Mean, min-max)	
Male	40 (18-82)
Female	44 (19-80)
All	42 (18-82)
Education (%)	
None	1.37
Primary school	5.02
Secondary school	67.12
University (undergraduate)	22.83
Master/PhD	3.66
Occupation in healthcare setting (%)	
Yes	14.16
No	85.84
Type of respondent (%)	
Patient	43.38
Companion	56.62
Medical field of the the patient's appointment (%)	
Diagnostic	58.90
Surgical area	22.84
Onco-hematologic	18.26

DISCUSSION

The results show that the people interviewed had a good general knowledge of the clinical trial process. In fact, the number of correct answers to the questions

Table 2
Answers to the questionnaire items divided by thematic blocks

Blocks	Final number (%)
Total	219
Block 1 **What is in your opinion a "clinical trial"?**	
A study authorized by the institutions responsible for public health policies	77.62
A study not yet authorized by the institutions responsible for public health policies	15.53
The administration of an innovative drug or treatment outside of a hospital facility	5.02
I don't know	1.83
Is it possible to administer an investigational drug to human beings?	
Yes	74.42
No	15.53
I don't know	10.05
How long do you think the testing process is for the development of a new drug or treatment ?	
Two/three months	1.37
One year	30.14
Between seven and ten years	52.05
I don't know	16.44
Which of the following definitions of "compassionate use" of a drug is, in your opinion, most correct?	
Use of a drug outside the testing process	10.97
Use of a drug outside the national regulatory procedures	21.00
Use of a drug while the trial is not over yet	33.33
I don't know	34.70
Is the compassionate use of a drug possible in Italy?	
Yes	17.35
No	30.14
I don't' Know	52.51
Block 2 **Have you ever heard of stem cell treatments?**	
Yes	95.89
No	1.37
I don't know	2.74
In Italy it is possible to use stem cell therapy?	
Yes	36.99
No	29.22
I don't know	33.79
Are there diseases for which stem cell treatments have proven effective?	
Yes. more than a hundred different diseases	22.83
Yes. a very small number of diseases	33.79
No	0.91
I don't know	42.47
Have you ever heard of patients who travel to foreign countries to undergo stem cell-based treatments that are not authorized in Italy?	
Yes	72.60
No	27.40
Do you believe it is a right of patients to use treatments that have not been authorized by the competent authorities?	
Yes	41.55
No	43.38
I don't know	15.07
Block 3 **You can vote from -3 to +3 (-3 = no trust +3 = great trust) to express your confidence in regulatory activity of clinical trials of the following institutions***	
Italian Medicines Agency (AIFA)	75.8
Ministry of Health	71.3
Italian National Institute of Health (ISS)	79.9
World Health Organization (WHO)	89.5
Ethical Committees	76.3
*The percentages were calculated by summing the positive opinions, from 0 upwards.	
Do you think that in Italy the regulation protects the interests of patients?	
Yes	43.01
Not	56.98

related to this thematic area is significantly high, with the exception of the questions on the meaning of "compassionate use". These responses correlate with the perception of protection by the institutions that regulate the process suggesting that good information could increase the degree of trust in people. The recent 2018 Edelman Trust Barometer seems to confirm this position in showing a dramatic distrust mainly at the media level, due to the lack of reliability of and transparency in information [20]. The data also shows that the meaning of the "compassionate use" procedure is not well known to the population, suggesting that in this field general information about the possibilities of access to experimental treatments, in a regulated manner, need to be improved.

Regarding the right to use unregulated treatments, responses were homogeneously distributed between the belief that it is a patient right to use treatments outside of a regulation and the belief that it is not. These responses have no correlation with the answers regarding knowledge of the experimentation process. It seems that the perception of this "right" is independent of the degree of information about and trust in the institutions: correct information does not seem to influence opinion. It would be useful to study more in depth the question of "patients' right", to see if when responding to the question on "right", people understand the term as a general right to access to compassionate use (about which they do not seem to have sufficient information) or as a general right to try any treatment regardless of whether it is located within or outside a shared and regulated path. About stem-cell based therapies, the respondents in general did not have a good understanding of how these therapies are regulated and the real possibilities of use, although the vast majority of them had heard of it. The fact that one out of three people is unaware that in Italy it is possible to use stem cell-based treatments, provided within a regulated process, explains in part the misunderstanding we have discussed above. The same misunderstanding is implicit in US "Right To Try" movements, namely that regulators do not contemplate a right to try innovative treatments in specific circumstances. Information in this sense must certainly be expanded and managed responsibly and transparently to avoid the risk that patients find themselves alone in seeking life-saving treatments at a time when they are extremely vulnerable. Interestingly, 72% of the sample had heard of patients going abroad to undergo treatments unauthorized in Italy.

CONCLUSIONS

Our sample shows a good general knowledge of the regulated process of developing new drugs and treatments and a strong confidence in the institutions responsible for the control. At the same time, it shows a lack of knowledge about the regulation of innovative treatments based on stem cells. Probably, in this field, alongside media overexposure, there has not been sufficient institutional communication. In our view, it is very important that there be a multi-level commitment to increase awareness among the population of the possibility of using innovative treatments, even if the formal testing process has not been completed yet, and that unregulated treatment, often offered without guarantees, is very different from the compassionate use or hospital exemption of a product. The "Right to Try" movements in the US, by using the word "right", implicitly suggested that a right to try is denied within the regulated system, whereas what is denied is exclusively use that is not secure, ineffective and that exposes the person to unreasonable risks.

Within a regulated system, compassionate use procedures can be improved to allow easier or faster patients access, but this is a different matter. The possibility of relying on risky therapies whose validity is not recognized can perhaps be viewed by some as a right, within the conceptual framework of personal autonomy and freedom of choice. In our view, the right to try something whose level of safety and/or risk has not been previously considered acceptable and that does not follow a protocol in line with good clinical practice is not sustainable. Furthermore, autonomy and free choice cannot be considered as such where there is inadequate information and thus the State and the medical community in general have, at the least, a moral duty to educate people through real information about the risks they run. The lack of awareness and comprehension affects dramatically the possibility of free choice, especially in situations of strong vulnerability. Transparent and effective communication on how to access clinical trials, and on available treatment possibilities, within the doctor-patients relationship as well as within the institution-citizen relationship is a preventive act to protect the vulnerable population.

A limitation of this study lies certainly in the size of the sample that does not allow us to make inferences about the general population. It provides, however, some useful food for thought for further research aimed at widely exploring the dimension of people's views on innovative therapies, the theme of building a relationship of trust, founded primarily on responsible and transparent communication, and the empowerment of people in the era of cell therapy and regenerative medicine.

Author's contribution to the manuscript

LR and VT: conceptualization and methodology; LR: investigation; LR, LC and GR: writing the draft and the original article; LC and MV: formal analysis and data curation.

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Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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REFERENCES

1. Lysaght T, Lipworth W, Hendl T, Kerridge I, Lee TL, Munsie M, et al. The deadly business of an unregulated global stem cell industry. J Med Ethics. 2017;43:744-6.
2. Committee for Advanced Therapies and CAT Scientific Secretariat. Use of unregulated stem-cell based medicinal products. The Lancet. 2010;376:514.
3. Committee for Advanced Therapies (CAT). Reflection paper on stem cell-based medicinal products. CAT; 2009. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079932.pdf.
4. International Society for Stem Cell Research (ISSCR). Guidelines for stem cell research and clinical translation. ISSCR; 2016. Available from: www.isscr.org/guidelines2016.
5. Frati P, Scopetti M, Santurro A, Gatto V, Fineschi V. Stem cell research and clinical translation. A roadmap about good clinical practice and patient care. Stem Cells Int. 2017. Article ID 5080259. Available from: http://doi.org/10.1155/2017/5080259.
6. Kimmelman J, Hyun I, Benvenisty N, Caulfield T, Heslope HE, Murry CE, et al. Policy. Global standards for stem-cell research. Nature. 2016;533:311-3.
7. Solarino B, Laforgia M, Dell'Erba A, Laforgia N. Stem cell therapy: medico-legal perspectives in Italy. Front Cell Neurosci. 2015;9:240.
8. Abbot A. Leaked files slam stem-cell therapy. Nature. 2014;505:139-40.
9. European Court of Human Rights. Durisotto vs. Italy. ECHR 153 (2014) 28.05.2014. Available from: https://hudoc.echr.coe.int/eng#{%22itemid%22:[%22001-144670%22]}.
10. Borysowski J, Ehni HG, Górski A. Ethics review in compassionate use. BMC Med. 2017;15:136.
11. Comitato Nazionale per la Bioetica, Cura del caso singolo e trattamenti non validati (c.d. "uso compassionevole"). 27 febbraio 2015. Available from: http://bioetica.governo.it/media/170732/p119_2015_cura_del_singolo_trattamenti_non_validati_it.pdf.
12. Dresser, R. "Right to Try" Laws: The gap between experts and advocates. Hastings Center Report. 2015;45:9-10.
13. Flanigan J. Three arguments against prescription requirements. J Med Ethics. 2012;38: 579-86.
14. European Union. Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004, Official Journal of the European Union. Available from: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c.
15. European Medicines Agency (EMA). Guideline on compassionate use of medicinal products, pursuant to article 83 of Regulation (EC) No 726/2004. Available from: www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf.
16. Whitfield K, Huemer KH, Winter D, Thirstrup S, Libersa C, Barraud B, et al. Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries. Trials. 2010;11:104.
17. Balasubramanian G, Morampudi S, Chhabra P, Gowda A, Zomorodi B, Gayathri et al. An overview of compassionate use programs in the European Union Member States. Intractable Rare Dis Res. 2016;5:244-54.
18. Decreto Ministeriale 07/09/2017. Disciplina dell'uso terapeutico di medicinale sottoposto a sperimentazione clinica. Available from: www.aifa.gov.it/sites/default/files/DM_7SETTEMBRE2017_0.pdf.
19. Samanta J, Samanta A. Quackery or quality: the ethico-legal basis for a legislative framework for medical innovation. J Med Ethics. 2015;41(6):474-7.
20. Edelman Trust Barometer. Global Report. Available from: https://cms.edelman.com/sites/default/files/2018-01/2018%20Edelman%20Trust%20Barometer%20Global%20Report.pdf.

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ORIGINAL ARTICLES AND REVIEWS

The impact of pictorial health warnings on tobacco products in smokers behaviours and knowledge: the first quasi-experimental field trial after the implementation of the tobacco law in Italy

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Abstract

Background. The aim of the study was to evaluate in the Italian smokers, the effects of implementation of the law about Pictorial Health Warnings (PHWs) on tobacco products.

Methods. A quasi-experimental longitudinal design was conducted between 2016 and 2017. The data were collected before (pre-PHW/Wave 1) and after (post-PHW/Wave 2) the implementation of the law. The adopted questionnaire included impact of advertisement (Label Impact Index, LII), quitting behavior and knowledge of tobacco related diseases.

Results. 455 respondents completed both the Waves. 7.7% of smokers declared to have stopped smoking in Wave 2 and 29% of these declared the PHWs as one of the reasons to quit. The knowledge of tobacco related diseases was significantly ($p < 0.001$) increased from Wave 1 to Wave 2 (58% *versus* 72%), similarly the LII (mean = 26.9, SD = 16.7 and mean = 40.4, SD = 16.2).

Conclusion. Tobacco addiction is a problem that needs to be addressed from different angles. PHWs confirm their complementary role as a support for smokers along with other strategies such as text warnings and the tobacco quit line of the Istituto Superiore di Sanità (Italian National Institute of Health) reported on the packages. Nonetheless, over the years these measures have been not enough and policy makers should consider more strategies synergistically acting in the fight against tabagism.

Key words

- pictorial warnings
- health labels
- health warnings
- tobacco advertisement
- quasi-experimental study

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INTRODUCTION

WHO has recommended the application of pictorial warnings on tobacco products since 2008 [1].

Pictorial Health Warnings (PHWs) constituted an important policy to inform adult smokers on the impact of smoking on health [2, 3], but at European level pictorial warnings have not been implemented in all countries in the same time [4].

The first European Tobacco Products Directive (TPD), which regulated aspects such as manufacture, sale and presentation of tobacco products, was approved in 2001. In 2009 the European Commission decided to review the TPD. The ordinary legislative process began immediately after this, on January 2013, finishing in October 2015, when the final act was signed [4, 5].

In April 2014 the European Parliament and of the Council approved a Directive on "the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products". In particular the Articles 11, 12 and 13 of TPD on "Labelling of tobacco products for smoking other than cigarettes, roll-your-own tobacco and waterpipe tobacco", "Labelling of smokeless tobacco products" and "Product presentation" underlined that the attractive, modern packages and trendy brand names attractive to young people and thus might increase smoking initiation. The Article 13, letters a), b) and c), invited to the Members States to introduce more stringent rules concerning the labelling and the outside packaging of tobacco products that delete the erroneous impression about its characteristics, health effects, risks or emissions; quit any possible suggestive references to the less harmfulness of some tobacco products than others; and remove references to taste, smell, any flavorings [6].

In 2015, the European Commission implement a decision on "the technical specifications for the layout, design and shape of the combined health warnings for tobacco products for smoking" [7]. The key provisions of this TPD refers to the size and position of health warnings, to increase the sizes of pictorial and textual health warning labels, to information on smoking cessation and to present a colour photograph on smoking-related harm. The introduction of pictorial warnings is according to the Article 5 of the executive protocol compiled by the National Comprehensive Law on Tobacco Control presented published by WHO in 2004: "PHWs should be applied to cigarette packs" [8].

The recommendation on the health warnings and on the product presentation were present in tobacco packages across the whole EU in 2016. Several European Counties adopted the pictorial health warnings (PHWs) on tobacco products in 2016, including Italy [7, 9]. In particular, the Italian Minister of Health issued a decree for the introduction of the PHWs in May 2016 [6].

Hammond *et al.* published in 2007 a study on the impact of the pictorial warnings before and after the implementation of the warnings in UK [10]. In this study, the smokers reported greater levels of awareness, salience and considered the warning as a more effective deterrent. Heydari *et al.* conducted a similar study in the city of Tehran. The research was designed and conducted in two phases before the implementation of pictorial health warning labels law on tobacco products and after nine months, and evaluated the effect of it on smokers' knowledge, attitude and pattern of smoking. Their study showed that 7.7% of smokers decreased their smoking rate [11]. The same conclusion was found by Gravely *et al.* [12]: their study tested the effectiveness in terms of warning salience, cognitive, emotional, and behavioral responses to the warnings on adult smokeless tobacco users from the symbolic warning (pre-policy) to graphic health warning labels (post-policy).

A systematic review published in 2015 reported an evidence against the use of pictorial warnings on cigarette packages (PWCP), suggesting that the effects of PWCP on behavioral were quite modest [13]. Yong *et al.* reported the value of labelling which acts through the ability to stimulate thoughts about risks of smoking, which in turn increase one's health concerns, with a subsequent increase in the intention to quit, an important predictor of the increase in the likelihood of making an attempt to quit [14]. Bewer *et al.* performed a randomized clinical trial and found that the PHWs effectively increased intentions to quit, forgoing cigarettes, quit attempts, and successfully quitting smoking over 4 weeks [15]. Although the limited effect, according to international studies, its implementation is beneficial in any case [16-20].

In Italy two studies have explored the possible impact of the introduction of the PHW and the plain packaging in 2012 and 2013. They underlined that the perception of the pictorial warnings are more effective to communicate the health damages in the smokers and lead to the reduction of the tobacco consumption [3, 21].

Another crucial aspect to be taken into account is the need for reliable and validated measures in this kind of studies, as reported in Francis *et al.*, which stresses "Accurate measurement tools are vital to identify factors associated with cigarette pack pictorial warning perceived and actual effectiveness. Data from such studies is critical for building the evidence regarding the role of cigarette pack warnings in impacting smoking-related beliefs and behaviors" [22]. However, there are no studies that assess the impact before and after the introduction of the new law in Italy. The aim of our study was to evaluate the effects of the introduction of the PHWs on tobacco products on smokers in terms of tobacco related behaviors, knowledge and perception using a standardized tool in Italy.

MATERIALS AND METHODS

We conducted a longitudinal study organized as a quasi-experimental national survey. It was conducted in 2 phases before and after the implementation of the law on tobacco packaging. Wave 1 of the study was conducted six months before the implementation of the PHWs law (November 2015-April 2016: pre-PHW); Wave 2 was conducted 8-18 months (January 2017-November 2017: post-PHW) post-implementation.

Participants

We considered eligible for our study people belonging to the general population, smokers at the time of

the Wave 1 and adult (>18years). Only those who completed both the surveys (Wave 1 and 2) were considered for the final analysis.

The definition adopted to define the smokers was: "who had smoked more than 100 cigarettes in their lifetime" and "smoked at least once in the past 30 days at recruitment".

The individuals involved in the study were contacted in the opportunistic places: University Campus, waiting rooms of hospitals and in front of supermarket area. An informed consent from participants was obtained before their participation in the study.

Data collection

Data were collected through a face-to-face interview for the first Wave, and a telephone-administered questionnaire for the second-round interview. The average time to complete the interview was 20 min. The collected socio-demographic characteristics were: gender, age, educational level (graduated versus not graduated), civil status (married/cohabitant versus single/divorced), sons (yes/no), socio-economic status (SES) (low, medium or high, based on a combination of homeownership, number of travels in the last years, educational level and type of works).

The followed smoking related variables were considered:

- number of smoked cigarettes per day;
- number of quit attempts (0, 1, 2 or more than 2);
- age of starting to smoke;
- smoking dependence using Fagerström Test for Nicotine Dependence [23];
- smoking dependence using Fagerström Test divided into four groups; no (0), less dependent (score 1-3), moderately dependent (score 4-7) and strong dependent (score 8-10) [23, 24].

In order to compare the impact of the health warnings, we adopted the Label Impact Index (LII) [25] Germany (2007. LII is an international validated tool evaluating four dimensions related to the perception of labeling: SALIENCE; HARM; QUITTING; FORGO.

The knowledge was investigated showing to each participant a list of twenty diseases. Participants were asked to identify tobacco related illnesses and the answer was defined as dichotomous variable (correct/wrong). The list of diseases was created on the basis of the scientific evidence [26]. The Knowledge Score (KS) was computed adding the correct answers (1 = correct; 0 = wrong): the KS ranged from 0 to 20.

In the Wave 2 two questions were included to establish a change in smoking habits:

- the smokers have stopped to smoke after the implementation of the law (yes/no);
- the smokers who stopped attribute their choice to the PHWs (yes/no).

Research ethics approval was obtained from the Teaching Hospital Umberto I, Sapienza University of Rome.

Sample size

Sample size calculation was done with a 95% confidence interval (95% CI) and a precision of 5%. The percentage of Italian adults smokers who have quitted is around 18% [27]; the hypothesis was that the proportion in the population post implementation would have been 5% more (23%). The calculated sample size was represented by at least 491 smokers. The target sample size was increased to 40% in order to contain non-response bias.

Statistical analysis

The statistical analysis was carried out using IBM-SPSS version 19 software for Windows Release (IBM Corp. released in 2010 IBM SPSS Statistics for Windows, Version 19; IBM Corporation, Armonk, NY, USA).

Categorical data were described as absolute frequencies and percentages. Continuous data were presented as means and SD.

The dichotomous nicotine dependence was compared between groups using the χ^2 test.

To compare the LII pre-PHW and post-PHW the t-student test for paired samples was applied. The Mann-Whitney test was applied to assess the difference between current smokers versus ex-smokers in the Wave 2.

The Kolmogorov-Smirnov's test was adopted to control the assumption of normality distribution before using some parametric test.

The statistical significance was set at a p-value <0.05.

Ethics approval

The study was reviewed and approved by the Research Ethics Committee of the Teaching Hospital Umberto I, Sapienza University of Rome (Prot. N. 279/16 RIF.CE: 4024).

RESULTS

Characteristics of studied sample and of the participants lost to follow-up

Eight hundred-fifty smokers were invited to participate but the response rate in Wave 1 was 93% (N = 788 enrolled).

Sixty-two persons refused to participate: 48% (of the refusals) were females and the mean age was 35.6, SD = 14.6.

The flow chart of the quasi-experimental study design is shown in *Figure 1*.

Among the participants in Wave 1, 58% (N = 455) were then surveyed also in the Wave 2.

The characteristics and the comparisons of the lost participants to Wave 2 (N = 333) and the sample that completed the study are shown in *Table 1*.

No significant differences were found between the two groups for the following characteristics: gender, age group, age to starting to smoke and nicotine dependence classes (all p >0.05). There was a significant difference in occupational level: the percentage of the students was lower in the sample that completed the entire study (Waves 1+2) compared to the sample that completed only the Wave 1 (p = 0.045).

Impact of pictorial warnings on smoking habits

Thirty-five smokers (7.7%, Group A) declared that have quit to smoke after May 2017 (post-PHW), 20 smokers declared that have quit to smoke before May

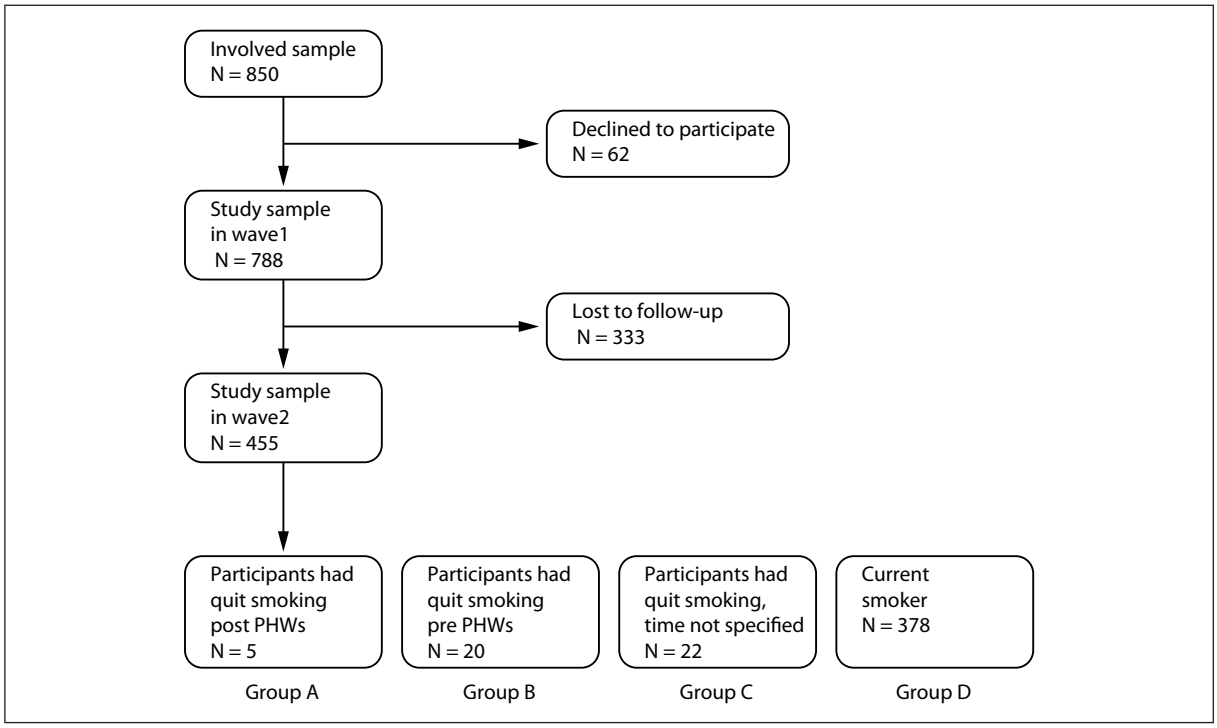

Figure 1
Flow diagram of the participants included in the study.
PHW: pictorial health warnings.

Table 1
Demographic characteristics and smoking habits of the studied sample (participants enrolled in waves 1 and 2) and the sample lost to the follow-up

Variables		Participants in Wave 1 and lost in the Wave 2 N = 33		Participants in the Waves 1 and 2 N = 455		p
		N	%	N	%	
Gender	male	167	50	198	44	0.083
	female	166	49	254	56	
Age	<25 yrs	120	45	148	38	0.121
	25-35 yrs	90	34	140	36	
	>35 yrs	56	21	104	26	
Occupational level	student	152	50	172	43	0.045
	employed	114	38	186	48	
	unemployed	27	9	23	6	
	pensioners	10	3	12	3	
Age of starting to smoke	<14 yrs	60	18	71	16	0.333
	14-17 yrs	212	65	285	64	
	>17yrs	54	17	91	20	
Nicotine dependence (Fagerström test)	no	141	50	200	55	0.248
	less	96	34	125	34	
	moderately	35	13	31	9	
	strong	9	3	7	2	

2017 (pre-PHW, Group B) (4.4%) and 22 did not specify the date (5%, Group C) (*Figure1*). Ten of those who quitted post-PHW declared that pictorial warnings have supported them to quit (29%). Nobody reported having stopped exclusively thanks to the PHWs.

The univariate analysis (*Table 2*) that assessed the characteristics associated to the group A versus the one of current smokers (group D) did not report significant differences by: gender (p = 0.255), age group (p = 0.873), civil status (0.768), number of smoked cigarettes (p = 0.876), nicotine dependence level (p = 0.246), number of quit attempts (p=0.555) and age of starting to smoke (0.157) (data not showed). Occupational level was not analyzed because the assumption of the χ^2 test was not satisfied: two cells (25.0%) have expected count less than 5 and the minimum expected count is 0.89.

Table 2
Comparison of Label Impact Index and Knowledge Score before and after the implementation of the law

Variables	Pre-PHWs Mean (SD)	Post-PHWs Mean (SD)	p
LII (0-100)	26.9 (16.7)	40.4 (16.2)	<0.001
KS (0-20)	11.6 (2.5)	14.6 (1.8)	<0.001

PHW: pictorial health warnings; LII: Label Impact Index; KS: Knowledge Score.

LII of health warnings

Considering only the current smokers in Waves 1 and 2 (N = 378, group D), the mean values of the LII standardized score increased significantly from pre-PHW to post-PHW (p <0.001 with mean = 26.9, SD=16.7 to mean = 40.4, SD = 16.2).

Considering the group of ex-smokers in Wave 2 (N = 35) the mean value LII pre-PHW was 14.8 with SD = 4.5 (the mean value of LII post-PHW was not computable because the LII was designed only for current smokers).

Knowledge Score on tobacco related diseases

433 respondents completed the section about knowledge (response rate 96%). A significant difference was found: the KS was significantly increased from Wave 1 to Wave 2: mean = 11.6 SD = 2.5 and mean = 14.6 SD = 1.8 respectively, with p <0.001. The distributions of answers are shown in *Figure 2*.

The major increments of tobacco related knowledge were registered in the followed health aspects: gangrene (from 11.6% to 68.2%); risk of blindness (from 12.2% to 60.6%); premature labor (from 24% to 70.9%); erectile dysfunction (from 42.9 to 87.2).

The KS at Wave 2 between Group A versus Group D has shown not significant difference (p = 0.656): mean = 14.4, SD = 1.9 (median = 14, interquartile range = 3) versus mean = 14.6 SD = 1.8 (median = 15, interquartile range = 2.5) respectively.

DISCUSSION

This paper presents the methodology for and results of the first before and after assessment of PHWs on tobacco products in Italy. To the best of our knowledge, there are no similar assessments for Italy. Also this study presents a measure standardized to assess the effectiveness of PHWs and it could provide a model for

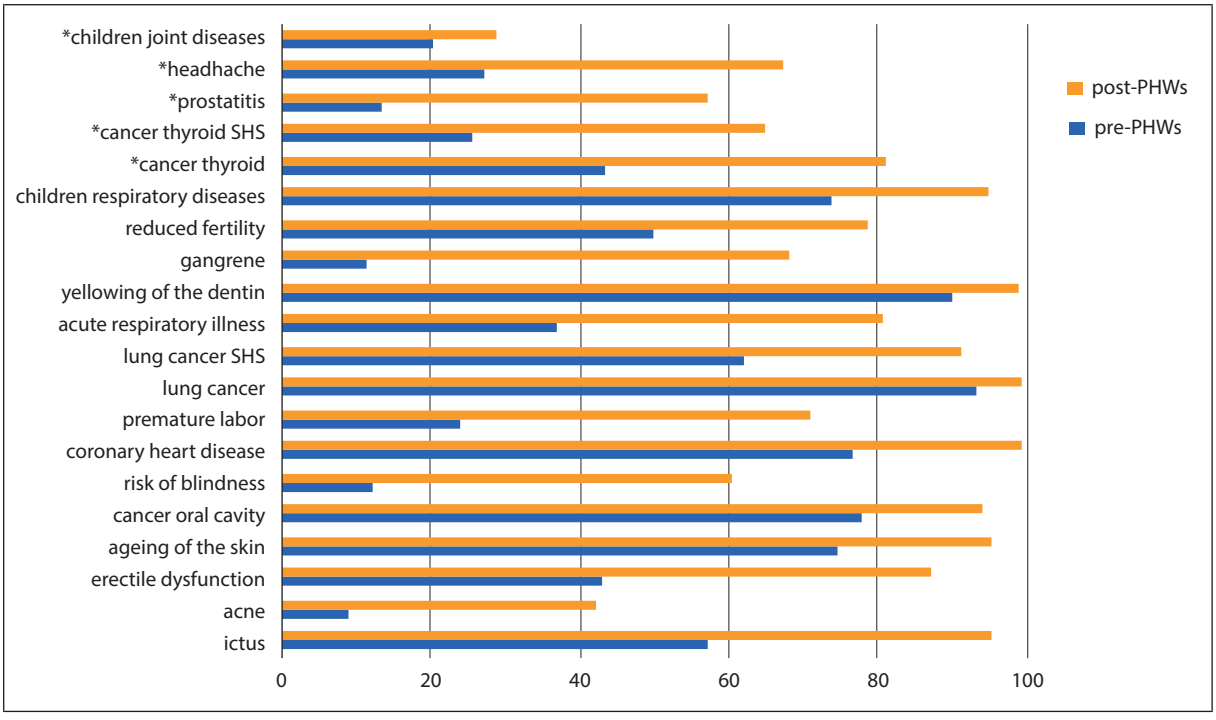

Figure 2
Distribution of the tobacco-related diseases pre-PHWs and post-PHWs implementation.
PHW: pictorial health warnings; *not tobacco-related disease; SHS: second-hand tobacco smoke exposure.

Italian Country to monitoring the effectiveness of tobacco labeling.

The results reported in the research underline significant increases of knowledge of health tobacco risk after the PHWs introduction in a short period (8-18 months). These results are in accordance with other studies conducted in different and same income Countries [28-36]. In fact, the knowledge about some pathologies (considered "tobacco related") significantly increased. The awareness about gangrene, blindness, premature labour and erectile dysfunction registered the higher increase before and after the law on PHWs. This datum suggested the possible progress from stage of pre-contemplation into contemplation according to the trans-theoretical approach model [37, 38]. These findings underlined the power of the graphic warnings in the communication of health messages and prevention compared to the textual ones and agreed with the scientific literature [34, 39-42]. On the other hand, it must also take into consideration that evidence concludes that the effectiveness of PHWs peaks shortly after implementation, like in this study, and that salience is the first dimension to suffer erosion thereafter [33].

It should be noticed that studies assessing the impact of plain packaging on behavioral outcomes are limited, and current evidence suggests that plain packaging may increase quit attempts and calls to quit-lines, as well as reduce smoking consumption and prevalence [43]. Concerning the smoking cessation, this research has shown that the implementation of PHWs could have a positive but limited impact: only 2% of the sample declared to have stopped smoking thanks to the graphical messages. However, if these results are extended to general population, it will be a considerable result. This modest impact is confirmed by other scientific studies [13, 36, 44].

Several investigations have evaluated both the combination and evolution of polices with PHWs and increase the smoking cessation. An interesting way to increase its efficacy is suggested by Saha *et al.*, that is to increase the coverage: health warning has to be mandatorily displayed in the cigarette packet and the graphic picture and text warning should cover 60% and 25% of the package, respectively [45]. In compliance with this, India decided that the new graphic health warnings should cover 85% of the principal display area on all tobacco products packages on both sides from 1 April 2016 [46].

In this direction the recent literature underlines that the ways to decrease the influence of cigarette packaging on tobacco consumption could include warnings and plain packaging [41, 47-49]. Warnings on packs can both counteract appealing pack design elements and communicate health messages to consumers. Compared to text-only warnings, pictorial warnings on cigarette packs attract more attention, evoke more negative affect and attitudes towards the product, and more effectively limit the initiation and promote intentions to quit [41].

The world's first legislation mandating plain packaging of tobacco products was implemented in Australia on 1 December 2012. An Australian study conducted by Dunlop *et al.* found a considerable positive response to plain packaging among Australian adolescents and young adults, including quitting-related behaviours and thoughts, behavioural and emotional indicators of social denormalisation and high levels of support for the policy [49].

The systematic review of Stead *et al.* suggests that standardized packaging will reduce the appeal of packaging and of smoking in general; that it will go some way to reduce consumer misperceptions regarding product harm based upon package design; and will help make the legally required on-pack health warnings more salient [47]. These effects are confirmed by the review of Smith *et al.*: their study reported that plain packaging represents one potential policy measure that can be deployed as part of a suite of comprehensive public health strategies to reduce morbidity and mortality caused by tobacco use [48].

Others approaches and combinations of policies are implemented to reduce the tobacco epidemic were reported by Bhutan, where a strong political commitment, strict legislations, and the influence of religious leaders in anti-tobacco propaganda led to a great success [50]. Another example comes from Finland's plan to be tobacco free, which included making the country smoker free by imposing ban on even milder products such as e-cigarettes and snuff, increasing the product price and cost for the vendors selling the products enormously, not allowing residents to smoke in private cars in the presence of minors aged 15 years or less and other stringent enforcements [51]. Also Australia represents another example of a successful country in tobacco control applying synergic strategies [52]. In the last ten years this Country implemented along with plain packaging, complete ban on point-of-sale tobacco product displays, reduction in duty free tobacco allowance, harmonization of the taxation of roll-your-own tobacco, reduction in the duty free allowance from 250 cigarettes to 25 cigarettes, 12.5% excise increase about every year [53].

Strengths and limitations

The major strength of the study is the originality of the collected data since available information on the issue from Italy is limited. Secondly the before-after design: the longitudinal study design permitted to assess the possible change on tobacco habits in the same subject.

Several limitations should be cited and explained:

i) the relatively small sample size, thus the main result is based on a limited number of smokers;

ii) the lack of consideration of non-smokers (i.e., never and ex-smokers) in the study population so we have not studied its potential unfavourable effect on smoking initiation or relapse among non-smokers;

iii) the self-reported nature of data: in the group of smokers who quitted after the adoption of the PHWs, this information was not validated by the measurement of biomarkers (e.g., CO or cotinine levels) or by 6-month (or 1-year) abstinence;

iv) the two different methods used to collect the same data (face to face for the first Wave and telephone for

the second one);

v) the percentage of the participants lost to the follow-up (Wave 2) was high (42%), and a significant different professional level was present in the lost group compared to the remaining one. This aspect could introduce a bias and an external validity;

vi) 5% of the smokers who declared to quit smoking did not precisely report the period: they didn't remember the month but only the year or they were confused. This aspect could have an impact on the analysis for the PHW;

vii) the selection of participants was performed without random methods: a possible effect of the selection bias could have determined a reduction of external validity of the study;

viii) the time window of the investigation considers the effect after different periods 8-18 months and, also, the effectiveness of PWLs should be peaks shortly after implementation;

ix) finally, it is not possible to estimate the influence of PHWs on the decision to quit smoking: in the study nobody declared to have quit smoking exclusively thanks to the PHWs. In order to determine the single impact of PHWs on cessation, further studies based on strong methodological designs should be conducted, preferably with longer follow-up periods and a small proportion of individuals lost to follow-up. Moreover, as another ecological study has suggested, it would be interesting to develop scales, based in the original Tobacco Control Scale (TCS), for larger settings in order to be able to compare the results of these processes [54].

CONCLUSIONS

The present study represents a first step in order to assess the effectiveness of the PHWs policy and more research is recommended especially with a longer follow-up. Nevertheless the reported limitations, this study showed that also in Italy the PHWs could support smokers who want to quit and could increase significantly the knowledge on the tobacco related diseases independently by the tobacco habit. The PHWs despite the not so high effectiveness to quit, are a no-cost intervention that should be encouraged and diffused. If considered alone, it does not lead to strong resolution of tobacco addiction. Since 10 years the smoking prevalence in Italy has not changed at all (according to the National survey on smoking in Italy 2018 by "The Observatory on drugs alcohol and tobacco").

Therefore, in order to significantly reduce the prevalence of smoking epidemic, the policy makers have to develop and combine different strategies in order to amplify the power of each intervention to combat it.

In the last twenty years Italy approved several antismoking polices: bans on smoking in public buildings (restaurant, coffee, stations, schools), institutional telephone quit line, smoking ban in cars with minors and pictorial wanings, but much is still to be done following the Australian example such as increase the price, bans on point-of-sale tobacco image, more antismoking education in school and including antismoking medications in healthcare basket benefits.

Authors' contributions

Conceptualization: AM, DM and GLT; Methodology: AM, DM; Formal Analysis: AM; Investigation: AM; Data Collection: AM, DM, GT, EL, MF, AF, SP, MRG, MF, GB, GM and EDV; Data Entry: AM, FM; Writing – Original Draft Preparation: AM and GT; Writing – Review & Editing: GLT, RS and PV; Supervision: GLT; Project Administration: AM.

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Conflicts of interest statement

The authors declare no conflict of interest.

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REFERENCES

1. 1. World Health Organization. WHO report on the global tobacco epidemic, 2008: the MPOWER package. Geneva: WHO; 2008.
2. Mannocci A, Colamesta V, Conti V, Cattaruzza MS, Paone G, Cafolla M, et al. Demographic characteristics, nicotine dependence, and motivation to quit as possible determinants of smoking behaviors and acceptability of shocking warnings in Italy. Biomed Res Int. 2014;2014:723035. doi: 10.1155/2014/723035
3. Mannocci A, Colamesta V, Mipatrini D, Messina G, Gualano MR, Gianfagna F, et al. From directive to practice: are pictorial warnings and plain packaging effective to reduce the tobacco addiction? Publ Health. 2015;129:1563-70. doi: 10.1016/j.puhe.2015.08.014
4. Bertollini R, Ribeiro S, Mauer-Stender K, Galea G. Tobacco control in Europe: a policy review. Eur Respir Rev. 2016;25:151-7. doi: 10.1183/16000617.0021-2016
5. Fong GT, Hammond D, Hitchman SC. The impact of pictures on the effectiveness of tobacco warnings. Bull World Health Org. 2009;87:640-3.
6. European Commission. Commission Implementing Decision (EU) 2015/1842 of 9 October 2015 on the technical specifications for the layout, design and shape of the combined health warnings for tobacco products for smoking (notified under document C(2015) 6729). vol. 267. 2015.
7. World Health Organization. WHO framework convention on tobacco control. Geneva: World Health Organization; 2004.
8. Canadian Cancer Society. Cigarette Package Health Warnings: International Status Report 2018.
9. Parlamento Italiano. Legislative Decree 12th January 2016 no.6. Recepimento della direttiva 2014/40/UE sul

ravvicinamento delle disposizioni legislative, regolamentari e amministrative degli Stati membri relative alla lavorazione, alla presentazione e alla vendita dei prodotti del tabacco e dei prodotti correlati e che abroga la direttiva 2001/37/CE. 2016.
10. Hammond D, Abrams DB, Fong GT, Borland R, Cummings KM, McNeill A, et al. Text and graphic warnings on cigarette packages: findings from the international tobacco control four country study. Am J Prev Med. 2007;32:202-9. doi: 10.1016/j.amepre.2006.11.011
11. Heydari GR, Ramezankhani A, Talischi F. The impacts of cigarette packaging pictorial warning labels on smokers in the city of Tehran. Tanaffos. 2011;10:40-7.
12. Gravely S, Fong GT, Driezen P, Xu S, Quah ACK, Sansone G, et al. An examination of the effectiveness of health warning labels on smokeless tobacco products in four states in India: findings from the TCP India cohort survey. BMC Public Health. 2016;16:1246. doi: 10.1186/s12889-016-3899-7
13. Monárrez-Espino J, Liu B, Greiner F, Bremberg S, Galanti R. [Systematic review of the effect of pictorial warnings on cigarette packages in smoking behavior]. Rev Panam Salud Publica. 2015;38:515-32.
14. Yong H-H, Borland R, Siahpush M. Quitting-related beliefs, intentions, and motivations of older smokers in four countries: Findings from the international tobacco control policy evaluation survey. Addict Behav. 2005;30:777-88. doi: 10.1016/j.addbeh.2004.08.023
15. Brewer NT, Hall MG, Noar SM, Parada H, Stein-Seroussi A, Bach LE, et al. Effect of pictorial cigarette pack warnings on changes in smoking behavior. A randomized clinical trial. JAMA Intern Med. 2016;176:905-12. doi: 10.1001/jamainternmed.2016.2621
16. Woelbert E, d'Hombres B. Pictorial health warnings and wear-out effects: evidence from a web experiment in 10 European countries. Tob Control. 2019. doi: 10.1136/tobaccocontrol-2018-054402
17. Ratih SP, Susanna D. Perceived effectiveness of pictorial health warnings on changes in smoking behaviour in Asia: a literature review. BMC Public Health 2018;18:1165. doi:10.1186/s12889-018-6072-7.
18. Swayampakala K, Thrasher JF, Yong H-H, Nagelhout GE, Li L, Borland R, et al. Over-time impacts of pictorial health warning labels and their differences across smoker subgroups: Results from adult smokers in Canada and Australia. Nicotine Tob Res. 2018;20:88-96. doi: 10.1093/ntr/ntx134
19. Levy DT, Mays D, Yuan Z, Hammond D, Thrasher JF. Public health benefits from pictorial health warnings on US cigarette packs: a SimSmoke simulation. Tob Control. 2017;26:649-55. doi: 10.1136/tobaccocontrol-2016-053087
20. Kang E. Assessing Health Impacts of Pictorial Health Warning Labels on Cigarette Packs in Korea Using DYNAMO-HIA. J Prev Med Publ Health. 2017;50:251-61. doi: 10.3961/jpmph.17.032
21. Mannocci A, Colamesta V, Mipatrini D, Boccia A, Terzano C, La Torre G. [How would plain packaging and pictorial warning impact on smoking reduction, cessation and initiation?]. Epidemiol Prev. 2013;37:400-5.
22. Francis DB, Hall MG, Noar SM, Ribisl KM, Brewer NT. Systematic Review of Measures Used in Pictorial Cigarette Pack Warning Experiments. Nicotine Tob Res. 2017;19:1127-37. doi: 10.1093/ntr/ntx082
23. Fagerström KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav. 1978;3:235-41.
24. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire. Br J Addict. 1991;86:1119-27.
25. Hitchman SC, Mons U, Nagelhout GE, Guignard R, Mcneill A, Willemsen MC, et al. Effectiveness of the European Union text-only cigarette health warnings: findings from four countries. Eur J Public Health. 2012;22:693-9. doi: 10.1093/eurpub/ckr099
26. Colamesta V, Mannocci A, La Torre G. Health warnings on tobacco packaging in Italy: do they describe all possible smoking-related conditions? Sens Sci. 2014:77-81. doi: 10.14616/sands-2014-2-7781
27. La sorveglianza Passi. Abitudine al fumo dati sorveglianza Passi. 2013. Istituto Superiore di Sanità. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. Available from: www.epicentro.iss.it/passi/dati/fumo.asp.
28. Hammond D, Thrasher J, Reid JL, Driezen P, Boudreau C, Santillán EA. Perceived effectiveness of pictorial health warnings among Mexican youth and adults: a population-level intervention with potential to reduce tobacco-related inequities. Cancer Causes Control. 2012;23(Suppl 1):57-67. doi: 10.1007/s10552-012-9902-4
29. Mutti S, Reid JL, Gupta PC, Pednekar MS, Dhumal G, Nargis N, et al. Perceived effectiveness of text and pictorial health warnings for smokeless tobacco packages in Navi Mumbai, India, and Dhaka, Bangladesh: findings from an experimental study. Tob Control. 2016;25:437-43. doi: 10.1136/tobaccocontrol-2015-052315
30. Lingwall C, Nehl E, Topuridze M, Sturua L, Maglakelidze N, Berg CJ. Perceived Effectiveness of Differing Health Warning Label Messaging Strategies among Adults in the Republic of Georgia: One Size Does Not Fit All. Int J Environ Res Publ Health. 2018;15. doi:10.3390/ijerph15102221.
31. Reid JL, Mutti-Packer S, Gupta PC, Li Q, Yuan J, Nargis N, et al. Influence of Health Warnings on Beliefs about the Health Effects of Cigarette Smoking, in the Context of an Experimental Study in Four Asian Countries. Int J Environ Res Public Health 2017;14. doi: 10.3390/ijerph14080868
32. Mansour AY, Bakhsh Z. Factors affecting the perceived effectiveness of pictorial health warnings on cigarette packages in Gulf Countries. A cross-sectional study. Tob Use Insights. 2017;10:1179173X17698462. doi: 10.1177/1179173X17698462
33. Bader RK, Shihab RA, Al-Rimawi DH, Hawari FI. Informing tobacco control policy in Jordan: assessing the effectiveness of pictorial warning labels on cigarette packs. BMC Public Health. 2017;18:84. doi: 10.1186/s12889-017-4642-8
34. Green AC, Kaai SC, Fong GT, Driezen P, Quah ACK, Burhoo P. Investigating the effectiveness of pictorial health warnings in Mauritius: findings from the ITC Mauritius survey. Nicotine Tob Res. 2014;16:1240-7. doi:10.1093/ntr/ntu062
35. Borland R, Wilson N, Fong GT, Hammond D, Cummings KM, Yong H-H, et al. Impact of graphic and text warnings on cigarette packs: findings from four countries over five years. Tob Control. 2009;18:358-64. doi: 10.1136/tc.2008.028043
36. Hammond D, Fong GT, McDonald PW, Cameron R, Brown KS. Impact of the graphic Canadian warning labels on adult smoking behaviour. Tob Control. 2003;12:391-5.
37. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. Prog Behav Modif. 1992;28:183-218.
38. Prochaska JO, DiClemente CC. Stages and processes of

self-change of smoking: toward an integrative model of change. J Consult Clin Psychol. 1983;51:390-5.
39. Fong GT, Hammond D, Jiang Y, Li Q, Quah ACK, Driezen P, et al. Perceptions of tobacco health warnings in China compared with picture and text-only health warnings from other countries: an experimental study. Tob Control. 2010;19(Suppl. 2):i69-77. doi: 10.1136/tc.2010.036483.
40. Agaku IT, Filippidis FT, Vardavas CI. Effectiveness of text versus pictorial health warning labels and predictors of support for plain packaging of tobacco products within the European Union. Eur Addict Res. 2015;21:47-52. doi: 10.1159/000366019
41. Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial cigarette pack warnings: a meta-analysis of experimental studies. Tob Control. 2015. doi: 10.1136/tobaccocontrol-2014-051978
42. Thrasher JF, Pérez-Hernández R, Arillo-Santillán E, Barrientos-Gutiérrez I. [Towards informed tobacco consumption in Mexico: effect of pictorial warning labels in smokers]. Salud Publica Mex 2012;54:242–53.
43. McNeill A, Gravely S, Hitchman SC, Bauld L, Hammond D, Hartmann-Boyce J. Tobacco packaging design for reducing tobacco use. Cochrane Database Syst Rev. 2017;4:CD011244. doi: 10.1002/14651858.CD011244.pub2
44. Malouff JM, Schutte NS, Rooke SE, MacDonell G. Effects on smokers of exposure to graphic 46.
45. Saha I, Paul B. War against tobacco. Where do we stand? Ind J Pub Health. 2018;62:55-7. doi: 10.4103/ijph.IJPH_166_17
46. India Details | Tobacco Control Laws 2018. Available from: www.tobaccocontrollaws.org/legislation/country/india/summary.
47. Stead M, Moodie C, Angus K, Bauld L, McNeill A, Thomas J, et al. Is consumer response to plain/standardised tobacco packaging consistent with framework convention on tobacco control guidelines? A systematic review of quantitative studies. PLoS ONE 2013;8:e75919. doi: 10.1371/journal.pone.0075919
48. Smith CN, Kraemer JD, Johnson AC, Mays D. Plain packaging of cigarettes: do we have sufficient evidence? Risk Manag Healthc Policy 2015;8:21-30. doi: 10.2147/RMHP.S63042
49. Dunlop S, Perez D, Dessaix A, Currow D. Australia's plain tobacco packs: anticipated and actual responses among adolescents and young adults 2010-2013. Tob Control. 2016. doi: 10.1136/tobaccocontrol-2016-053166
50. Ugen S. Bhutan: the world's most advanced tobacco control nation? Tob Control. 2003;12:431-3.
51. What Finland's plan to be tobacco-free can teach the world - CNN 2017. Available from: https://edition.cnn.com/2017/01/26/health/finland-tobacco-free-plan/index.html.
52. Australian Government – Department of Health. Tobacco Control. Available from: .www.health.gov.au/internet/main/publishing.nsf/Content/tobacco
53. Australian Government – Department of Health. Tobacco control timeline 2017. Available from: www.health.gov.au/internet/publications/publishing.nsf/Content/tobacco-control-toc~timeline.
54. Feliu A, Filippidis FT, Joossens L, Fong GT, Vardavas CI, Baena A, et al. Impact of tobacco control policies on smoking prevalence and quit ratios in 27 European Union countries from 2006 to 2014. Tob Control. 2019;28:101-9. doi: 10.1136/tobaccocontrol-2017-054119

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Communication and basic health counselling skills to tackle vaccine hesitancy

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Abstract
The Italian law 119/2017 mandates ten childhood vaccinations to allow population aged 0-16 attend educational places and state school. This law enforcement is due to low coverage rates for some vaccine-preventable diseases and to a complex phenomenon known as vaccine hesitancy. Basic health counselling skills represent relevant resources to let healthcare workers effectively address vaccine hesitancy in the population. We indicated recommended communication approaches and basic health counselling skills to be applied by public health professionals according to the specific target population with vaccine deficit that means people not at all or partially reached by vaccinations. Public health professionals are called to know, acquire, use, and adapt basic health counselling skills to effectively address vaccine hesitancy diversely affecting different groups of population.

Key words
- vaccination
- communication
- counselling

INTRODUCTION

The law 119/2017, as conversion of the decree 73/2017, made ten childhood vaccinations (tetanus, poliomyelitis, hepatitis B, diphtheria, pertussis, haemophilus B, measles, mumps, rubella, chicken pox) mandatory in Italy where coverage rates for various vaccine-preventable diseases have been decreasing since 2013 [1-3]. Vaccine hesitancy is defined as the reluctance or refusal to vaccinate despite the availability of vaccines [4], and enlisted among the ten major issues that demand attention from the World Health Organization (WHO) and health partners in 2019 [5]. Namely, it is a complex and context specific behaviour because it varies across time, place and vaccines and is influenced by a number of factors including issues of confidence, complacency, and convenience. Vaccine-hesitant individuals constitute a heterogeneous group of people who hold wide-ranged indecision on some vaccines as well as on vaccination overall: they may accept vaccines but remain concerned, may refuse or delay some vaccines but accept others, or may refuse all vaccines. Basing on this complexity, to date immunization coverage are the proxy data mostly used even if it is known that they are proven to be reliable for small samples and vaccine decrease does not fully coincide with vaccine hesitancy [6]. This relevant issue in public health broadly encompasses communication approaches that public health professionals can adopt to address vaccine hesitancy effectively. An Italian study shows that, even if paediatricians are favourable to vaccines and vaccinations, gaps are retrieved between their overall positive attitudes on one hand and knowledge, beliefs and practices on the other hand, consequently affecting their response capacity to address parents' questions [7]. In general, public health institutions should communicate using strategically established methods and avoiding rushed communication which leads to implementing wrong interventions and losing credibility. In 2010, the WHO suggested that to improve communication effectiveness within the healthcare system some elements are needed, such as development of networks and empowerment of communication competences [8-14]. Moreover, within vaccine communication, public health professionals deal with an even more highly complex process that involves several different stakeholders who are featured by own worldviews, perceptions and needs. In this framework, vaccine communication does not correspond to performing one-way informative interventions or teaching, but initiates mutual dialogue and reciprocal exchange among all people involved, despite their different roles and diverse responsibilities. It entails that communication methods and tools have to be adequately aligned with the specific setting and intended target groups. Both individuals and the com-

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munity as a whole shall be effectively involved so that homogenous, consistent and strategically coordinated interventions can be implemented [15].

In particular, to effectively address vaccine hesitancy in the general population, basic health counselling skills represent relevant resources to professionals because they are key elements to make healthcare workers create effective relationships with people who can activate their own resources and choose solutions that are consistent with their needs. Basic counselling skills actually stand for in fact the components of a well-structured intervention aimed at helping people to actively face health-related challenges.

Basing on the categorisation by the European Centre for Disease Prevention and Control (ECDC) [16] that identifies four population groups with vaccine deficit, meaning not at all or partially reached by vaccinations (hesitant, unconcerned, active resisters, poorly reached), the authors have associated communication and basic health counselling skills which healthcare professionals need to apply accordingly *(Table 1)*.

As reported in *Table 1*, it emerges that the use of basic health counselling skills mainly applies to three out of four population categories which are hesitant, unconcerned and poorly reached. Above all in the two cases of hesitant and unconcerned people, who are characterised by a strong misinformation, public health professionals should implement the basic techniques for active listening, such as reformulation or investigative skill, as well as be prepared engaging in information discussions. In the case of poorly reached individuals (people not accessing vaccinations because of social exclusion or work/time pressure), vaccine promotion is required to be developed mostly at community level, concerning the wider institutional and professional network that involves integrated collaboration overall. On the contrary, regarding the two subcategories of active resisters, i.e., "convinced and content" and "committed and missionary", extensive discussions and debate are supposed to be avoided because they shall reveal to be seldom productive, non-productive or even counter-productive. However, the other's point of view does not have to be underestimated and healthcare professionals should show openness and a non-judging attitude to allow antivaccination activists further contacts or a re-examination position in future.

COMMUNICATION AND BASIC HEALTH COUNSELLING SKILLS

Basic health counselling skills consist of:

- knowledge of the counselling scope that does not correspond with giving advice and quick solutions or general information, but relates to facilitation process in order to activate personal resources in the individual who shall be able to deal with difficulties or perplexities responsibly and manage the own worries in an aware and informed manner;
- self-awareness both of qualities that can favour or hinder the relationship and of personal communication style;
- knowledge of and capacity to use the relational skills (empathy, self-awareness, active listening) which are fundamental to the relation creation and maintenance;
- knowledge of the counselling process to structure an intervention in phases that in turn envisage some fundamental steps (initial greeting, relationship building by active listening, main problem assessment, feasible goal setting, alternative solution proposal, summarising, evaluation, termination or referral, closure and final greeting);
- strengthening the capacity of team working and networking.

The relational skills (empathy, self-awareness, active listening) are integral parts of counselling and can be learned and perfected with specific training [17, 18].

Empathy is the ability to know how to enter into another person's scheme of reference, the capacity to see the world through the other person's eyes and, grasping information from his/her rational and emotional point of view (thoughts, experiences, emotions, and mean-

Table 1
Communication and basic health counselling skills to be applied by public health professionals per target population with vaccine deficit

Target population with vaccine deficit		Communication and basic health counselling skills to be applied by public health professionals
Hesitant	Uninformed Misinformed Well-read and open-minded	Need to be prepared for discussion Reformulating objection Recognising emotional status Issue(s)/concern(s) expressed not to be minimised Delivering scientifically-grounded and personalised information
Unconcerned	Uninformed Informed but self-serving	Need to be prepared for discussion Informing appropriately (few information) Stimulating questions according to investigative skill Summing-up Verifying levels of effective understanding
Active resisters	Convinced and content Committed and missionary	Favouring exchange of views to allow a position re-examination Extensive discussions and debate to be avoided (seldom productive, non-productive or counter-productive) Other's point of view not to be underestimated
Poorly reached	Socially excluded Working and time pressured	Networking and integrated collaboration among health professionals and institutions which promote vaccination, even to facilitate services' access

ings), to understand the person's requests and needs. By showing empathy, healthcare workers live "as if" they were the others but staying separate from the others, otherwise they would no longer be able to help people and meet people needs. Being empathic does not mean confusing the two viewpoints: empathy is in fact supported by distinction and not confusion. In the professional relationship between experts and lay public, empathy contributes to maintain separation between the two different roles [19-23].

Self-awareness relates to being familiar with the own "inner world" that is the cultural reference scheme, value system, perceptions, emotions, and personal conceptual maps. Other factors to be aware of are: the context, the self-observation and self-monitoring capacity, the management of nonverbal and paraverbal language that is the emotional expression underlying the verbal content [17].

Active listening helps both professionals and people focusing on the other's point of view, it can be triggered through bidirectional communicative channels that facilitate useful information exchange flows and participatory processes. It is fully based on empathy and on accepting the other's point of view, as well as on creating a positive relationship and a non-judging approach [19]. To listen actively, the adoption of a reference methodology articulated in empathic reflecting is necessary. It encompasses the use of four specific communicative techniques: reformulation, clarification, investigative skill, first-person messages [24]. In particular:

- reformulation corresponds with repeating what the other has just said, using the same words or rephrasing in a more concise way by other terms, without adding any other concepts or different content (*"Then you are telling me that…", "This means that you think…", "In other words…"*);
- clarification uses the outlining emotions associated with the content communicated, referring to verbal, paraverbal and non-verbal communication (*"From the look on your face it seems to me that you are worried"; "From the tone of your voice, I can feel you are uncertain about what I am saying"*);
- the investigative skill is the ability to ask, selecting the most appropriate question type according to the specific situation: "open questions" to be preferred at the beginning of the conversation because they allow wider answer options, extend and deepen the relationship, encourage opinion and thought expression; closed-ended questions are clearly defined, they induce a unique answer, and often stress only one reply option, limit the communication and make it more focussed, demand only objective facts and sometimes may seem restrictive and obstructing (*"When…?", "Where?", "Who?"*). Questions starting with *"Why"* can be perceived as accusatory, and should be preferably avoided;
- the use of first-person messages helps to distinguish between professional's and another person's opinions contributing to avoid conflicts. This technique serves also to create a non-judgmental and an autonomous decision-making process (*"I think that…", "In my opinion…"*) [17, 18].

THE USE OF COMMUNICATION AND BASIC HEALTH COUNSELLING SKILLS TO ADDRESS VACCINE HESITANCY

As indicated, public health professionals need to know, acquire and implement basic vaccine counselling skills when dealing above all with seven out of nine challenging population groups, even if such these competences can be also helpful somehow with people totally refusing vaccinations. Knowledge and correct use of basic health counselling skills allow in fact healthcare workers achieve an effective vaccine communication because relying on a structured and personalised intervention. Vaccine communication need to acknowledge individual risk perception that does not depend only on the effective hazard but to a greater extent also on the outrage linked to it, basically related to emotional factors prevailing on the hazard itself [25-27]. Within vaccine communication, by "actively listening" to people fears and being aware of the wide-ranged determinants for the perceived risk, public health authorities have better opportunities to understand and to deal with the origin of perception [28-30]. Especially as far as particular groups are concerned, in the case of childhood vaccinations the main parents' fears and worries refer to adverse reaction effects or vaccine safety [31, 2]. If people perceive empathy and consideration to their doubts and opinions, they will be in turn more willing to listen and trust. On the contrary, when people perceive sense of distance, the trust level would be reduced and emotional components of perception prevail on the rational part, not activating listening triggers even if adequate scientific communication was developed. Vaccine communication bases on the participatory communication model featured by an interactive exchange assessment overall, where the understanding of social and personal issues is decisive to make scientific information a useful knowledge to citizens [32, 33].

People should not perceive to be passively advised as "just getting reassurance by experts": in the current communication approach the public sphere is put at the centre of the whole process [25, 27].

If vaccine communication can be considered an interactive process of information and opinion sharing among individuals, groups and institutions, healthcare workers provide people with constructive, up-to-date and meaningful messages and direct-access information services, using a varied range of tools in order to allow them make the best possible decisions about their own health. This make that an important step within the counselling intervention relates to verifying levels of effective understanding in people after having provided scientifically-grounded and personalised information. Looking at the big picture as a whole, in fact, in a multistakeholder scenario the position of public health professionals toward individuals or communities is fundamental as per their key advocacy role in being at the helm of the processes, from planning to development, monitoring and evaluation. Such a framework necessarily demands for strategic communication planning, favoured by the integrated participation and collaboration of institutions, services and systems involved at different levels (national, regional and local) [34-38].

The professional practice of healthcare workers is framed in a specific organisational system and, more broadly, in a complex context where they refer to other stakeholders, institutions and media. Thus, health professionals need to be aware of web-based and new media for two reasons: on the one hand, knowing the kind of information that flows through the net could be useful to forestall some possible criticism; on the other hand, groups on social networks may constitute extremely valuable tools to keep individuals up to date with advices and to promptly hinder false or ambiguous knowledge they could have found on the web. Health information-seeking behaviour on the web shows, in fact, how often people turn first to the Internet both using information to formulate their thoughts and making their own judgements on preferred treatments [39]. Web 2.0, forums and social networks, which enable two-way and multi-way communication flows, have spread out anti-vaccination voices to broader reach than ever before while, years ago, they would have been restricted to certain countries [40]. Health professionals are getting used to situations where the "health blogger" or the "concerned mother" are as important as – or even more influent than – a general practitioner or paediatrician, strongly influencing individual decision-making process [41-45]. Aware and skilled communication processes can facilitate relationships because even in presence of a world wide web 2.0, they do represent significant tools for collaboration building and achieving shared solutions. The public health goal is actually to stimulate professionals to reflect upon the need to recognize, develop and adapt basic health counselling skills in order to provide adequate information and emotional support to people who show hesitant attitudes towards vaccinations and can be allowed to activate informed and responsible decisions.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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REFERENCES

1. Italia. Legge 31 luglio 2017, n. 119. Conversione in legge, con modificazioni, del decreto-legge 7 giugno 2017, n. 73, recante disposizioni urgenti in materia di prevenzione vaccinale. Gazzetta Ufficiale della Repubblica Italiana – Serie Generale n. 182, 05 agosto 2017. Available from: www.gazzettaufficiale.it/eli/id/2017/08/5/17G00132/sg.
2. Giambi C, Fabiani M, D'Ancona F, et al. Parental vaccine hesitancy in Italy – Results from a national survey. Vaccine. 2018;36(6):779-87. doi:10.1016/j.vaccine.2017.12.074
3. Istituto Superiore di Sanità. EpiCentro. Il portale dell'epidemiologia per la sanità pubblica. Morbillo, ultimi aggiornamenti. Available from: www.epicentro.iss.it/problemi/morbillo/aggiornamenti.asp.
4. World Health Organization. Report of the SAGE working group on vaccine hesitancy. Geneva: WHO; 2014. Available from: www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf?ua=1.
5. World Health Organization. Ten threats to global health in 2019. Geneva: WHO; 2019. Available from: www.who.int/emergencies/ten-threats-to-global-health-in-2019.
6. Petrelli F, Contratti CM, Tanzi E, Grappasonni I. Vaccine hesitancy, a public health problem. Ann Ig. 2018;30:86-103. doi:10.7416/ai.2018.2200
7. Filia A, Bella A, D'Ancona F, Fabiani M, Giambi C, Rizzo C, Ferrara L, Pascucci MG, Rota MC. Childhood vaccinations: knowledge, attitudes and practices of paediatricians and factors associated with their confidence in addressing parental concerns, Italy, 2016. Euro Surveill. 2019;24(6):pii=1800275. doi: https://doi.org/10.2807/1560-7917.ES.2019.24.6.1800275
8. Sweet M. Pandemic lessons learned from Australia. BMJ. 2009;339:424-6.
9. Deirdre HD. The 2009 influenza pandemic. An independent review of the UK response to the 2009 influenza pandemic. 2010. Available from:
10. http://webarchive.nationalarchives.gov.uk/+/http://www.cabinetoffice.gov.uk/media/416533/the2009influenza-pandemic-review.pdf.
11. Tay J, Ng YF, Cutter JL, James L. Influenza A (H1N1/2009) pandemic in Singapore public health control measures implemented and lessons learnt. AAMS. 2010;39(4):313-24.
12. World Health Organization, Regional Office for Europe, University of Nottingham. Recommendations for good practice in pandemic preparedness. Copenhagen, Denmark: WHO Regional Office for Europe; 2010. Available from: www.euro.who.int/__data/assets/pdf_file/0017/128060/e94534.pdf.
13. World Health Organization. Report of the review committee on the functioning of the international health regulations (2005) in relation to Pandemic (H1N1) 2009. Geneva: WHO; 2011. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf.
14. Greco D, Stern EK, Marks G. Review of ECDC's response to the influenza pandemic 2009-2010. Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/aboutus/Key%20Documents/241111COR_Pandemic_response.pdf.
15. World Health Organization. Public health measures during the influenza A(H1N1) 2009 pandemic. Meeting report. WHO Technical Consultation 26-28 October 2010, Gammarth, Tunisia. WHO; 2010. Available from: http://whqlibdoc.who.int/hq/2011/WHO_HSE_GIP_ITP_2011.3_eng.pdf.
16. ASSET. Action plan on science in society related issues in epidemics and total pandemics. Action plan handbook. Available from: www.asset-scienceinsociety.eu/outputs/deliverables/action-plan-handbook.
17. European Centre for Disease Prevention and Control. Let's talk about protection. Stockholm: ECDC; 2016. doi: 10.2900/573817
18. Luzi AM, De Mei B, Colucci A, Gallo P. Criteria for standardizing counselling for HIV testing. Ann Ist Super Sanità. 2010;46(1):42-50. doi: 10.4415/ANN_10_01_06
19. TELLME. Transparent communication in epidemics:

learning lessons from experience, delivering effective messages, providing evidence. Practical guide for health risk communication. New communication strategies for institutional actors. Available from: www.tellmeproject.eu/node/390.
20. Rogers CR. La terapia centrata sul cliente. Firenze: Martinelli; 1989.
21. Watzlavick P, Beavin JH, Jackson DD. Pragmatica della comunicazione umana. Boringhieri; 1976.
22. Gadotti G (Ed). La comunicazione sociale. Soggetti, strumenti e linguaggi. Milano: Arcipelago; 2001.
23. Gadotti G, Bernocchi R. La pubblicità sociale. Maneggiare con cura. Roma: Carocci; 2010.
24. Polesana MA. La pubblicità intelligente. L'uso dell'ironia in pubblicità. Milano: Franco Angeli; 2005.
25. De Mei B, Luzi AM. Le competenze di counselling per una gestione consapevole delle reazioni personali e dei comportamenti dell'operatore nella relazione professionale. Dossier. Milano: Zadig; 2011.
26. TELLME. Transparent communication in epidemics: Learning Lessons from experience, delivering effective messages, providing evidence. A new model for risk communication in health. Available from: www.tellmeproject.eu/node/314.
27. Sandman PM. Risk = Hazard + Outrage: Coping with controversy about utility risks. Engineering News-Record; 1999. p. A19-A23.
28. Covello VT. Social and behavioral research on risk: uses in risk management decisionmaking. In: Covello VT, Mumpower JL, Stallen PJ, Uppuluri VRR (Eds). Environmental impact assessment, technology assessment, and risk analysis. Berlin, Heidelberg, New York, Tokyo: Springer-Verlag; 1985.
29. European Commission. Assessment report on EU-wide pandemic vaccine strategies. 2010. Available from: http://ec.europa.eu/health/communicable_diseases/docs/assessment_vaccine_en.pdf.
30. Centers for Disease Control and Prevention. Provider resources for vaccine conversations with parents. Available from: www.cdc.gov/vaccines/hcp/conversations/about-vacc-conversations.html.
31. Sjoberg L. Risk Perception by the public and by experts: a dilemma in risk management. Human Ecology Review. 1999;6(2):1-9.
32. Lambert TW, Soskolne LC, Bergum V, Howell J, Dossetor JB. Ethical perspectives for public and environmental health: fostering autonomy and the right to know. Environmental Health Perspectives. 2003;111(2):133-7.
33. Leiss W, Krewski D. Risk communication: theory and practice. In: Leiss W (Ed). Prospects and problems in risk communication. Waterloo, Ontario: University of Waterloo Press; 1989. p. 89-112.
34. Slovic P. The perception of risk. London and Sterling: Earthscan Publ. Ltd; 2000.
35. Biasio LR. Vaccine hesitancy and health literacy. Hum Vaccin Immunother. 2017;13(3):701-2. doi: 10.1080/21645515.2016.1243633
36. Beck U. La società del rischio. Roma: Carrocci Editore; 2000.
37. Biocca M. La comunicazione sul rischio per la salute. Nel Teatro di Sagredo: verso una seconda modernità. Torino: Centro Scientifico Editore; 2002. (Comunicazione in Sanità Vol. 6).
38. Leiss W. Three phases in the evolution of risk communication practice. Annals of the American Academy of Political and Social Science. 1996;545:85-94.
39. National Research Council. Improving risk communication. Washington, DC: National Academy Press; 1989.
40. Kata A. Anti-vaccine activists, Web 2.0 and the postmodern paradigm. An overview of tactics and tropes used online by the anti-vaccination movement. Vaccine. 2012;30:3778-89.
41. European Centre for Disease Prevention and Control. Communication on immunisation – building trust". Technical document. Stockholm: ECDC; 2012.
42. CDC Facebook page. Available from: https://www.facebook.com/CDC/.
43. Markoff J. Entrepreneurs see a Web guided by common sense. New York Times; 2006.
44. De Mei B, Luzi AM. Il valore aggiunto delle competenze di counselling per una comunicazione efficace in ambito professionale. Dossier. Milano: Zadig; 2011.
45. Catalan-Matamoros D, Peñafiel-Saiz C. How is communication of vaccines in traditional media: a systematic review. Perspectives in Public Health. 2018;138(4). doi: 10.1177/1757913918780142

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Book Reviews, Notes and Comments

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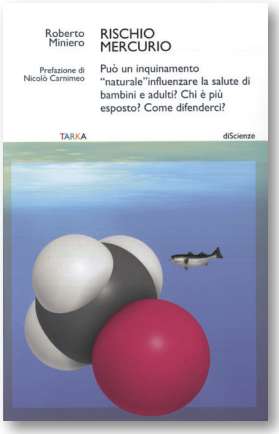

RISCHIO MERCURIO
Roberto Miniero
Mulazzo (MS): Tarka Edizioni; 2019. 129 p.
ISBN 978-88-99898-84-7.
€ 15,50.

[The risk of mercury]

Rischio mercurio by Roberto Miniero is a well-balanced mix of environmental health literacy and public health advocacy aimed at raising public awareness on the burden of disease related to methylmercury exposure caused by fish consumption in Italy.

Cinnabar (mercury sulphide) is largely present in the Mediterranean area and has been extensively mined and processed, in order to obtain mercury, since ancient times. Methylmercury is an organometallic compound widely present in aqueous environment as consequence of the activity of anaerobic organisms on cinnabar ore. Methylmercury in the marine environment migrates in living organisms thus contaminating the food chain, especially with respect to predatory fish like swordfish and tunafish. While natural methylmercury contamination of fish is ubiquitous, localized hotspots can be explained by the presence of specific industrial sites, like petrochemical plants that used mercury cathode cells for the chlorine soda process.

Considering firstly the abundance of naturally occurring mercury and the contributions from mines and industries, we can easily understand the statement made by Professor Aristeo Renzoni of Siena University already in 1998: "*In consideration of the high content of mercury in Mediterranean fish, there is a higher risk for those who live in this basin and consume large amounts of local sea-food, with respect to others residing in different areas of the world. This risk seems to specifically concern fishermen and their families, who maintain traditional eating habits and eat, on average, more than four fish meals by week*".

The health impact of methylmercury in humans has been dramatically discovered in the Fifties in Minamata (Japan), where a chemical industry that used mercury cathode cells released large amounts of methylmercury in the sea, thus contaminating the environment and the food chain. Local fish was extensively consumed by fishermen, their families and the resident population. The most affected segment of the population was constituted by children whose mothers were exposed to methylmercury during their pregnancy. A severe neurologic syndrome affected infants and children, with a high fatality rate and a devastating impairment of the health of survivors. In the subsequent years several independent studies performed in other parts of the world confirmed the causal link between exposure to methylmercury and severe neurological damage.

Subsequently to this first series of studies, focused on "extreme" settings, a large number of investigations was performed on populations of families of fishermen, whose diet was largely based on fish consumption. These "second generation" studies detected adverse effects of methylmercury at levels much lower than those that determined death or severe neurological disease. These adverse effects were mainly constituted by cognitive impairment in children, and also by cardiologic diseases. From this body of evidence regulatory agencies defined exposure levels regarded as "*tolerable*", that eventually decreased over time inasmuch as the available scientific evidence increased in quality and quantity. In the early Nineties, the European regulation indicated a common limit of 0.5 microgram per gram of fish for all species, except tunafish and swordfish whose limit value was 1 microgram per gram.

A large Italian survey conducted between 2004 and 2007 showed an average concentration of methylmercury of 0.190 micrograms per gram of fish. Twenty per cent of fish had a methylmercury concentration exceeding 0.5 micrograms per gram. These findings provided the rationale for a subsequent thorough review of the Italian situation that showed noncompliance of the mercury limit levels in 36% of the fish being distributed.

In addition to these findings, that represent an important indication of a potential hazard for human health, several studies have investigated the actual body burden of mercury in the Italian population by measuring the concentration of mercury in hair.

The maximum level of mercury regarded as tolerable by the international agencies corresponds to 1 microgram per gram of hair. A value higher than 4 micrograms per gram of hair is regarded as a threshold separating "*low*" exposures from "*high*" exposures. On average, the Italian population has an exposure level of 0.42 micrograms per gram of hair, which is complying with international standards. Frequent tunafish consumers have an average exposure level of 9 micrograms per gram of hair, about 20 times that of the general population. All other population subgroups whose average exposure values exceed 4 micrograms per gram of hair are mainly constituted by fishermen. Among the population subgroups that exceed the tolerable level of 1 microgram per gram of hair, several studies document the presence of sub-

jects resident in the Eastern coast of Sicily where a major industrial settlement released large amounts of mercury (municipalities of Augusta, Priolo and Melilli).

In light of the abovementioned available evidence, the Italian situation can be summarized as follows: the great majority of the population has a level of mercury exposure complying with international standards. Major departures from this level are shown for fishermen, high fisher consumers and communities resident near industrial settlements characterized by (previous) uncontrolled release of mercury in the sea water.

These are the population subgroups within which an observable burden of mercury-related disease can be regarded as certain, even if no systematic ad hoc study has so far been realized.

Mercury-caused health impact on fishermen and high consumers is a so-called invisible disaster. Considerations of health equity and environmental justice should first of all trigger a national health survey on these population subgroups aimed at detecting mercury victims and providing support to them and their families.

In the meanwhile, a major prevention and information initiative is badly needed. This campaign should be carried on in Italian coastal areas with a main focus on fishermen and their families. The aim should be to find modes of fish consumption that ensure all the ascertained benefits of this precious resource without implying excessive mercury absorption. This means, among else, an active involvement of general practitioners who should advice their patients on how to meet these two objectives taking into account variables such as age, gender and phase of reproductive life.

By reading the rich reference list on which this book is based, the leading role of the Author in investigating the issue of mercury-related disease in Italy becomes quite clear. Dr Miniero, together with his colleagues has spent twenty years addressing this issue, and now he provides us with this exhaustive and remarkable publication, that will hopefully be endorsed by our national health Authorities.

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Articles in journal

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Books and chapters in a book

Godlee F, Jefferson T. Peer review in health sciences. London: BMJ Books; 1999.
Van Weely S, Leufkens HGM. Background paper: orphan diseases. In: Kaplan W, Laing R (Eds). Priority medicines for Europe and the world – a public health approach to innovation. Geneva: World Health Organization; 2004.

Proceedings

Fadda A, Giacomozzi C, Macellari V. Comparative measurements to validate a new telemetric pressure insoles system. In: 2. International Symposium on measurement, analysis and modelling of human functions. 1. Mediterranean Conference on measurement. Workshop on evaluation check of traceability. Proceedings. Genova: June 14-16, 2004. p. 425-7.

Technical reports

Della Seta M, Di Benedetto C, Leone L, Pizzarelli S, Siegmund U. ETHICSWEB technical guides. Manual for the creation of standards and guidelines for sharing information about knowledge organization systems on ethics and science. Roma: Istituto Superiore di Sanità; 2011. (Rapporti ISTISAN, 11/32).

Legislation

Italia. Decreto legislativo 29 ottobre, n. 419. Riordinamento del sistema degli enti pubblici nazionali, a norma degli articoli 11 e 14 della legge 15 marzo 1997, n. 59. Gazzetta Ufficiale – Serie Generale n. 268, 15 ottobre 1999.

US Social Security Administration. Evidentiary requirements for making findings about medical equivalence. Final rules. Fed Reg. 2006 Mar 1;71(40):10419-33.

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