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Education degree predicts cardiovascular outcomes in men suffering from erectile dysfunction

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Abstract

Background: The level of education has been recognized as a cardiovascular risk factor; nevertheless, it is often neglected in cardiovascular risk prediction.

Objectives: To evaluate the psychobiological correlates of the level of education and if it could predict incident major adverse cardiovascular events in men consulting for erectile dysfunction.

Methods: Total 3733 men (49.8 ± 13.7 years old) attending an andrology outpatient clinic for erectile dysfunction were studied. Sexual and psychological symptoms, hormonal and metabolic, as well as instrumental (penile color Doppler ultrasound) parameters were evaluated according to the education level (university, upper secondary, lower secondary, and primary degree). For a subset of 956 patients, data on incident major adverse cardiovascular events were retrospectively collected for 3.9 ± 2.4 years.

Results: As compared with men with university degree, those with a lower education had an increased frequency of moderate–severe erectile dysfunction (odds ratio = 1.21 [0.99;1.48], 1.41 [1.14;1.73], 1.70 [1.26;2.30] for upper secondary, lower secondary, and primary school, respectively) and reduced flaccid peak systolic velocity at penile color Doppler ultrasound. Men with a lower level of education tend to suffer from metabolic syndrome (odds ratio = 1.38 [1.06;1.79], 1.73 [1.34;2.24], 1.72 [1.24;2.37] for upper secondary, lower secondary, and primary school, respectively) and were more likely to have history of previous cardiovascular events. In the longitudinal study, men with a higher level of education had a significantly lower incidence of major adverse cardiovascular events. The role of higher education as an independent predictor of major adverse cardiovascular events was established by multivariable Cox regressions (hazard ratio = 2.14 [1.24–3.69]).

Discussion: In erectile dysfunction subjects, lower level of education is associated with a more severely impaired erectile function with atherogenic pathogenesis and with a worse cardio-metabolic profile. In addition, a lower level of education predicts

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forthcoming major adverse cardiovascular events. Therefore, education level should be considered as a costless but valuable information in the assessment of cardiovascular risk in patients with erectile dysfunction.

KEYWORDS
cardiovascular risk, erectile dysfunction, level of education, metabolic syndrome

1 | INTRODUCTION

Cardiovascular (CV) diseases (CVD) represent the highest cause of death in the world. Since 2000, ischemic heart disease has been responsible for up to 16% of the world's total deaths, becoming the biggest killer (WHO 2020 https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). Hence, it is pivotal to individuate precocious CV predictors for correcting the modifiable ones by ameliorating lifestyle or by using specific medications, thus preventing fatal and non-fatal CV events.

It is well known that erectile dysfunction (ED) is a marker of arterial damage and an early and independent predictor for major adverse CV events (MACE).[1] Therefore, a medical examination for sexual dysfunction represents an unmissable chance for defining a patient's CV risk status. ED shares several risk factors with CV diseases,[2] most of which are included in common risk algorithms for CV risk stratification (e.g., Framingham risk score, SCORE). Despite their practicality and simplicity, these engines are not accurate for all populations as they could be deemed reliable only if applied in contexts comparable to those in which they were developed.[3] Hence, in men suffering from ED, known to be at higher CV risk, it becomes fundamental focusing attention also on unconventional risk factors not included in current risk equations. In the last years, our research group focused the attention on this topic: several hormones (low testosterone and prolactin), intrapsychic (depression) and couple conditions (partner's decreased libido and cheating on the partner), as well as parenthood,[4] emerged as markers of an increased CV risk. Among the risk factors tested in our population of ED men, a low level of education emerged to play a relevant role in the assessment of CV risk, so much that, in low educated subjects with ED, the predictive efficacy of the Progetto Cuore risk engine, developed for the Italian population, is undermined.[5] The level of education attained is one of the most widely explored socioeconomic factors in the context of CV risk assessment, providing the most consistent results.[6] A lower level of education represents a surrogate marker of lower socioeconomic conditions as well as individuals' capability to catch and apply health advice provided in both healthcare and non-professional settings. Lower education levels have been associated, independently of other sociodemographic factors, with a higher lifetime risk of CV events, a higher CV morbidity and mortality. Despite this evidence, patients' level of education is not routinely collected in clinical settings, and it is not generally considered for CV risk assessment. Moreover, the CV risk profile according to the level of education attained in high-risk subjects, such as ED men, has not been thoroughly assessed. Therefore, the aim of the present study is to evaluate the association between the level of education and clinical, biochemical, and instrumental parameters known as related with higher CV risk in men seeking medical care for ED. Moreover, taking advantage of information on the occurrence of MACE retrospectively obtained in a subset of the same population, the present study assesses the role of a lower level of education as a predictor of incident MACE.

2 | MATERIALS AND METHODS

2.1 | Cross-sectional study

The data of a consecutive series of 3733 men attending for the first time an outpatient andrology clinic for ED were collected in the period between 2002 and 2015. Table 1 describes the sample. Data were retrospectively collected from medical records of subjects, which underwent a standard diagnostic protocol applied as for clinical practice to each patient referred for ED to the Andrology Outpatient Clinic of the Careggi Teaching Hospital (University of Florence). All participants provided informed consent. Medical history data including smoking habits, alcohol intake, medications used, and previous CV events were collected. Patients were also asked which level of education they achieved. Data were categorized, according to the Italian education system, as follows: none/primary education (that begins at age 6 and lasts 5 years); lower secondary education (that begins at age 11 and lasts 3 years); upper secondary education (that begins at age 14 and lasts 5 years); and higher education (e.g., university and post-university degree). Men were interviewed before the beginning of any specific diagnostic procedure or treatment using the Structured Interview on Erectile Dysfunction (SIEDY)[7,8] and ANDROTEST.[9] SIEDY is a 13-item validated structured interview investigating several characteristics of ED with answers reported as a Likert scale.[7,10] The questions grouped into three scales allow identifying and quantifying the three pathogenic components concurring with ED (i.e., organic, relational, and psychic).[7] ANDROTEST is a 12-item validated structured interview for the screening of testosterone deficiency in subjects with ED, with answers reported as a Likert scale.[9] Information on severity of ED was obtained with the following question (SIEDY, question 1A): "Is the erection sufficient for penetration?" Answers were categorized as a dummy variable being "erection sufficient for penetration in more than 50% of cases" corresponding to "no/mild ED," whereas "erection sufficient for penetration in less than 50% of the cases" corresponds to "moderate/severe ED." Libido was assessed by question #14 of SIEDY7 and the replies were then

TABLE 1 Characteristics of the sample

	Cross-sectional *n* = 3733	Longitudinal*n* = 956
Age (years)	49.8 ± 13.7	51.4 ± 13.3
Level of education (%)		
None/primary education	11.3	16.7
Lower secondary education	30.9	29.4
Upper secondary education	36.9	33.8
Higher education (university, etc.)	20.9	20.1
Current smoker (%)	30.4	35.1
Alcohol consumption (more than 4 drinks per day) (%)	3.2	4.1
Moderate–severe ED (erection sufficient for penetration <50% of the time) (%)	61.1	65.9
Decrease in sexual desire (%)	17.3	16.2
Reduced masturbation frequency (%)	71.9	78.7
Body mass index (kg/m^2)	26.5 ± 4.4	26.3 ± 3.8
Waist circumference (cm)	97.3 ± 11.5	97.0 ± 9.9
Blood glucose (g/L)	105.3 ± 37.5	105.1 ± 36.8
Glycated hemoglobin (%)	6.4 ± 1.7	7.0 ± 1.7
Total cholesterol (mg/dl)	198.7 ± 41.0	204.0 ± 41.3
High-density lipoprotein (HDL) cholesterol (mg/dl)	48.8 ± 12.8	49.6 ± 12.0
Triglycerides (mg/dl)	112.0 [79.0–160.0]	116.5 [82.0–164.8]
Systolic blood pressure (mmHg)	130.0 [120.0–140.0]	140.0 [130.0–150.0]
Diastolic blood pressure (mmHg)	80.0 [80.0–90.0]	85.0 [80.0–90.0]
Metabolic syndrome (%)	39.3	39.8
Diabetes mellitus (%)	21.1	19.8
Previous cardiovascular diseases (%)	10.8	10.3
Psychiatric condition (%)	8.3	8.4
Total testosterone (nmol/L)	15.5 ± 6.5	16.5 ± 6.1
Calculated free testosterone (pmol/L)	303.4 ± 133.8	324.3 ± 127.8
Luteinizing hormone (U/L)	3.8 [2.6–5.6]	3.9 [2.7–5.8]
CDS score	0.0 [0.0–4.0]	0.0 [0.0–3.0]
Penile color Doppler ultrasound		
Penile flaccid peak systolic velocity (cm/s)	17.1 ± 5.8	15.8 ± 5.6
Flaccid acceleration (m/s^2)	3.0 ± 1.4	2.8 ± 1.3
Penile dynamic peak systolic velocity (cm/s)	53.7 ± 19.4	53.0 ± 20.4
Middlesex Hospital Questionnaire (MHQ)		
Free-floating anxiety (MHQ-A)	5.2 ± 3.7	6.0 ± 3.5
Phobic anxiety (MHQ-F)	4.5 ± 2.7	5.3 ± 2.3
Obsessive-compulsive traits and symptoms (MHQ-O)	6.0 ± 3.9	6.9 ± 3.3
Somatization (MHQ-S)	3.5 ± 2.9	4.1 ± 2.8
Depressive symptoms (MHQ-D)	4.5 ± 3.3	5.6 ± 3.2
Histrionic/hysterical symptoms (MHQ-I)	5.1 ± 3.2	5.8 ± 2.9
Total score (∑MHQ)	28.6 ± 15.5	33.6 ± 12.6

Note: Data are expressed as mean ± standard deviation when normally distributed, median (quartiles) when not normally distributed, and as percentages when categorical.

categorized as a dummy variable being "unmodified or moderately reduced desire" correspondent to "No/mildly impaired sexual desire," whereas "remarkably reduced or absent desire" correspondent to "Moderately/severely impaired sexual desire." Frequency of masturbation was investigated by question #7 of ANDROTEST[9] and categorized in a dummy variable with autoeroticism in the last 3 months more frequent than or equal to three times for week was defined as "normal," whereas autoeroticism less frequent than three times for week was considered reduced. Patients filled out the Middlesex Hospital Questionnaire (MHQ), a self-administered questionnaire made of 48 items for the screening of psychological traits and symptoms.[11] The MHQ includes scales for free-floating, phobic and somatic anxiety, obsessive and depressive symptoms, and histrionic traits (MHQ-A, P, S, O, D and H, respectively), with a higher score indicating a higher level of psychopathology in each category. The sum of the aforementioned scores (ΣMHQ) is a broad index of psychopathology. Serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), glycated hemoglobin, total testosterone (TT), and luteinizing hormone (LH) were measured on fasting morning blood samples at the central laboratory of the Careggi Teaching Hospital (University of Florence). TT was measured by an immunoassay (electrochemiluminescent method; Modular Roche, Milan, Italy). Sex hormone binding globulin (SHBG) was available for a subset of 1808 patients, studied between September 2006 and September 2015. In this subset of our sample, calculated free T was derived using the Vermuelen formula.[12] The American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria for metabolic syndrome (MetS) definition were used.[13] Penile color Doppler ultrasound (PCDU) was performed according to international standard procedures[14] using 10 μg of alprostadil for inducing erection. Based on the medications used, the Chronic Diseases Score (CDS) was calculated and used as a summary of chronic illnesses.[15] The assessment of CV risk was evaluated using the Progetto Cuore risk engine developed in the Italian population to estimate the 10-year risk of occurrence of a first MACE, considering sex, age, and the presence of several conventional CV risk factors.[16]

2.2 | Longitudinal study

A longitudinal study was also performed for 956 out of the 3733 individuals who were included in the cross-sectional cohorts (Table 1). MACE occurred in this cohort were retrospectively collected for a mean of 3.9 ± 2.4 years. The identification of CV events through the International Classification of Diseases codes was previously described.[5]

3 | STATISTICAL ANALYSIS

Mean ± standard deviation and median (quartiles) were used as measures of central tendency for parameters with normal or non-normal distribution, respectively, unless otherwise specified. Analysis of covariance (ANCOVA) and binary logistic regression were applied for multivariate analysis for continuous and binary dependent variables, respectively. The results obtained by the ANCOVA were reported as estimated mean and 95% confidence interval (CI) of the dependent variable for each level of the independent variable (i.e., the categories of education level attained), the statistical significance of the difference in means between the degrees of education was assessed by the least significant difference method. The results of the binary logistic regressions were expressed as odds ratio (OR) and 95% CI. The analyses for incidence of MACE were performed using log-rank tests with between-group comparisons for the estimation of hazard ratio (HR) and 95% CI. Kaplan–Meier curves were used to represent the gradual decay of subjects free of MACE. Stepwise Cox regressions were carried out for multivariable analysis. Adjustment for age, smoking habits, and alcohol intake was applied to all the analyses; further adjustment for waist circumference (WC) and CDS was specified when applied. The software SPSS 27 (IBM Corporation, Armonk, NY, USA) was used to run the analyses.

4 | RESULTS

4.1 | Cross-sectional study

Among the 3733 individuals studied, 782 (20.9%), 1377 (36.9%), 1155 (30.9%), and 419 (11.3%) completed a higher, upper secondary, lower secondary, or primary education cycle, respectively.

Age, smoking habit, and alcohol intake showed a significant association with the level of education and, therefore, were introduced as confounders in the following analyses.

When compared to the category with the highest degree of education, patients belonging to the other groups showed, independently of age, smoking habit, and alcohol intake, a higher body mass index (BMI) (Figure 1A) and WC (Figure 1B). After adjusting for the aforementioned confounders, a lower level of education was associated with higher values of glycated hemoglobin (Figure 1C) and blood glucose (Figure 1D). In contrast, no significant difference was found when considering blood lipid levels (data not shown).

As compared with subjects with university and post-university degrees, patients in the lowest categories of education showed a higher number of comorbidities, as expressed by the stepwise increase in CDS (Figure 2A). In particular, they presented a higher prevalence of diabetes, MetS, and CVD (Figure 2B).

Among sexual parameters, after the adjustment for the aforementioned confounders and CDS, lower education was associated with a reduced prevalence of low libido (Figure 3A). Conversely, subjects with the lowest levels of education had an increased probability of having moderate–severe ED and reporting a reduced frequency of masturbation, as compared with subjects with university or post-university degree. Accordingly, patients who completed primary education showed decreased flaccid peak systolic velocity (PSV) levels (Figure 3B).

Individuals with lower secondary or primary education showed significantly higher levels of LH compared to the group with the

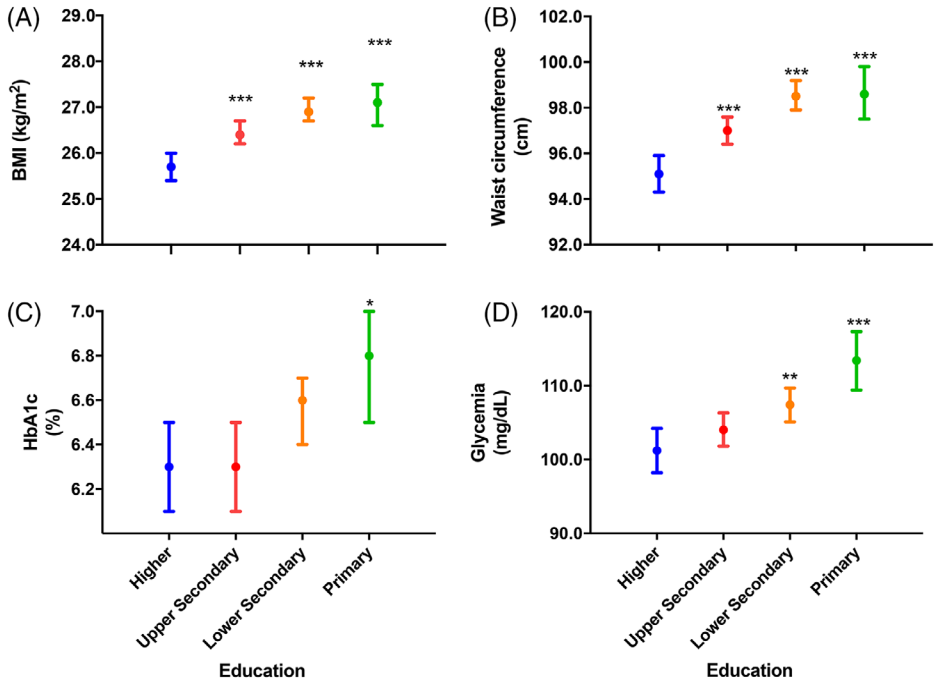

FIGURE 1 Association between education level and metabolic parameters. Means and 95% confidence interval of body mass index (BMI, panel A), waist circumference (panel B); glycated hemoglobin (panel C) and blood glucose (panel D) in different education level groups. $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.0001$ versus higher education (university and post-university degree). Data reported in panels A and B are adjusted for age, smoking habit, and alcohol intake; data reported in panels C and D are adjusted for age, smoking, alcohol intake, and waist circumference.

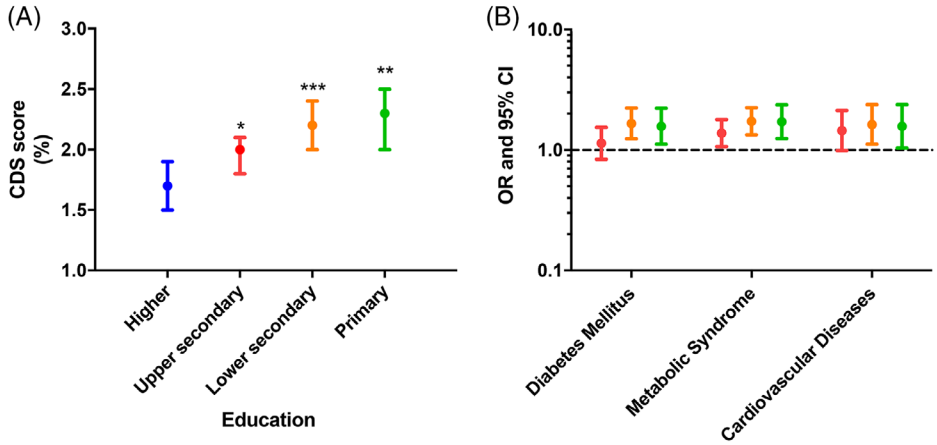

FIGURE 2 Association between education level and chronic morbidities. Means and 95% confidence interval (CI) of Chronic Disease Score (CDS, panel A) in different educational level groups. $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.0001$ versus higher education (university and post-university degree). Odds ratio (OR) and 95% CI of diabetes mellitus, metabolic syndrome, and cardiovascular diseases among different education level groups (upper secondary: red symbol, lower secondary: orange symbol, and primary: green symbol) (panel B). Data are adjusted for age, smoking habit, alcohol intake, and waist circumference.

highest grade of education (Figure 4A), while no differences in TT levels were observed (Figure 4B). Similar results were obtained when free T was considered ($p = 0.702$, 209 and 397 for upper secondary, lower secondary, and primary education vs. higher education, respectively).

When considering the psychological parameters, subjects with an intermediate level of education (lower and upper secondary education) scored higher than the group with university or post-university degrees in most of the sub-categories explored by the MHQ (with higher scores denoting more severe symptoms), with significant differences observed for patients with lower secondary education. Interestingly, at variance with other outcomes explored, subjects who completed primary education scored similar to patients in the highest education group in most of the sub-categories, reaching even significantly lower scores for phobic anxiety symptoms (Figure 5B–F). Accordingly, patients with a primary education degree reported a history of psychopathology less frequently than those in the highest education group (Figure 5A).

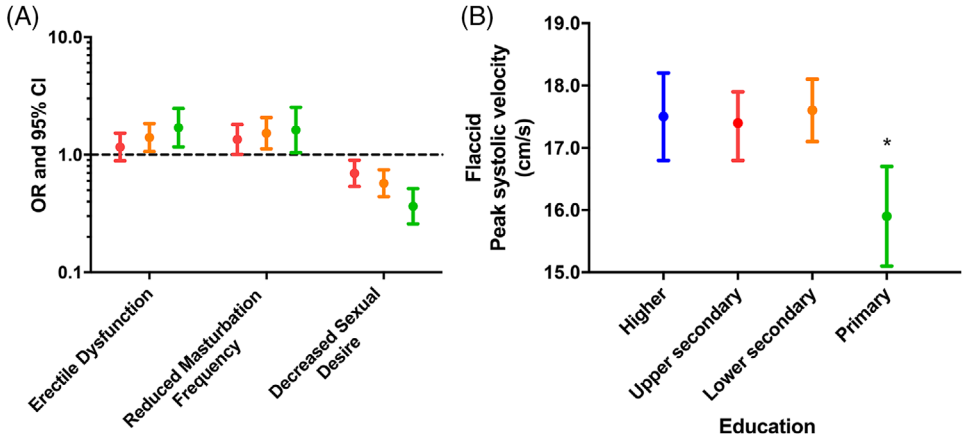

FIGURE 3 Association between education level and sexual function parameters. Odds ratio (OR) and 95% confidence interval (CI) of erectile dysfunction, reduced masturbation frequency, and decreased sexual desire among different educational level groups (upper secondary: red symbol, lower secondary: orange symbol, and primary: green symbol, panel A); means and 95% CI of flaccid peak systolic velocity among different education level groups (panel B). Data are adjusted for age, smoking habit and alcohol intake, waist circumference, and chronic diseases score. *$p < 0.05$ versus higher education (university and post-university degree)

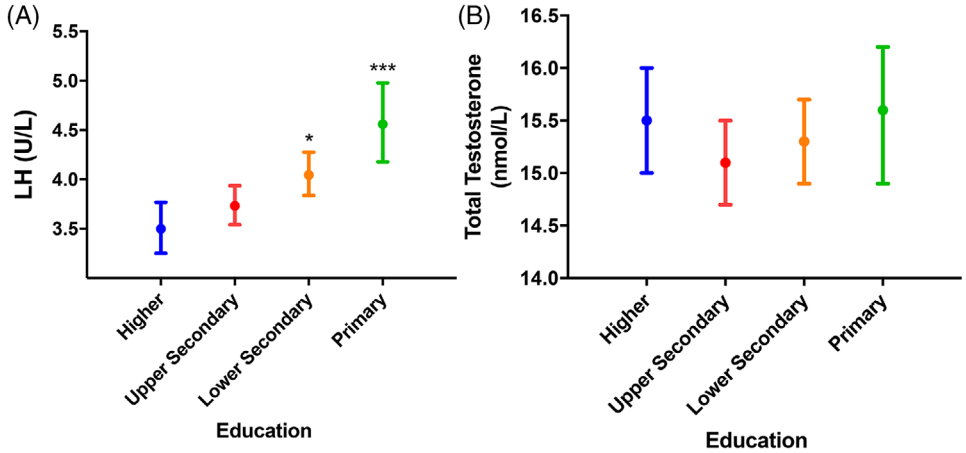

FIGURE 4 Association between education level and hormone levels. Means and 95% confidence interval of plasmatic luteinizing hormone (LH, panel A) and total testosterone (panel B) among different educational level groups. Data are adjusted for age, smoking habit and alcohol intake, waist circumference, and Chronic Diseases Score. *$p < 0.05$, ***$p < 0.0001$ versus higher education (university and post-university degree)

The comparison of the estimated 10-year CV risk derived from the Progetto CUORE algorithm showed that patients with lower or upper secondary education had a similar risk to those with university or post-university degrees, whereas the risk was significantly higher in patients with primary education, even after adjusting for confounders (Figure 6A).

4.2 | Longitudinal study

Among the 956 individuals studied, 192 (20.1%), 323 (33.8%), 281 (29.4%), and 160 (16.7%) completed a higher, upper secondary, lower secondary, and primary education cycle (Table 1). Over a mean follow-up of 3.9 ± 2.4 years, 80 MACE were observed, among which 55 (68.8%) were ischemic heart diseases, 19 (23.8%) were cerebral events (strokes or transient ischemic attacks), and six (7.5%) were peripheral artery diseases. The survival analysis showed a stepwise increased risk of MACE with lower education level (HR = 1.59 [1.27–2.00], $p < 0.0001$). A pairwise post hoc evaluation showed that individuals with lower secondary or primary education had a significantly higher incidence of MACE as compared to individuals who completed either an upper secondary or higher education cycle (Figure 6B). When patients with a primary or lower secondary education degree were considered together and compared with those with upper secondary or university degree, the incidence of MACE was more than two-fold higher with an HR = 2.49 [1.56–3.96], $p < 0.0001$. This result was confirmed in a Cox regression model, after adjusting for age, WC, smoking habit, alcohol intake, and CDS (HR = 2.14 [1.24–3.69], $p < 0.0001$).

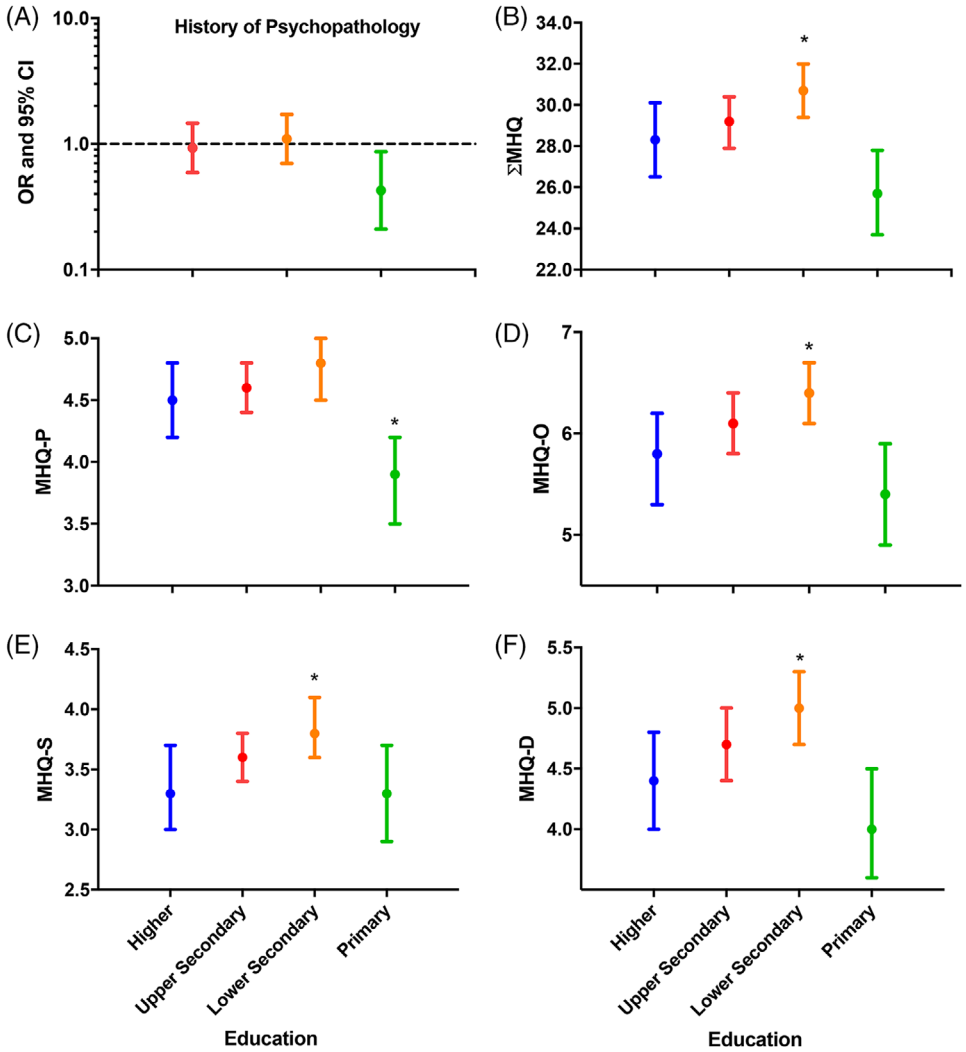

FIGURE 5 Association between education level and psychological symptoms. Odds ratio and 95% confidence interval (CI) of history of psychopathology (panel A) among different educational level groups (upper secondary: red symbol, lower secondary: orange symbol, and primary: green symbol); means and 95% CI of MiddleSex Hospital Questionnaire (MHQ) total scores (panel B); phobic-anxiety symptoms (MHQ-P, panel C), obsessive symptoms (MHQ-O, panel D), somatized anxiety symptoms (MHQ-S, panel E), and depressive symptoms (MHQ-D, panel F) scores. Higher MHQ scores denote more severe symptoms. Data are adjusted for age, smoking habit and alcohol intake, waist circumference, and Chronic Diseases Score. *$p < 0.05$ versus higher education (university and post-university degree)

5 | DISCUSSION

In the present study, we demonstrated that in people suffering from ED, a lower level of education is associated with a worse CV risk profile. This result translates into an increased incidence of MACE associated with a lower education level.

It is well known that low socioeconomic status (SES) is associated with an increased risk of CVD, and level of education has widely been used as an indicator for socioeconomic position.[6] A lower educational level is associated with a higher prevalence of traditional CV risk factors. Some studies showed an inverse correlation between blood pressure and level of education.[17] Diabetes seems to affect more often low-educated and low-income people, and this is probably secondary to obesity and physical inactivity.[18] Also, cigarette smoking seems to be more frequent in patients with a low level of education in the general population.[19,20] Kubota and colleagues evaluated the association between educational level and CV risk in a large biracial cohort of 13,948 American men and women aged 45–64 years.[21] Individuals with a lower educational level showed a higher prevalence of cardio-metabolic risk conditions such as obesity, diabetes, hypertension, and hypercholesterolemia and of subclinical organ damage indicators—such as carotid intima media thickness greater than 0.9 mm or the presence of a plaque—and left ventricular hypertrophy. In the same study, an inverse dose–response relation between educational level and lifetime CV risk was found in both men and women. Interestingly, this association was confirmed regardless of other socioeconomic characteristics such as income, occupation, and parental educational level.[21] Several other studies reported a higher incidence of CV events (including ischemic heart disease and stroke) and higher CV mortality in people with low education, both in high- and low-income countries

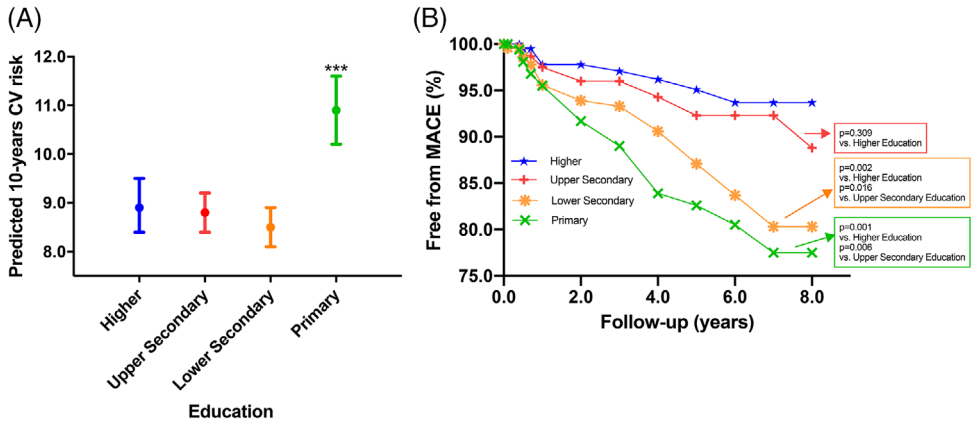

FIGURE 6 Estimated and observed cardiovascular risk associated with education level. Means and 95% confidence interval of predicted 10-year cardiovascular (CV) risk, according to Progetto Cuore risk score, in different education level groups (panel A). Data are adjusted for waist circumference and alcoholic consumption. ***$p < 0.0001$ versus higher education. Kaplan–Meier curves for major adverse cardiovascular events (MACE) over 8 years of follow-up (panel B)

and independently of other sociodemographic factors.[22–24] In line with these data, in the present study, ED patients with lower levels of education presented worse values for several typical CV risk factors such as higher BMI and WC, higher level of glycated hemoglobin and glucose, higher prevalence of MetS, diabetes, and previous CV events. The reason for this association is still unknown, but some hypotheses can be proposed. A higher SES tends to be associated with healthier behaviors and working conditions, as well as with easier access to health care, thus obtaining earlier diagnoses and therapies.[21,25] Medical interventions aimed at improving risk factor control and CV outcomes might have a reduced efficacy in lower educated patients because of low health literacy or numeracy.[6] Moreover, low-educated patients might tend to drop off treatments more easily further worsening their CV risk profile, as it was shown regarding anti-hypertensive treatments.[26] It should be also considered that healthcare is more and more becoming a technological matter, as it is evident from the increasing introduction of devices for treatment administration and monitoring as well as the growing use of telehealth and telemedicine. These instruments, while favoring a dynamic and readily control of the diseases, may represent a barrier for low-educated subjects with limited knowledge of technology.

The adverse risk factor profile is in line with the finding of a more frequent complaint of moderate to severe ED among patients in the lowest categories of education. Accordingly, a relevant reduction in flaccid PSV levels in patients with a lower level of education suggests an arterial damage underlying the pathogenesis of ED. On the other hand, hormonal factors seem to play a minor role in the pathogenesis of ED associated with low education. Despite a progressive increase in LH levels with lower education levels, TT does not change. This hormone pattern recapitulates the so-called "compensated hypogonadism," which, however, is known to be associated with limited androgen-deficiency symptoms.[27] In line with our results, the European Male Ageing Study has shown that a rise in LH not accompanied by TT change develops more frequently in lower educated men and it is a marker of poor health in the general population.[28]

Concerning the psychological symptoms, these could be claimed as possible risk factors for ED in lower educated subjects, except for those in the lowest education category. In fact, men in the intermediate education categories score worse at the MHQ. Conversely, in patients with primary education level, the trend is inverted as their symptoms are similar to patients in the highest education category and, for phobic anxiety, even less pronounced. Consistently, in the lowest education category, history of psychopathology is reported less frequently. Despite low SES is generally reported as a risk factor for psychiatric conditions,[29,30] the education degree behaves differently, as shown by a large Swedish study on a population of 24,510 subjects from adult general population[31] in which lower education was associated with decreased psychological distress independently of other socioeconomic factors.

In line with the adverse CV risk profile and reduced flaccid PSV,[32] patients with the lowest education level had a higher estimated CV risk. When actual incident MACE has been considered, patients with primary education confirmed a higher risk as compared with more educated ones. Conversely, patients with lower secondary education, whose predicted risk was similar to subjects with higher education, had significantly higher occurrence of actual MACE. Not only the CV risk in comparison with higher educated patients was higher but also the absolute risk within the lower educated groups was underestimated. Indeed, when comparing the predicted versus the observed CV risk among subjects with primary or lower secondary education, an average of 20%–25% experienced a MACE at 8 years of follow-up, whereas according to the Progetto Cuore algorithm, less than a half of these would be expected. Although CV risk assessment using few major CV risk factors included in clinical prediction models is a simple and efficient approach in many settings, there is still a gap between the estimated and the observed CV events (the so called "residual risk"). This can be explained by factors other than those considered in the standard-risk algorithms, with a specific and independent role in determining an adverse CV outcome. Despite its role as a CV risk factor, the level of education (as any other socioeconomic factor) is not included

in most CV risk algorithms. Several studies have evaluated the impact of including socioeconomic factors into CV risk algorithms showing that the addition of the level of education can increase their prediction accuracy.[33–35] For instance, Fiscella and colleagues demonstrated that the Framingham Risk Scoring underestimates coronary heart disease risk for those at low SES (including education and income), and adding this information to the CV risk assessment reduces this bias. In particular, when adjusting for the level of SES, a total of 15.1% of low-SES persons were reclassified to a higher treatment threshold.[35] Even if education does not represent a direct cause of increased CV risk, it represents a surrogate marker for other risk factors. Some of these are risk factors commonly included in predictive models. As shown in the present study, lower education correlates with a worse cardio metabolic profile. However, the unsatisfactory predictive value of the estimation algorithms suggests that the risk associated with education level is mediated by further factors. Therefore, as suggested by the present findings, the addition of socioeconomic factors to the CV risk algorithms may lead to an improvement in the prediction. Investigating the education level and recognizing this as a marker of CV risk may help in focusing the attention on the modifiable CV risk factors to encourage lifestyle modifications and implement pharmacological treatments. This, in turn, may reduce health disparities among the most vulnerable sections of society.

The possible underestimation of the CV risk when considering only few major CV risk factors is particularly important for men with ED who represent a high-risk population independently of traditional risk factors. In these patients, a more precise CV risk assessment using other secondary risk factors may be useful. We previously reported that in men with ED and two unconventional CV risk factors such as low education and reported partner's hypoactive sexual desire, the observed number of events is significantly higher than the number estimated using a common CV risk algorithm (i.e., Progetto CUORE).[5] The risk of underestimating CV risk is particularly true for relatively healthy and younger individuals. In a recent study, we demonstrated that in men with ED, family history for cardio-metabolic diseases is associated with an adverse cardio-metabolic profile, and it is a predictor for incident MACE, particularly in low-risk individuals (younger and without major CV risk factors).[36] Hence, incorporating a simple information such as the level of education in the CV assessment in men with ED may better define CV risk profile resulting in more precise treatment decisions, especially in people without clearly determined risk factors.

Several limitations should be recognized. These results are derived from men consulting an andrology clinic for sexual dysfunctions; therefore, they could not be directly applied to subject without ED or with ED consulting non-specialist healthcare providers or not seeking medical care. Moreover, information about the level of education was obtained through participants' reports; however, this self-reported information has limited risk of recall bias. Finally, the identification of non-fatal MACE through registers may lead to misclassification. However, for the last two issues, the large sample size is likely to dilute possible mistakes.

6 | CONCLUSION

In men suffering from erectile dysfunction, a lower education is associated with a more severe erectile dysfunction of atherogenic pathogenesis and with a worse cardio-metabolic profile. Moreover, it is a predictor of forthcoming major adverse cardiovascular events with a risk that overcomes that predicted by the Progetto Cuore risk scoring system.

There is a significant relationship between socioeconomic factors and cardiovascular health. Among them, the level of education is a costless but valuable information that should be always part of the cardiovascular risk assessment in men with erectile dysfunction. A low level of education, along with other secondary cardiovascular determinants, can help in the identification of men who may benefit from stricter risk factor control and whose risk would otherwise be underestimated.

AUTHOR CONTRIBUTIONS

Conceptualization: Mario Maggi and Giulia Rastrelli. Methodology: Dimitri Yannas, Elena Zago, Tommaso Todisco, Mario Maggi, and Giulia Rastrelli. Formal analysis: Dimitri Yannas, Elena Zago, Elena Cavallini, Mario Maggi, and Giulia Rastrelli. Investigation: Elena Cavallini, Tommaso Todisco, Giovanni Corona, and Giulia Rastrelli. Data curation: Dimitri Yannas, Elena Zago, Mario Maggi, and Giulia Rastrelli. Writing—original draft: Dimitri Yannas, Elena Zago, and Giulia Rastrelli. Writing–review and editing: Dimitri Yannas, Elena Zago, Tommaso Todisco, Linda Vignozzi, Giovanni Corona, Mario Maggi, and Giulia Rastrelli. Visualization: Dimitri Yannas, Elena Zago, Elena Cavallini, and Giulia Rastrelli. Supervision: Mario Maggi and Giulia Rastrelli. Project administration: Linda Vignozzi, Mario Maggi, and Giulia Rastrelli.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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