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Gender differences in the association between mortality and socioeconomic-marital status in the Moli-sani Study cohort

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Summary. *Introduction.* Socioeconomic disparities in health outcomes are well-established, with lower-status groups being at higher risk of disease/mortality. However, few are the studies which estimated possible gender-related differences in the association between the socioeconomic status (SES) and mortality. We aimed to investigate gender differences in the association between socioeconomic indicators and mortality, as well as the possible mechanisms of such association.

Methods. Longitudinal analysis of 10,655 men (mean age 55.7 ± 11.8) and 11,539 women (mean age 54.6 ± 11.5) enrolled in the Moli-sani Study, Italy (2005-2010). Education level, housing tenure and occupational social class were used as indicators of SES, while marital status represented the social factor. We tested health conditions (e.g. history of disease) and the behavioural (e.g. diet), traditional (e.g. blood cholesterol) and inflammatory (e.g. C-reactive protein) pathways as mediators of the SES-mortality gradient. Potential gender-related differences were tested by appropriate interaction terms.

Results. In the course of an average follow-up of 8.3 years (182,924 person-years), 1155 all-cause deaths were established. Among men, lower education and poor housing-tenure were associated with a 56% and a 72% increase in the risk of death, respectively; unemployed/unclassified men reported a lower survival rate versus professionals; likewise, divorced men showed to be at higher risk compared to their married counterparts. None of the SES factors was associated with reduced survival among women. Behavioural factors explained up to 23% of SES disparities in mortality among men. The mortality risk associated with housing tenure was higher in men than in women (p for interaction = 0.048). In addition, marital status and poor housing interacted among men, but less so among women, with a 2-fold increase in the risk of death among unmarried men with lower housing-tenure. On the contrary, the association between education and mortality did not vary with gender.

Discussion. Findings from this large cohort enrolled among the Italian general population indicate a clear SES gradient in mortality. Gender appears to modify the association between material SES indicators and the risk of death, but not that between education and mortality. Marital status and poor material resources interacted in such a way that unmarried men were at higher risk of long-term mortality than their married counterparts.

Key words. Socioeconomic disparities, marital status, gender differences, mortality, Molise region.

Differenze di genere nell'associazione tra mortalità e stato socioeconomico e civile nello studio Moli-sani

Riassunto. *Introduzione.* Le disparità socioeconomiche nella salute sono ampiamente consolidate e rivelano una maggiore incidenza di malattia e mortalità nei gruppi socioeconomici più bassi. Tuttavia, pochi studi hanno stimato possibili differenze legate al genere nell'associazione tra stato socioeconomico e mortalità. Pertanto, l'obiettivo di questo lavoro è stato quello di indagare le differenze di genere nell'associazione tra diversi indicatori socioeconomici e il rischio di mortalità e i possibili meccanismi in grado di spiegare queste associazioni.

Metodi. Analisi longitudinale su 10.655 uomini (età media 55,7 ± 11,8) e 11.539 donne (età media 54,6 ± 11,5) reclutati nell'ambito dello Studio Moli-sani (2005-2010). Livello di istruzione, tipologia abitativa e classe sociale sono stati usati come indicatori di stato socioeconomico mentre lo stato civile come fattore sociale. Lo studio ha testato diversi potenziali *pathway* di mediazione tra fattori socioeconomici e rischio di mortalità, come ad esempio le condizioni di salute al momento del reclutamento (es. evento cardiovascolare pregresso), fattori comportamentali (es. alimentazione), marcatori tradizionali di rischio cardiovascolare (es. colesterolo), e marcatori infiammatori (proteina C-reattiva). Le differenze potenziali correlate al genere sono state testate mediante termini di interazione.

Risultati. Nel corso di 8,3 anni di follow-up (182.924 anni-persona), abbiamo accertato 1155 decessi per tutte le cause. Tra gli uomini, un basso livello di istruzione e una tipologia abitativa inferiore (affitto) sono stati associati a un sostanziale aumento del rischio di mortalità (56% e 72% rispettivamente); uomini disoccupati /non classificati avevano una sopravvivenza inferiore rispetto ai professionisti, così come gli uomini divorziati sono risultati a più alto rischio rispetto agli uomini sposati o conviventi. Tra le donne, nessuno dei fattori socioeconomici era associato a una ridotta sopravvivenza. I fattori comportamentali spiegano fino al 23% delle disparità socioeconomiche nella mortalità tra gli uomini.

Il rischio di mortalità associato alle risorse materiali è risultato più evidente negli uomini che nelle donne (p di interazione = 0,048). Inoltre, stato civile e basso stato sociale e abitativo interagiscono evidenziando un rischio due volte maggiore tra gli uomini non sposati e con ridotte risorse

socioeconomiche. Al contrario, l'associazione tra istruzione e mortalità non varia in base al genere.
Discussione. I risultati ottenuti su questa ampia coorte di adulti reclutati nell'ambito della popolazione generale italiana indicano un chiaro gradiente socioeconomico nella mortalità. Il genere sembra modificare l'associazione tra indicatori materiali di tipo socioeconomico (tipologia abitativa) con il rischio di morte, ma non l'associazione istruzione-mortalità. Inoltre, si evidenzia un ruolo maggiore del basso stato socioeconomico negli uomini, in particolare tra quelli non sposati, in relazione al rischio di mortalità.

Parole chiave. Disparità socioeconomiche, stato civile, differenze di genere, mortalità, regione Molise.

Introduction

Socioeconomic disparities in health outcomes are well-established worldwide, with lower-status groups being at higher risk of disease/mortality.[1,2]

Part of the socioeconomic gradient in mortality has been explained by differentials in the distribution of a number of risk factors, including morbidity and health-related behaviours, which are likely to be more favourable within advantaged socioeconomic groups.[3]

Previous studies have shown that socioeconomic inequalities in mortality tend to be weaker among women versus men, and that gender differences in the extent of the inequality diverge highly between Countries.[4]

The apparently greater socioeconomic inequalities among men has been attributed to the fact that position within a social or economic hierarchy is measured with less precision among women than among men, or to the choice of the summary of measure of inequality applied in a given study.[5] However, it has been suggested that gender differences in the socioeconomic-mortality gradient should be analysed within the context of marital status, also in the light of the dissimilar access to health-enhancing social ties, such as marriage.[6]

Socioeconomic inequalities in mortality among men and women have been largely addressed in the US[6-8] and in Northern Europe,[9] but less is known about whether the position in a socioeconomic hierarchy could place different mortality risks on men and women among Mediterranean populations, with few exceptions.[4,10,11]

The purpose of the present study was a) to investigate gender differences in the association between socioeconomic indicators and all-cause mortality, using data from the Moli-sani Study, a Mediterranean cohort established in 2005; b) to examine whether the association between SES and mortality could be justified by SES differences in morbidity, behaviours or some biological factors, separately in men and women and c) to analyse the association between SES and mortality within the context of marriage.

Several socioeconomic factors will be used, each measuring a different aspect of the complex socioeconomic dimension, in order to possibly overcome the limitations associated with the choice of the measure of inequality.

Materials and methods

Study population

Data are from the Moli-sani Study, an on-going, prospective cohort study on 24,325 men and women (aged ≥35), randomly enrolled from the general population of the Molise region in southern Italy from March 2005 to April 2010,[12] with the aim of investigating the genetic and environmental risk factors in the onset of cardiovascular, cerebrovascular and tumour diseases.

For the purpose of this study, we did not include subjects with missing information about the exposure factors (childhood SES; education; housing; occupational class; number of cohabitants; number of rooms: 5.1%) and about the main variables of interest, including the outcomes (0.3%), and the subjects lost at follow-up (0.1%). A total of 22,194 individuals were eventually included in our analysis.

Compared to the discarded group (n = 2,131), the participants included in the present analysis were younger (55 ± 12 vs. 62 ± 13; p <.0001) and had a higher educational level (post-secondary education 12.8% vs. 7.8%; p <.0001). The two groups shared a similar prevalence of men (48% vs. 49%; p = 0.32, in the analysed and in the discarded group, respectively), major chronic diseases at baseline (CVD = 5.1% vs. 9.1%; cancer = 3.2% vs. 3.5%, age and sex-adjusted p values >0.05, for the enrolled and the discarded subjects, respectively).

The Moli-sani Study cohort was followed-up until 31 December 2015, with mortality as the main outcome of interest. Overall mortality was assessed through the Italian mortality registry (ReNCaM) and validated by Italian death certificates (ISTAT form).

The Moli-sani Study complies with the Declaration of Helsinki, and was approved by the ethical committee of the Università Cattolica in Rome, Italy. All participants provided their written informed consent.

Indicators of socioeconomic status

Socioeconomic information was self-reported and collected by a structured questionnaire administered by trained personnel. Education was based on the highest qualification attained and was categorized as up to lower secondary (≤8 years of study), upper secondary (8-13) and postsecondary (>13). Low-educated subjects were considered those who had attended up to a lower secondary school, while those with upper secondary school or higher were considered as having a higher education.

As previously described, the occupational social class within the Moli-sani population[13] was based on the Registrar General's occupation classification scheme, and was categorized as professional/managerial, skilled non-manual occupation, skilled manual occupation, partly skilled and unskilled occupation, unemployed and unclassified subjects (including retired subjects and housewife/house-husband).

Housing tenure was considered as rented, 1 dwelling ownership and >1 dwelling ownership.

Marital status (social factor) was categorized as married/cohabiting, divorced/separated, single or widowed, in addition to two aggregated categories that included married (married/cohabiting) and unmarried (single, divorced, separated or widowed).

Identification of risk factors at baseline

The history of CVD included documented angina, myocardial infarction, peripheral artery disease, revascularization procedures and cerebrovascular events. The history of cancer included previous diagnosis of cancer. Hypertension, diabetes and hypercholesterolemia were assessed based on the intake of medications.

Leisure-time physical activity (PA) was expressed as the daily energy expenditure in metabolic equivalent task-hours (MET-h/d) for sports, walking and gardening, and then dichotomized as < or ≥30 min/d. Abdominal obesity was defined as a waist-to-hip ratio ≥0.85 and ≥0.90 for women and men, respectively.[14]

Subjects were classified as never-smokers, current smokers or ex-smokers (stopped from at least 1 year).

The psychological assessment was categorized into 5 mutually exclusive groups: a) use of anti-depressive drugs at least once in their life; b) use of psychoactive drugs other than antidepressants at least once in their life; c) self-reported previous diagnosis of depression or anxiety or insomnia with no use of psychoactive drugs; d) psychologically healthy subjects (individuals not falling within categories a, b or c); e) missing information (individuals with missing data about any previous diagnosis of psychological disease or use of psychoactive drugs).

Dietary intake was collected through the validated Italian EPIC food frequency questionnaire[15] and adherence to the Mediterranean diet was defined according to the Mediterranean Diet Score.[16]

Blood pressure (BP) was measured by means of an automatic device (OMRON-HEM-705CP) three times on the non-dominant arm, and the last two values were considered. Measurements were made in a quiet room with a comfortable temperature, with participants lying down for at least 5 minutes.

All blood samples were obtained from participants who had fasted overnight and hadn't smoked for at least 6 h.

Serum lipids and blood glucose were assayed by enzymatic reaction methods, using an automatic analyser (ILab 350, Instrumentation Laboratory IL, Milan, Italy).

High sensitivity C-reactive protein (CRP) was measured in fresh serum samples through a particle-enhanced immunoturbidimetric assay (ILab 350, Instrumentation Laboratory IL, Milan, Italy). The hemocromocytometric analysis was performed by cell count (Coulter HMX, Backman Coulter, IL Milan, Italy) within 3 h from blood collection. No genetic analysis was performed.

Statistical analysis

The baseline characteristics of the study population are presented as percentages or means, with standard deviations for continuous variables (SD).

Associations between SES factors and health conditions and gender were examined by the chi-square test; p-values across levels of categorical variables were obtained through multiple comparisons by using the method of Sidak; and differences in age, Mediterranean diet and distribution of biomarkers were tested by the Student t test (Tables 1, 2).

Risk estimates for all-cause mortality were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CI) and calculated using Cox regression models with time-on-study on the time scale. HRs were obtained from a multivariable model (Model 1) adjusted for age (continuous) and sex and included all SES factors simultaneously. Appropriate multiplicative terms for testing interaction were included in Model 1, to test for a role of the gender in modulating the association between SES factors and the all-cause mortality risk.

The multivariable Model 1 served as the reference for the mediation analysis to estimate the contribution of each set of potential mediators, which were alternately included into Model 1.

Four main pathways were tested as possibly mediators of the association between SES trajectories and the CSD over life course and mortality.

The *health conditions* pathway included history of CVD, cancer, therapy for diabetes, lipid-lowering drugs, medication for hypertension, and a psychological assessment.

The *health-related behaviour* pathway included leisure-time physical activity, adherence to MD, energy intake, smoking status and abdominal obesity; the *traditional* pathway comprised classical CVD risk factors, such as blood lipids (total cholesterol, HDL-cholesterol, triglycerides), blood glucose, systolic and diastolic blood pressure; the *inflammatory* pathway consisted of CRP and WBC count.

For the mediation analysis we used the % MEDIATE macro in SAS software,[17] which allows to calculate the

point and 95% interval estimates of the percent of exposure effect (PEE) explained by one or more intermediate variables. Traditional and inflammatory biomarkers were entered into the mediation analysis as ordered quintiles. Dummy variables for missing values were created. A two-sided p-value <0.05 was considered as statistically significant. The data analysis was generated using SAS/STAT software, version 9.4 of the SAS System for Windows©2009.

Results

Baseline differences in SES factors by gender are reported in Table 1. Compared to men, women were more likely to report a lower educational level (up to lower secondary school), partly skilled/unskilled occupations, and a higher frequency of living in a rented house.

Comparisons for baseline risk factors revealed behaviour differentials, with women being more likely to be non-smokers, having a lower prevalence of abdominal obesity, with a trend towards worst psychological assessments (Table 2). Men reported higher levels of physical activity, a greater prevalence of CVD and diabetes and a lower prevalence of cancer, while no difference was found in the use of hypertension and lipid-lowering drugs.

Over a median follow-up of 8.3 years (interquartile range: 7.3-9.3 years), a total of 1,155 all-cause deaths were documented (no. of deaths among women = 393; among men = 762).

Overall, a lower education (up to lower secondary school) and a poorer housing tenure (rent) were associated with a 44 and a 43% increase in the risk of death, respectively (Supplementary Table 1, column Model 1),

Table 1. Demographic and socioeconomic characteristics of men and women from the Moli-sani Study cohort (n = 22,194)

	Whole sample	Women	Men	P for difference
N (%)	22,194 (100)	11,539 (52)	10,655 (48)	-
Age (y, mean (±SD))	55.1 (11.7)	54.6 (11.5)	55.7 (11.8)	<.0001
Education				***0.0002***
Postsecondary	2851 (12.9)	1495 (13.0)	1356 (12.7)	0.027
Upper secondary	7800 (35.1)	3909 (33.9)	3891 (36.5)	0.99
Up to lower secondary	11,543 (52.0)	6135 (53.1)	5408 (50.8)	0.0003
Housing tenure				***0.014***
>1 dwelling ownership	2026 (9.1)	1028 (8.9)	998 (9.4)	0.88
1 dwelling ownership	18,215 (82.1)	9437 (81.8)	8778 (82.4)	0.0003
Rent	1953 (8.8)	1074 (9.3)	879 (8.2)	0.0003
Occupational class				***<.0001***
Professional and managerial	4544 (20.4)	2300 (19.9)	2244 (21.1)	0.93
Skilled non-manual occupations	8137 (36.7)	4133 (35.8)	4004 (37.6)	0.56
Skilled manual occupations	4059 (18.3)	1701 (14.7)	2358 (22.1)	0.0005
Partly skilled and unskilled occupations	4125 (18.6)	2334 (20.1)	1791 (16.8)	0.0005
Unemployed, unclassified	1329 (6.0)	1071 (9.3)	258 (2.4)	0.0005
Marital status				***<.0001***
Married/cohabitant	19,086 (86.0)	9513 (82.4)	9573 (89.8)	0.99
Divorced/separated	583 (2.6)	348 (3.0)	235 (2.2)	0.0004
Single	1127 (5.1)	525 (4.6)	602 (5.7)	0.087
Widowed	1398 (6.3)	1153 (10.0)	245 (2.3)	0.0004

P-values across levels of categorical variables were obtained through multiple comparisons by the method of Sidak.

Table 2. Baseline risk factors among men and women from the Moli-sani Study cohort (n = 22,194)

	Whole sample	Women	Men	P for difference
N (%)	22,194 (100)	11,539 (52)	10,655 (48)	-
Health conditions				
Cardiovascular disease	5.1	3.1	7.2	<.0001
Cancer	3.2	3.8	2.5	<.0001
Drugs for diabetes	4.6	3.4	6.0	<.0001
Lipid-lowering drugs	7.6	7.0	8.3	0.0005
Medication for hypertension	26.8	26.4	27.2	0.21
Psychological assessment				<.0001
Psychologically healthy	*87.8*	*83.1*	*92.2*	*0.13*
Use of antidepressants	*3.0*	*4.4*	*1.4*	*0.0005*
*Use of psychoactive drugs**	*4.2*	*5.9*	*2.4*	*0.0005*
*Self-reported diagnosis of psychological disease***	*4.3*	*5.9*	*2.7*	*0.0005*
Unascertained	*0.6*	*0.7*	*0.5*	*0.16*
Health behaviours				
Smoking status				<.0001
Non-smokers	*49.2*	*65.1*	*32.1*	*0.0003*
Current	*23.2*	*20.7*	*25.9*	*0.0003*
Former	*27.5*	*14.2*	*42.0*	*0.0003*
Leisure-time PA ≥30 min/d	64.1	56.6	72.3	<.0001
Abdominal obesity	73.6	67.0	80.8	<.0001
Mediterranean diet (mean ± SD)	4.39 (1.64)	4.26 (1.63)	4.52 (1.65)	<.0001
Traditional markers (mean ± SD)				
Blood cholesterol (mg/dL)	213 (42)	216 (41)	210 (42)	<.0001
HDL-cholesterol (mg/dL)	57 (15)	63 (15)	52 (13)	<.0001
Triglycerides*** (mg/dL)	112 (111-113)	99 (98-99)	128 (127-130)	<.0001
Blood glucose*** (mg/dL)	99 (99-99)	95 (95-95)	103 (103-104)	<.0001
Systolic blood pressure (mmHg)	140 (21)	138 (21)	143 (19)	<.0001
Diastolic blood pressure (mmHg)	82 (10)	81 (9)	84 (9)	<.0001
Inflammatory markers (means ± SD)				
C-reactive protein*** (mg/L)	1.50 (1.48-1.52)	1.52 (1.50-1.55)	1.48 (1.45-1.51)	0.031
Leukocyte count*** (x109/L)	6.0 (6.0-6.0)	5.8 (5.7-5.8)	6.3 (6.3-6.3)	<.0001

Values are reported as percentage unless otherwise stated.

*Other than antidepressants; **depression, anxiety or insomnia without use of drugs; ***geometric mean with corresponding 95% confidence intervals.

P values across levels of categorical variables were obtained through multiple comparisons by using the method of Sidak. P values for the association between Mediterranean diet and gender were further controlled for energy intake (Kcal/d).

Supplementary Table 1. Mortality risk associated with socioeconomic factors and mediation analysis in the Moli-sani Study cohort (n = 22,194)

	Model 1	Model 1 + health conditions	Model 1 + behavioural factors	Model 1 + traditional risk factors	Model 1 + inflammatory markers
Education					
Postsecondary	-1-	-1-	-1-	-1-	-1-
Upper secondary	1.11 (0.85-1.44)	1.10 (0.84-1.43)	1.09 (0.84-1.43)	1.09 (0.84-1.42)	1.08 (0.83-1.41)
PEE	-	*11.4% (0.1% to 96.4%; p=0.31)*	*13.2% (0.4% to 86.3%; p=0.17)*	*16.7% (0.6% to 86.3%; p=0.096)*	*24.7% (1.0% to 91.6%; p=0.012)*
Up to lower secondary	1.44 (1.11-1.88)	1.43 (1.09-1.87)	1.44 (1.10-1.87)	1.43 (1.10-1.86)	1.37 (1.05-1.78)
PEE	-	*2.6% (0.0% to 83.8%; p=0.35)*	*1.1% (0.0% to 94.7%; p=0.39)*	*2.1% (0.1% to 43.0%; p=0.28)*	*14.6% (6.1% to 31.0%; p<.0001)*
Housing tenure					
>1 dwelling ownership	-1-	-1-	-1-	-1-	-1-
1 dwelling ownership	1.21 (0.99-1.47)	1.21 (0.99-1.47)	1.15 (0.94-1.39)	1.19 (0.99-1.45)	1.22 (1.00-1.48)
PEE	-	*Null*	*27.8% (7.2% to 65.7%; p=0.0004)*	*5.8% (0.6% to 38.1%; p=0.17)*	*Null*
Rent	1.43 (1.18-1.73)	1.38 (1.13-1.68)	1.28 (1.06-1.56)	1.37 (1.13-1.66)	1.42 (1.17-1.72)
PEE	-	*10.3% (2.5% to 34.0%; p=0.057)*	*29.6% (15.1% to 49.9%; p<.0001)*	*11.0% (5.1%-22.1%; p=0.0003)*	*1.5% (0.0% to 35.9%; p=0.29)*
Occupational social class					
Professional and managerial	-1-	-1-	-1-	-1-	-1-
Skilled non-manual occupations	0.97 (0.80-1.18)	0.98 (0.81-1.19)	0.95 (0.79-1.15)	0.98 (0.81-1.18)	0.99 (0.82-1.19)
PEE	-	*20.0% (0.0% to 100%; p=0.39)*	*Null*	*27.5% (0.0% to 100%; p=0.21)*	*Null*
Skilled manual occupations	0.97 (0.80-1.17)	0.98 (0.81-1.19)	0.95 (0.79-1.15)	0.97 (0.80-1.17)	0.96 (0.80-1.16)
PEE	-	*54.6% (0.0% to 100%; p=0.17)*	*Null*	*7.3% (0.0% to 99.9%; p=0.39)*	*Null*
Partly-skilled and unskilled occupations	0.91 (0.75-1.10)	0.95 (0.78-1.15)	0.93 (0.77-1.12)	0.93 (0.77-1.12)	0.92 (0.76-1.11)
PEE	-	*43.3% (1.3% to 97.7%; p=0.025)*	*21.0% (1.3% to 84.1%; p=0.055)*	*19.9% (1.5% to 79.8%; p=0.023)*	*4.5% (0.0% to 84.2%; p=0.32)*
Unemployed, unclassified	1.07 (0.89 -1.30)	1.09 (0.90-1.33)	1.09 (0.90 -1.31)	1.08 (0.89-1.31)	1.09 (0.90 -1.32)
PEE	-	*Null*	*Null*	*Null*	*Null*
Marital status					
Married/cohabitant	-1-	-1-	-1-	-1-	-1-
Divorced/separated	1.63 (1.09-2.44)	1.63 (1.09-2.45)	1.46 (0.96-2.22)	1.70 (1.14-2.54)	1.63 (1.09-2.44)
PEE	-	*Null*	*22.4% (6.5% to 54.5%; p=0.0013)*	*Null*	*Null*
Single	1.52 (1.01-2.28)	1.65 (1.10-2.47)	1.46 (0.96-2.21)	1.56 (1.04 -2.32)	1.55 (1.04-2.32)
PEE	-	*Null*	*10.3% (1.2% to 51.6%; p=0.12)*	*Null*	*Null*
Widowed	1.18 (0.79-1.77)	1.21 (0.81-1.82)	1.14 (0.75-1.73)	1.17 (0.79-1.75)	1.16 (0.78-1.74)
PEE	-	*Null*	*22.9% (0.5% to 94.9%; p=0.15)*	*4.9% (0.0% to 94.9%; p=0.36)*	*8.9% (0.2% to 82.9%; p=0.25)*

Hazard ratios with 95% confidence interval (95% CI) obtained from model 1 adjusted for age, sex, all SES factors simultaneously and marital status.

Health conditions include the presence at baseline of CVD, cancer, drugs for diabetes, lipid-lowering medication, drugs for hypertension, psychological assessment.

Behavioural factors include adherence to Mediterranean diet, smoking status, physical activity and abdominal obesity.

Traditional markers of CVD risk include total blood cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL; logarithm), blood glucose (mg/dL; logarithm), systolic BP (mmHg), diastolic BP (mmHg).

Inflammatory biomarkers of CVD risk include C-reactive protein (mg/dL; logarithm), white blood cell count (x109/L; logarithm).

PEE = percent of exposure effect with 95% confidence interval and P values. Null= not mediating the effect.

as compared to the relevant advantaged counterparts. Marital status was a strong predictor of mortality, with divorced/separated, single and widowed subjects being at higher risk of death compared to the married/cohabiting group, while occupational class was not associated with mortality. In the whole study sample, behavioural factors explained up to 29.6% of the housing-related gradient in mortality and 22.4% of the disparities observed among divorced/separated versus married subjects, and inflammation accounted for 14.6% of the educational gradient.

Socioeconomic status and mortality in men and women

An analysis by gender revealed that – with a decrease in SES – men experienced a generally consistent gradient of increasing mortality. Compared to those with post-secondary education, subjects with up to lower secondary school reported a 56% increase in the risk of death; similarly, subjects living in a rented house experienced a 72% greater risk of dying (Table 3). Divorced/separated men had a 2-fold risk of death compared to married individuals (column Model 1).

Behavioural factors explained about 25% of the housing-related gradient in mortality, while inflammatory biomarkers were likely to account for the largest, albeit modest, proportion of educational disparities.

The SES/mortality gradient among women was less pronounced, with the exception of the marital status, with single women showing an upward trend of mortality compared to married ones (Table 4, column Model 1).

A visual comparison of the findings reported in Table 3 (for men) and Table 4 (for women) would reveal some differences in the extent of the association between SES factors and marital status and mortality, but interaction tests were not significant (p values for interaction of education, housing, occupational class and marital status were 0.44, 0.093, 0.90 and 0.10, respectively; data not shown), suggesting that gender is not likely to modify the association between SES and mortality risk.

Supplementary Table 2 shows the association between each SES factor and marital status and mortality, separately in men and women of adult (≤65) vs older (>65) age; results did not differ substantially across the age groups, with the exception of marital status, which in women appeared to affect the mortality risk differently, according to age.

When considered as dichotomous variable, housing tenure was associated with an increased risk of death in men, but not in women (p for interaction = 0.048; Table 5), while educational gradients by gender were not statistically different (p for interaction = 0.20).

Finally, marital status and poor housing interacted for men, but less so for women, placing unmarried men with lower housing tenure at a 2-fold risk of death.

Discussion

Findings from this large population-based cohort of adult Italian men and women showed that lower SES, measured as education, housing tenure, and occupational social class, is associated with an increased risk in all-cause mortality.

Although male mortality was visually more unequal between the socioeconomic groups than female mortality, a lack of statistical significance in the gender difference within the SES gradient does not allow to support the existence of a gender gap in SES-associated mortality.

However, we found that – when considered as a dichotomous variable – poor housing tenure (an indicator of scarcer material resources) is associated with an increased risk of mortality in men, but not in women, in line with the previous evidence,[5,8] while educational gradients among men and women remained substantially unchanged.

Interestingly, our findings revealed that the marital and poverty status interacts for men, but not for women, with unmarried men showing a 2-fold risk of death compared to their married counterparts, in agreement with prior studies.[18]

Our findings are supported by the evidence of gender differences in the health benefits of marriage; indeed, men are more likely to show health-compromising behaviours than women, therefore, the social controls and spousal monitoring of health behaviours that often accompany marriage appear to disproportionately benefit men.[6]

With regard to education, statistical tests for interaction revealed no significant gender differences in mortality, in contrast with previous studies, which suggested – in the developed economies – a greater inequality in male vs. female mortality among the socioeconomic groups.[5]

The findings from four US-based population studies on elderly men and women suggested that the relation between SES and mortality was less consistent among women, and that income was a more robust predictor than education.[8]

A recent meta-analysis showed significant gender differences in the socioeconomic inequality of mortality attributable to alcohol abuse associated with the occupational status.[19]

In a sample of Northern Italians, the association between education and cardiovascular risk seems to vary by gender, with low education not being associated with CHD incidence in men, while women showed a 2-fold risk.[10]

All the aforementioned studies suggest the likely existence of differentials in mortality by gender, but few of them[10] have actually relied on statistical tests to support this visually impressive difference.

Table 3. Mortality risk associated with socioeconomic factors and mediation analysis among men from the Moli-sani Study cohort (n = 10,655)

	Model 1	Model 1 + health conditions		Model 1 + behavioural factors		Model 1 + traditional risk factors		Model 1 + inflammatory markers	
	HR (95% CI)	HR (95% CI)	*PEE, % (95% CI; p value)*	HR (95% CI)	*PEE, % (95% CI; p value)*	HR (95% CI)	*PEE, % (95% CI; p value)*	HR (95% CI)	*PEE, % (95% CI; p value)*
Education									
Postsecondary	-1-	-1-	-	-1-	-	-1-	-	-1-	-
Upper secondary	1.14 (0.83-1.56)	1.14 (0.83-1.58)	*Null*	1.10 (0.80-1.51)	*28.6 (0.9- 94.9; 0.045)*	1.11 (0.81-1.53)	*15.0 (0.7- 81.6; 0.083)*	1.10 (0.80-1.52)	*22.7 (0.9- 90.3; 0.035)*
Up to lower secondary	1.56 (1.13-2.14)	1.57 (1.14-2.16)	*Null*	1.48 (1.07-2.03)	*12.2 (4.0-31.5; 0.0060)*	1.55 (1.13-2.13)	*1.1 (0.0-77.7; 0.37)*	1.46 (1.06-2.01)	*14.2 (5.8-31.0; <.0001)*
Housing tenure									
>1 dwelling ownership	-1-	-1-	-	-1-	-	-1-	-	-1-	-
1 dwelling ownership	1.26 (1.00-1.60)	1.29 (1.02-1.64)	*Null*	1.19 (0.94-1.51)	*24.5 (5.8-63.2; 0.0094)*	1.26 (1.00-1.58)	*3.3 (0.2-36.7; 0.23)*	1.28 (1.01-1.61)	*Null*
Rent	1.72 (1.36-2.18)	1.73 (1.37-2.20)	*Null*	1.52 (1.20-1.92)	*23.5 (13.0-38.8; <.0001)*	1.66 (1.32-2.10)	*6.2 (3.0-12.3; 0.0006)*	1.70 (1.34-2.15)	*2.5 (0.3-16.1; 0.15)*
Occupational class									
Professional and managerial	-1-	-1-	-	-1-	-	-1-	-	-1-	-
Skilled non-manual	0.99 (0.79-1.23)	1.00 (0.80-1.26)	*Null*	0.98 (0.78-1.22)	*Null*	1.00 (0.80-1.24)	*71.8 (0.0-100; 0.14)*	1.00 (0.80-1.26)	*Null*
Skilled manual	0.94 (0.75-1.18)	0.98 (0.78-1.23)	*62.7 (0.0-100; 0.067)*	0.93 (0.74-1.17)	*Null*	0.94 (0.75-1.18)	*Null*	0.94 (0.75-1.17)	*Null*
Partly skilled/ Unskilled	0.89 (0.71-1.11)	0.93 (0.74-1.17)	*40.6 (1.8-96.3; 0.030)*	0.90 (0.72-1.13)	*8.8 (0.1-86.2; 0.28)*	0.90 (0.72-1.13)	*13.1 (1.3-63.5; 0.041)*	0.89 (0.71-1.12)	*2.9 (0.0-97.8; 0.39)*
Unemployed/ unclassified	1.26 (1.00-1.57)	1.22 (0.97-1.52)	*14.3 (2.0-57.3; 0.10)*	1.27 (1.02-1.60)	*Null*	1.22 (0.97-1.52)	*14.3 (4.6-36.7; 0.0001)*	1.28 (1.02-1.59)	*Null*
Marital status									
Married/ cohabitant	-1-	-1-	-	-1-	-	-1-	-	-1-	-
Divorced/ separated	2.13 (1.37-3.29)	2.10 (1.35-3.28)	*1.4 (0.0-99.8; 0.43)*	1.90 (1.19-3.03)	*14.8 (4.0-42.0; 0.024)*	2.22 (1.44-3.42)	*Null*	2.14 (1.39-3.30)	*Null*
Single	1.20 (0.77-1.85)	1.33 (0.85-2.07)	*Null*	1.22 (0.77-1.95)	*Null*	1.21 (0.79-1.87)	*Null*	1.20 (0.78-1.85)	*Null*
Widowed	1.25 (0.81-1.94)	1.30 (0.83-2.03)	*Null*	1.18 (0.74-1.88)	*26.6 (0.7-94.8; 0.14)*	1.23 (0.80-1.90)	*6.6 (0.1-78.1; 0.28)*	1.22 (0.79-1.88)	*10.9 (0.6-72.0; 0.19)*

Hazard ratios (HR) with 95% confidence interval (95% CI) obtained from model 1 adjusted for age, all SES factors simultaneously and marital status.

Health conditions include the presence at baseline of CVD, cancer, drugs for diabetes, lipid-lowering medication, drugs for hypertension, psychological assessment.

Behavioural factors include adherence to Mediterranean diet, smoking status, physical activity and abdominal obesity.

Traditional markers of CVD risk include total blood cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL; logarithm), blood glucose (mg/dL; logarithm), systolic BP (mmHg), diastolic BP (mmHg).

Inflammatory biomarkers of CVD risk include C-reactive protein (mg/dL; logarithm), white blood cell count (x109/L; logarithm).

PEE = percent of exposure effect with 95% confidence interval and P values.

Null = not mediating the effect.

Table 4. Mortality risk associated with socioeconomic factors and mediation analysis among women from the Moli-sani Study cohort (n = 11,539)

	Model 1	Model 1 + health conditions		Model 1 + behavioural factors		Model 1 + traditional risk factors		Model 1 + inflammatory markers	
	HR (95% CI)	HR (95% CI)	*PEE, % (95% CI; p value)*	HR (95% CI)	*PEE, % (95% CI; p value)*	HR (95% CI)	*PEE, % (95% CI; p value)*	HR (95% CI)	*PEE, % (95% CI; p value)*
Education									
Postsecondary	-1-	-1-	-	-1-	-	-1-	-	-1-	-
Upper secondary	0.96 (0.61-1.53)	0.92 (0.58-1.48)	*Null*	0.95 (0.59-1.51)	*Null*	0.96 (0.60-1.52)	*Null*	0.95 (0.60-1.51)	*Null*
Up to lower secondary	1.09 (0.68-1.73)	1.04 (0.65-1.66)	*57.0 (0.0-100; 0.13)*	1.07 (0.67-1.71)	*20.6 (0.0 99.9; 0.23)*	1.06 (0.66 -1.68)	*35.1 (0.0- 100; 0.14)*	1.06 (0.67-1.68)	*33.3 (0.0-100; 0.025)*
Housing tenure									
>1 dwelling ownership	-1-	-1-	-	-1-	-	-1-	-	-1-	-
1 dwelling ownership	1.08 (0.77 -1.53)	1.05 (0.74-1.49)	*39.6 (0.0-99.9; 0.18)*	1.05 (0.75-1.49)	*34.1 (0.1-99.8; 0.091)*	1.10 (0.78 -1.55)	*Null*	1.09 (0.77 -1.55)	*Null*
Rent	1.04 (0.74-1.47)	0.95 (0.67-1.34)	*Null*	0.97 (0.69-1.37)	*Null*	1.01 (0.71-1.42)	*78.7 (0.0-100; 0.19)*	1.06 (0.75 -1.49)	*Null*
Occupational class									
Professional and managerial	-1-	-1-	-	-1-	-	-1-	-	-1-	-
Skilled non-manual	0.98 (0.68-1.41)	0.94 (0.65-1.36)	*Null*	0.97 (0.67-1.41)	*Null*	0.97 (0.68-1.39)	*Null*	0.98 (0.68-1.41)	*5.9 (0.0-100; 0.46)*
Skilled manual	1.09 (0.76-1.57)	1.01 (0.70-1.45)	*89.3 (0.0-100; 0.0053)*	1.08 (0.75-1.56)	*11.9 (0.0-99.2; 0.31)*	1.02 (0.71-1.47)	*76.3 (0.0-100; 0.0017)*	1.08 (0.75-1.55)	*13.7 (0.1-96.6; 0.15)*
Partly-skilled/ Unskilled	1.02 (0.71-1.47)	1.03 (0.71-1.48)	*Null*	1.03 (0.71-1.49)	*Null*	0.98 (0.68-1.41)	*Null*	1.02 (0.71-1.46)	*13.7 (0.0-100; 0.41)*
Unemployed/ unclassified	1.15 (0.80 -1.65)	1.13 (0.78-1.62)	*14.7 (0.2-93.7; 0.25)*	1.13 (0.78 -1.64)	*13.9 (0.4-87.7; 0.20)*	1.13 (0.78 -1.62)	*13.9 (0.4-87.7; 0.20)*	1.14 (0.79-1.64)	*6.1 (0.1-74.7; 0.23)*
Marital status									
Married/ cohabitant	-1-	-1-	-	-1-	-	-1-	-	-1-	-
Divorced/ separated	0.61 (0.20-1.90)	0.62 (0.20-1.34)	*2.8 (0.0-99.6; 0.41)*	0.58 (0.18-1.83)	*10.5 (0.5-73.3%; 0.14)*	0.65 (0.21-2.00)	*10.5 (0.5-73.3; 0.14)*	0.61 (0.20-1.89)	*Null*
Single	1.72 (0.56-5.33)	1.78 (0.57-5.54)	*Null*	1.72 (0.54-5.43)	*Null*	1.81 (0.59-5.60)	*Null*	1.81 (0.59-5.56)	*Null*
Widowed	1.12 (0.36-3.46)	1.09 (0.35-3.40)	*17.0 (0.0-100; 0.38)*	1.09 (0.34-3.44)	*13.0 (0.0-100; 0.38)*	1.10 (0.36-3.40)	*13.0 (0.0-100; 0.38)*	1.11 (0.36-3.40)	*6.6 (0.0-100; 0.38)*

Hazard ratios (HR) with 95% confidence interval (95% CI) obtained from model 1 adjusted for age, all SES factors simultaneously and marital status.

Health conditions include the presence at baseline of CVD, cancer, drugs for diabetes, lipid-lowering medication, drugs for hypertension, psychological assessment.

Behavioural factors include adherence to Mediterranean diet, smoking status, physical activity and abdominal obesity.

Traditional markers of CVD risk include total blood cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL; logarithm), blood glucose (mg/dL; logarithm), systolic BP (mmHg), diastolic BP (mmHg).

Inflammatory biomarkers of CVD risk include C-reactive protein (mg/dL; logarithm), white blood cell count (x109/L; logarithm).

PEE = percent of exposure effect with 95% confidence interval and P values.

Null = not mediating the effect.

Supplementary Table 2. Mortality risk associated with socioeconomic factors across strata by sex and age from the Moli-sani Study cohort (n = 22,194)

	Women		Men	
	≤65 years	>65 years	≤65 years	>65 years
N of events/N of subjects	105/9173	288/2366	220/8156	542/2499
Education				
Postsecondary	-1-	-1-	-1-	-1-
Upper secondary	1.33 (0.65-2.71)	0.82 (0.43-1.54)	1.42 (0.82-2.47)	0.99 (0.67-1.46)
Up to lower secondary	1.71 (0.80-3.64)	0.99 (0.52-1.89)	1.99 (1.13-3.51)	1.32 (0.90-1.92)
P for interaction	*0.53*		*0.23*	
Housing tenure				
>1 dwelling ownership	-1-	-1-	-1-	-1-
1 dwelling ownership	0.76 (0.42-1.36)	1.22 (0.79-1.90)	1.62 (0.95-2.78)	1.17 (0.90-1.54)
Rent	0.37 (0.13-1.04)	1.40 (0.79-2.51)	2.15 (1.12-4.12)	1.64 (1.08-2.49)
P for interaction	*0.18*		*0.29*	
Occupational class				
Professional and managerial	-1-	-1-	-1-	-1-
Skilled non-manual	1.12 (0.63-2.00)	0.81 (0.51-1.30)	0.98 (0.66-1.46)	1.01 (0.77-1.32)
Skilled manual	1.13 (0.53-2.40)	0.93 (0.53-1.63)	0.96 (0.61-1.53)	0.95 (0.69-1.29)
Partly-skilled/unskilled	1.35 (0.67-2.73)	0.80 (0.49-1.33)	1.04 (0.64-1.70)	0.87 (0.64-1.18)
Unemployed/unclassified	1.13 (0.46-2.75)	0.96 (0.58-1.58)	1.52 (0.70-3.31)	1.18 (0.68-2.04)
P for interaction	*0.64*		*0.43*	
Marital status				
Married/cohabitant	-1-	-1-	-1-	-1-
Divorced/separated	0.40 (0.05-2.88)	0.98 (0.24-4.05)	2.16 (1.13-4.12)	2.04 (1.08-3.84)
Single	4.39 (2.37-8.16)	1.03 (0.59-1.80)	1.53 (0.85-2.78)	0.81 (0.38-1.74)
Widowed	0.58 (0.20-1.66)	1.02 (0.77-1.35)	1.29 (0.41-4.04)	1.25 (0.96-1.64)
P for interaction	*0.0030*		*0.58*	

Hazard ratios with 95% confidence interval (95% CI) obtained from the model adjusted for age (continuous), all SES factors simultaneously and marital status.

Interaction was tested by introducing in Cox analysis a product term of each SES factor times a potential effect modifier represented by two classes of age (≤65 and >65 years) among men and women separately.

Overall, the results from our study indicate that behavioural factors, including diet and physical activity, explained the largest part of the SES gradient in mortality (up to 30%), both in the whole study sample and among men only. Inflammation was likely to account for a modest proportion of the educational inequalities in mortality, while a weaker role was observed for traditional CVD risk factors (e.g. blood cholesterol).

Different inter-related pathways have been proposed to justify social inequalities in health, and the major mechanisms have been identified in health behaviours, psychosocial factors and material factors.[20]

In our study, the impact of health behaviours in explaining social inequalities in health turned out to be greater than other potential pathways, such as the biological factors, and this is in accordance with previous reports, which showed that behavioural factors largely contributed to the mitigation of SES disparities.[3,21]

However, our analysis does not allow to draw conclusions on the relative importance of health behaviours in relation to other equally important factors, such as the psychosocial ones, since these were not considered in the present paper. Furthermore, the effect of material and psychosocial factors on health, as well as the impact of biological factors, is likely to be mediated through health behaviours.[20]

Strengths and limitations

The strengths of the present study include its large sample size, the relatively long follow-up and its prospective design, along with the use of different SES indicators and the number of covariates, to limit confounding, at least in part.

However, our findings should be interpreted in light of some limitations. The observational nature of our study cannot support causality, nor it can fully rule out residual confounding or confounding by unmeasured factors (e.g. psychosocial factors); in addition, socioeconomic data were based on self-reported information,

Table 5. Risk of death associated with housing tenure (low vs high) or educational level (low vs high), separately for men and women and within the context of marital status

	No. of cases/no. of subjects (death rate, %)	Housing (low vs high) HR (95% CI)	Education (low vs high) HR (95% CI)
Whole study sample	1155/22,194 (5.2)	1.21 (0.98-1.50)	1.32 (1.13-1.55)
Men	762/10,655 (7.1)	1.41 (1.09-1.83)	1.42 (1.18-1.72)
Women	393/11,539 (3.4)	0.94 (0.65-1.37)	1.11 (0.82-1.50)
P for interaction		*0.048*	*0.20*
Married women	222/9513 (2.3)	0.81 (0.45-1.46)	1.22 (0.83-1.79)
Unmarried women	171/2026 (8.4)	1.06 (0.65-1.71)	1.01 (0.62-1.65)
Married men	655/9573 (6.8)	1.28 (0.95-1.74)	1.40 (1.15-1.72)
Unmarried men	107/1082 (9.9)	2.00 (1.16-3.43)	1.70 (1.03-2.82)
P for interaction	-	*0.064*	*0.31*

Hazard ratios (HR) with 95% confidence interval (95% CI) from the model adjusted for age, all SES factors simultaneously and marital status.
HRs for housing were obtained by opposing lower housing tenure (rented) vs ownership (≥1 property dwelling).
HRs for education were obtained by opposing lower (up to lower secondary school) vs high education (upper secondary/postsecondary school).
Each risk estimate for low vs high SES indicator was obtained among the whole study sample and within different subgroups (men, women, married women, unmarried women, married men and unmarried men).
Interaction was tested by introducing in the multivariable Cox analysis a product term of housing or education (low vs high) times a potential effect modifier represented by gender or by a 4-level variable combining gender (male/female) and marital status (married/unmarried).

and therefore could have been susceptible to error and bias. Yet, the assessment of the baseline health conditions (e.g. hypertension and psychological disorders) was made based on the use of medications or on self-reported information, and this may be a source of disease underestimation; however, the dataset of the Molisani Study provides accurate information on the use (frequency, dose, compliance) of medications for any disease, collected during the enrolment, and the questionnaire on drug usage was directly linked to the Italian National Drug Index.

Finally, our data were gathered among an adult cohort from a small Southern Italian region, which might limit the generalizability of our findings.

Conclusions

In summary, our data support the existence of a SES gradient in mortality among a large Mediterranean population of men and women. Disparities were related to both educational and material circumstances (i.e. housing tenure), and were partly justified by behavioural factors. We also documented a difference in survival rate associated with marital status.

The graded SES-mortality association when measured by housing-tenure was present among men, but not among women; the lack of statistical differentials prevents us from stating that the association between education and mortality is likely to vary by gender. Moreover, our findings indicate a synergy between marital status and gender, with unmarried men reporting lower material resources being at higher risk of death.

Key messages

- A socioeconomic gradient in mortality was observed in a large Mediterranean population.
- Male mortality is likely to be more unequal than female mortality across socioeconomic groups (measured by housing tenure).
- Marital and poverty status interact in such a way that unmarried men showed a 2-fold risk of death compared to their married counterparts.
- Behavioural factors were likely to account for up to 30% of the association between material circumstances (i.e. housing) and mortality.
- Inflammatory pathways explain a modest proportion of the association between educational disparities and mortality.

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