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Does lifestyle explain the relationship between socioeconomic position and multimorbidity of cancer and cardiometabolic diseases? A mediation analysis applied to the European Prospective Investigation into Cancer and Nutrition

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ABSTRACT

Background Multimorbidity is socially patterned, with lower socioeconomic position (SEP) linked to higher risk. We examined whether a Healthy Lifestyle Index (HLI) mediates the SEP–multimorbidity association and whether pathways differ by sex.

Methods We used data from 244 886 participants in the European Prospective Investigation into Cancer and Nutrition study. HLI was derived from smoking, alcohol consumption, physical activity, body mass index and diet. SEP was categorised into low, medium and high-SEP based on education. Multimorbidity was defined as the coexistence of at least two diseases among cancer, type 2 diabetes and cardiovascular diseases. Logistic regression assessed SEP-HLI association, Cox regression SEP-multimorbidity and HLI-multimorbidity associations. Counterfactual mediation analysis estimated the natural indirect effect (NIE) and pure direct effect (PDE). Analyses were stratified by sex.

Results Participants from lower SEP categories were older with worse health outcomes. Women had a healthier lifestyle than men across all SEP levels. In men, the hazard ratio of developing multimorbidity was 1.40 (95% CI: 1.26 to 1.54) for those with low SEP compared with high SEP, in women 1.74 (95% CI: 1.52 to 2.00). Comparing low versus high SEP, PDE for men was 1.28 (95% CI: 1.15 to 1.41), NIE was 1.09 (95% CI: 1.07 to 1.11) (proportion mediated (PM)=29%). In women, PDE was 1.65 (95% CI: 1.47 to 1.90), NIE 1.05 (95% CI: 1.03 to 1.06) (PM=11%).

Conclusions Lifestyle behaviours partly mediated the SEP-multimorbidity association, underscoring the need to integrate considerations of socioeconomic disparities into the planning of lifestyle interventions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lifestyle factors significantly influence the risk of developing non-communicable diseases like type 2 diabetes, cancer and cardiovascular diseases and can modify health trajectories towards multimorbidity.

⇒ Socioeconomic position (SEP) is a key determinant of health outcomes and is recognised as a driver of inequalities in the risk of multimorbidity.

INTRODUCTION

The prevalence of multimorbidity, defined as the coexistence of two or more chronic conditions in an individual,[1] has increased worldwide in the last two decades, with over half of the global adult population aged 60 and older living with multimorbidity.[1] Driven by the improvement in healthcare, the rise of life expectancy in an ageing population, especially in western countries, has resulted in a higher survival from individual chronic conditions and consequently has increased the likelihood of individuals developing multimorbidity.[2] The control and prevention of multimorbidity is a growing challenge for traditional models of disease management, as patients living with multimorbidity are high users of medical services, which poses a substantial economic burden on the healthcare systems.[1 2]

Cancer, type 2 diabetes (T2D) and cardiovascular diseases (CVDs) are the most prevalent non-communicable diseases (NCDs) responsible for the highest number of annual global deaths, along with disability and diminished quality of life.[3 4] While risk factors for individual NCDs have been extensively investigated, understanding the aetiological mechanisms leading to multimorbidity is a more complex task. Different mechanisms, such as the many biological processes involved with ageing, are expected to be interrelated, including the social determinants of health (SDoH).[1 2 5] In particular, evidence on the role

WHAT THIS STUDY ADDS

⇒ The study suggests that lifestyle factors partially mediate the relationship between SEP and the development of multimorbidity. However, this also indicates that other factors beyond lifestyle, such as biological or social determinants, may be at play.

⇒ The mediation effect of lifestyle factors seems to differ between men and women. Differences may stem from factors unique to women, such as early menarche, age at menopause, infertility and others.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study contributes to a deeper understanding of the mechanisms through which SEP influences multimorbidity. However, lifestyle factors only partially mediate the social inequalities and other factors should be investigated in future research.

⇒ The findings emphasise the importance of accounting for socioeconomic inequalities when designing lifestyle interventions, to ensure they are effective to reduce inequalities in multimorbidity risk across socioeconomic groups, with particular attention to potential gender differences. Additionally, they underscore the need to address structural health determinants that tackle the root causes of health inequalities, beyond the individual level.

of established lifestyle risk factors for NCDs,[6] including obesity, tobacco use, physical inactivity, alcohol and unhealthy diets on multimorbidity has been emerging in recent years.

Moreover, among the SDoH, socioeconomic position (SEP) is known to be a key factor for the most prevalent NCDs[7 8] and its importance in driving inequalities in the risk of multimorbidity has been acknowledged.[1 9] As lifestyle factors are known to be the main cause of NCDs,[10] socioeconomic deprivation has been found to play a similar role in driving morbidity and mortality.[11] Furthermore, the concentration of unhealthy lifestyle behaviours in socioeconomically deprived contexts is likely to cause disproportionate harm.[10] These elements support the hypothesis that lifestyle factors act as important mediators in the pathway through which SEP shapes NCDs and multimorbidity trajectories.

A related aspect is the possibility that both modifiable and non-modifiable risk factors for multimorbidity operate differently by sex. In fact, the literature suggests that, at least for individual NCDs, SEP can affect men and women in non-comparable ways depending on the specific NCD.[7 12] Also, while men and women tend to experience similar overall rates of multimorbidity as they age, the patterns, functional outcomes and health trajectories may differ considerably.[13]

The aim of the present study was to investigate the potential mediating role of five lifestyle factors, namely body mass index (BMI), smoking status, alcohol consumption, dietary intake and physical activity, summarised in the Healthy Lifestyle Index (HLI), in explaining the relationship between SEP and multimorbidity, and to explore whether these lifestyle-related mechanisms differ by sex.

MATERIALS AND METHODS

Study design

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is one of the largest cohort studies in Europe. Ten European countries have participated in the study (Italy, France, Spain, Greece, UK, the Netherlands, Germany, Norway, Sweden and Denmark) and data have been collected during the period 1992–2000 from 23 centres.[14] The primary purpose of the study was to assess the relationship between diet, lifestyle, genetics and cancer. About 520 000 adults mostly aged 35–70 were recruited on voluntary basis and have been followed up to monitor cancer events and mortality status. The flow chart of the study is shown in online supplemental figure S1.

Mediating factor

Participants were asked to complete two questionnaires, one regarding dietary habits and the other about lifestyle. Additionally, a visit to a reference centre was arranged to collect anthropometric measurements and biological samples.[14] All lifestyle information was collected at baseline.

BMI was calculated using height and weight, while physical activity levels were computed according to the Cambridge Index.[15] Dietary intake information was drawn by centre-specific questionnaires, based on usual food intake over the previous 12 months. Adherence to a healthy diet was evaluated using a modified Mediterranean dietary score.[16]

The HLI[17] summarised the five lifestyle factors in a single score ranging from 0 to 20, where a higher score indicates healthier behaviour. Since these behaviours are often interrelated, analysing them jointly can provide a more comprehensive assessment of overall lifestyle.[17] For each factor, a value ranging from 0 to 4 was assigned by categorising the variables into quintiles. In particular, the HLI was categorised into classes by dividing it into four equal intervals: (0, 5)=unhealthy, (5, 10)=not very healthy, (10, 15)=quite healthy, and (15, 20)=very healthy. More details can be found in online supplemental material.

Exposure

The SEP was obtained through the educational level information from the questionnaires. The original question considered five categories: 0—no education, 1—primary school, 2—technical/professional school, 3—high school diploma and 4—university degree. From those initial scores, the Relative Index of Inequality (RII) was estimated, to obtain a standardised measure across different countries, sexes and 10-year birth cohorts. Within those strata, the RII was computed using the midpoint of the cumulative proportional distributions of each educational level. Subsequently, the measure was divided into tertiles, defining the low, medium and high-SEP categories.[9]

Endpoints

Clinical and pathological data on cancer at any site, excluding non-melanoma skin cancer, have been standardised through guidelines from a protocol used in all EPIC enrolment centres. Follow-up aimed at identifying cases of cancer within the EPIC cohort is based on information from various sources.[14] The International Classification of Diseases for Oncology, Third Edition (ICD-O-3)[18] was used to classify cancer data and mortality data were collected using the mortality registries of the enrolment centres.[14]

Data on T2D cases were collected within the EPIC-Interact study, a case-cohort study nested within EPIC. Follow-up for T2D cases was completed up to 31 December 2007.[19] Incident T2D cases were identified and verified by retrieving evidence from at least two independent sources. Information was collected from self-report, linkage to primary care and secondary care registers, drug registers, hospital admissions and mortality data.[16 19]

The CVD events were partially obtained from data on cause-specific mortality collected within the EPIC study. In particular, similarly to T2D, CVD cases were ascertained within the EPIC-CVD study, a case-cohort study nested within EPIC (sharing the same random subcohort of EPIC-Interact), with an active follow-up that ended between 2003 and 2010, depending on the centre.[20] As regards first non-fatal coronary events, the centres used different methods of ascertainment, requiring validation studies to assess the accuracy of those outcomes.[20] The outcomes taken into consideration were classified according to the ICD, 10th Edition (ICD-10)[21] (details can be found in the online supplemental material).

In order to harmonise the follow-up time for the three conditions, incident cases of cancer and CVD ascertained after 31 December 2007 were censored.

Participants from France, Greece and Norway were excluded from the analysis because they did not have information about CVDs and/or T2D. Moreover, prevalent cases of T2D, cancer, MI, angina and stroke were removed and participants with missing education and lifestyle data and those who were underweight (BMI<18.5) were excluded. Multimorbidity was defined as the presence of at least two chronic conditions in the same participant. Subsequently, the participants who developed a single disease during the follow-up were classified as non-cases.

Statistical analysis

Descriptive statistics were presented with medians and percentages separated by SEP category. A multinomial logistic regression was fitted to assess the association between SEP and the HLI score. The model was adjusted for age at enrolment and enrolment centre. Cox regression models were used to evaluate SEP-multimorbidity and HLI-multimorbidity associations, stratifying by enrolment centre and age (details in online supplemental material). The proportional hazards assumption was verified using the Schoenfeld residuals test.

A mediation analysis approach was used to examine if and to what extent HLI might be involved in a causal pathway that determines socioeconomic inequalities in multimorbidity. A causal diagram representing the assumed relationships among the variables of interest is presented in figure 1. The weighting approach developed by Vanderweele and Vansteelandt[22] was followed. The methodology was further expanded by Fasanelli *et al*,[23] to include the possibility of estimating marginal time-dependent effects for survival data. This methodology allowed us to estimate the natural indirect effect (NIE), the pure direct effect (PDE) and total effect (TE) as their product. The survival function was estimated by means of a Royston-Parmar model. 95% CIs were estimated for the effects with a bootstrap procedure encompassing 500 replications. More details on the models specification are provided in online supplemental material.

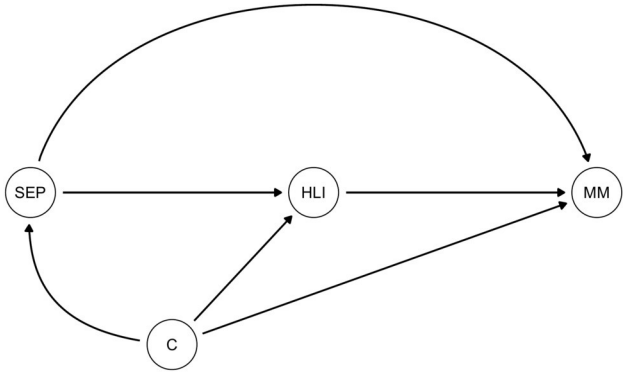

Figure 1 Causal structure represented by a directed acyclic graph. C, confounders vector (age at enrolment, enrolment centre, year of enrolment, menopausal status (women)); HLI, Healthy Lifestyle Index; MM, multimorbidity; SEP, socioeconomic position.

Both the main associations and the mediation analysis were investigated separately for each sex.

Analysis was conducted using the statistical software R (V.4.3.1).[24]

Patient and public involvement

This study used pseudo-anonymised data, and hence we had no means of contacting the study participants. Participants of this study were, therefore, not involved in this research.

RESULTS

Descriptive statistics

Data consisted of 244 886 participants (62% women), whose median age at the time of recruitment was 53.0 years. The median follow-up time was 12.13 years (IQR 11.10–13.13). Participants in the lower SEP level were slightly older and had worse values regarding health for BMI, dietary score and HLI score. Descriptive statistics according to SEP are reported in table 1 (details on individual lifestyle variables are shown in online supplemental table S1).

Overall, women tended to have a healthier lifestyle than men (14.4% vs 4.6% in the highest HLI category) with similar differences across all SEP levels. Moreover, incident cases of multimorbidity were more common among men. The incidence rate for the entire cohort was 1.31 cases per 1000 person-years. In particular, multimorbidity incidence rate was 2.74 cases per 1000 person-years among men with low SEP, while it was 1.20 cases per 1000 person-years famong women with low SEP (the incidence rates by sex and SEP are shown in online supplemental table S2. Regarding the single lifestyle factors, major differences between sexes have been found for alcohol intake and smoking habits, where on average, men tended to smoke and drink more than women. More details can be found in the online supplemental material, descriptive statistics separated by sex are shown in online supplemental table S3.

SEP and the risk of multimorbidity

When considering the TE of SEP on the risk of developing multimorbidity in men, the hazard ratio (HR) of developing multimorbidity was 1.40 (95% CI: 1.26 to 1.54) for those with low SEP compared with those with high SEP (table 2). A similar association was found for women, since the HR was 1.74 (95% CI: 1.52 to 2.00) for those with low SEP compared with those with high SEP (table 2).

A lower SEP level was associated with an increase in the odds ratio of having a lifestyle that belongs to the lowest category, compared with the next category, so those with a higher SEP were more likely to adopt healthier behaviours. In women, the results showed a similar trend to that observed in men, although with a less pronounced reduction in the risk of having an unhealthy lifestyle in the higher SEP categories (online supplemental table S4).

Participants with high HLI showed a marked decrease in risk of developing multimorbidity compared with participants with unhealthy behaviours: among men, those who had an unhealthy lifestyle had a HR of 4.73 (95% CI: 3.49 to 6.42) of developing multimorbidity compared with those who presented a very healthy lifestyle (online supplemental table S5). Among women, those who had an unhealthy lifestyle had a HR of 5.77

Table 1 Descriptive characteristics of the study participants by socioeconomic position (SEP) categories

Variables N	Tot 244 8861*	High SEP 83 4151*	Medium SEP 86 1981*	Low SEP 75 2731*
Median age (IQR)	52.97 (46.76, 58.91)	52.50 (46.21, 58.44)	52.58 (46.14, 58.01)	54.29 (47.77, 60.39)
Sex				
Men	93 868 (38.33%)	34 975 (41.93%)	27 344 (31.72%)	31 549 (41.91%)
Women	151 018 (61.67%)	48 440 (58.07%)	58 854 (68.27%)	43 724 (58.09%)
HLI				
0	9563 (3.91%)	2584 (3.09%)	3259 (3.78%)	3720 (4.94%)
5	82 522 (33.70%)	26 191 (31.40%)	28 609 (33.19%)	27 722 (36.83%)
10	126 786 (51.77%)	44 284 (53.09%)	45 084 (52.30%)	37 418 (49.71%)
15	26 015 (10.62%)	10 356 (12.42%)	9246 (10.73%)	6413 (8.52%)
Country				
Italy	42 099 (17.19%)	15 286 (18.33%)	15 274 (17.72%)	11 539 (15.33%)
Spain	35 000 (14.29%)	11 038 (13.23%)	13 804 (16.01%)	10 158 (13.49%)
UK	24 714 (10.09%)	8359 (10.02%)	6914 (8.02%)	9441 (12.54%)
The Netherlands	27 667 (11.30%)	10 546 (12.64%)	8564 (9.94%)	8557 (11.37%)
Germany	41 916 (17.12%)	15 136 (18.15%)	17 148 (19.89%)	9632 (12.80%)
Sweden	22 612 (9.23%)	8294 (9.94%)	4935 (5.73%)	9383 (12.47%)
Denmark	50 878 (20.78%)	14 756 (17.69%)	19 559 (22.69%)	16 563 (22.00%)

*n (%), median (IQR).
0, unhealthy; 5, not very healthy; 10, quite healthy; 15, very healthy; HLI, Healthy Lifestyle Index.

(95% CI: 4.25 to 7.85) of developing multimorbidity compared with women who followed very healthy lifestyle habits (online supplemental table S5).

Mediation analysis

The mediation analysis, conducted separately by sex, showed that lifestyle, measured by the HLI, partly mediated the association between SEP and multimorbidity. In women (online supplemental figure S2), the PDE of medium versus high SEP was 1.54 (95% CI: 1.36 to 1.80), and the PDE of low vs high SEP was 1.65 (95% CI: 1.47 to 1.90). Regarding the NIE, the direction of the mediating role of lifestyle differed depending on the SEP comparison. The NIE was 0.91 (95% CI: 0.89 to 0.93) for medium versus high SEP, and 1.05 (95% CI: 1.03 to 1.06) when for low versus high SEP. The proportion mediated (PM) for low versus high SEP was approximately 11% (table 3).

Among men (online supplemental figure S3), lifestyle also appeared to be a mediator of the relationship between SEP and multimorbidity. The PDE of medium versus high SEP was 1.26 (95% CI: 1.11 to 1.40), and the PDE of low versus high SEP was 1.28 (95% CI: 1.15 to 1.41), while the NIE was 1.01 (95% CI: 1.00 to 1.04) (medium vs high) and 1.09 (95% CI: 1.07 to 1.11) (low vs high). The PM comparing low SEP to high SEP was approximately 29%, while the PM comparing medium SEP to high SEP was approximately 5% (table 4).

The positivity hypothesis was checked for both men and women (online supplemental tables S6–S9).

Table 2 HRs of socioeconomic position (SEP) categories in relation to multimorbidity

HRs 95% CIs		
Men		
High SEP	1	
Medium SEP	1.32	(1.17 to 1.47)
Low SEP	1.40	(1.26 to 1.54)
Women		
High SEP	1	
Medium SEP	1.56	(1.35 to 1.80)
Low SEP	1.74	(1.52 to 2.00)

Cox regression model stratified by enrolment centre and age class, including years of enrolment as fixed effect (and adjusted for menopausal status in women).

Table 3 HRs for multimorbidity according to socioeconomic position (SEP) and considering Healthy Lifestyle Index as a mediator (women, results for median follow-up time)

HRs 95% CIs			PM
TE			
SEP medium vs high	1.40	(1.22 to 1.63)	
SEP low vs high	1.74	(1.54 to 2.03)	
PDE			
SEP medium vs high	1.54	(1.36 to 1.80)	
SEP low vs high	1.65	(1.47 to 1.90)	
NIE			
SEP medium vs high	0.91	(0.89 to 0.93)	–
SEP low vs high	1.05	(1.03 to 1.06)	11%

NIE, natural indirect effect; PDE, pure direct effect; PM, proportion mediated; TE, total effect.

DISCUSSION

The results obtained suggest that the HLI explained the relationship between SEP and multimorbidity to some degree. The PM was higher among men than women. Although the modifiable lifestyle risk factors analysed by the HLI were found to mediate the SEP-multimorbidity relationship, a substantial proportion of

Table 4 HRs for multimorbidity according to socioeconomic position (SEP) and considering Healthy Lifestyle Index as a mediator (men, results for median follow-up time)

HRs 95% CIs			PM
TE			
SEP medium vs high	1.27	(1.12 to 1.42)	
SEP low vs high	1.39	(1.26 to 1.52)	
PDE			
SEP medium vs high	1.26	(1.11 to 1.40)	
SEP low vs high	1.28	(1.15 to 1.41)	
NIE			
SEP medium vs high	1.01	(1.00 to 1.04)	5%
SEP low vs high	1.09	(1.07 to 1.11)	29%

NIE, natural indirect effect; PDE, pure direct effect; PM, proportion mediated; TE, total effect.

the social inequalities in the risk of developing multimorbidity remains unexplained.

Analogous findings were reported in a similar European cohort study,[25] in which the same lifestyle risk factors were proven to only partially mediate the relationship between socioeconomic deprivation and multimorbidity. In that study, the mediating role of the five joint mediators was higher compared with our findings (roughly 40% in the entire cohort). Moreover, the same modifiable risk factors were also shown to partially explain the relationship between SEP and all-cause mortality, to a higher percentage compared with the present study, in particular for women (34% and 38% PM for women and men respectively).[26]

Differences in the mediating effect of HLI between men and women may have several reasons. In women, factors such as early menarche, age at menopause and infertility can increase the risk of CVDs,[27] modify cardiometabolic trajectories,[28] as well as play a role in the development of some cancers such as ovarian and breast cancer.[29] It is likely that the mediating role of HLI was less pronounced in women, given a possible greater influence of these factors. Also, we used a synthetic lifestyle indicator, while in a Canadian study conducted by Nejatinamini *et al*[30] smoking, excess alcohol consumption, low fruit and vegetable intake, physical inactivity and obesity were treated as separate mediators. The results from the study showed a higher proportion of the effect mediated by these factors compared with our findings and highlighted differences in the lifestyle factors' importance for men and women. Smoking was the most important mediator for men, obesity for women. Even though the endpoint of the study (cancer morbidity and mortality) was different from ours, it nevertheless may shed some light on the differences we found. Indeed, in our sample, one of the major sex-wise differences was observed in smoking and alcohol consumption habits. These differences might underlie the sex-related differences in the relation between SEP and lifestyle that we observed. There is evidence, even though not entirely conclusive, that men's lifestyle behaviours may be more strongly shaped by SEP than women's. In particular, men in the lower SEP categories tend to show more consistent negative gradients in smoking, unhealthy food consumption and drinking, whereas women from low-SEP backgrounds are less likely to engage in leisure-time physical activity.[31] These sex differences likely result from a complex interplay of factors such as socially constructed roles, external stressors and differences in the support networks.[32]

Furthermore, in women, a suppressor effect was found, whereby healthier lifestyle behaviours in the medium SEP group partially offset the increased risk associated with lower SEP. This finding may be explained by several contextual factors: the fact that SEP groups—particularly medium and high SEP—were likely to be more similar in women than in men; the limited number of women with very low HLI; the presence of single NCDs among individuals classified as not multimorbid, who may have a profile similar to those with multimorbidity. Moreover, it should be noted that the effect is very close to null. Taken together, these findings suggest that, in this population, women in the medium and high SEP categories are likely more alike than different in terms of lifestyle and baseline health status.

Finally, other causes can probably be traced back to factors outside the lifestyle realm. In particular, lack of social support,[33] access to health resources[34] and psychosocial factors are likely to play an independent role in driving inequalities in multimorbidity. These aspects are also likely to vary by sex, with psychosocial factors, including depression, more prevalent in women with multimorbidity.[35] Moreover, education and income influence social support and health behaviours differently by sex, indirectly impacting healthcare access.[33]

The present study has several strengths. It used individual-level data with a median follow-up of about 12 years, within one of the largest cohort studies in Europe. The longitudinal design allowed us to take temporality into account, diminishing the risk of reverse causality. The use of mediation analysis enabled to delve deeper into the underlying mechanisms linking social deprivation to the risk of multimorbidity, considering lifestyle as a possible causal pathway.

However, several limitations must be considered. First, lifestyle information was collected at baseline, while enrolled participants might have changed their habits, particularly following their initial diagnosis. Nonetheless, it has been specified that the associations analysed in the study consider lifestyle habits before the diagnosis and assess the extent to which those habits influence the probability of developing multimorbidity. Moreover, a change in the lifestyle habits after the enrolment would have likely weakened the estimated associations. Health behaviour patterns tend to cluster and remain relatively stable from middle adulthood into later life. Some positive changes, like smoking cessation following diagnosis of chronic illness, occur but only among a minority, and exercise levels generally do not increase significantly after diagnosis.[36] Cancer and cardiometabolic risk have a clear dose-response and time-response relationship: the longer the duration of an unhealthy habit, the greater the cumulative damage and thus the higher the risk. Therefore, assuming relatively stable lifestyle habits among cohort participants, the likelihood of substantial bias is reduced, although it cannot be entirely ruled out. Furthermore, the study relied on self-reported conditions and habits, which could potentially introduce measurement error. All self-reported assessments concerning cancer cases have been validated through medical verification, and validation studies have been carried out for cases of T2D, myocardial infarction and stroke. However, under-reporting of unhealthy lifestyle habits could not be assessed, likely determining an attenuation of the mediation estimates. Moreover, while attenuation is the most probable scenario due to the potential for non-differential random error, we cannot rule out the possibility that systematic over-reporting or under-reporting occurred within certain subgroups, leading to an overestimation of the mediating role of lifestyle in some cases. Another limitation regarded the lack of a clear temporal sequence between diseases, which makes it complex to accurately assess possible different multimorbidity and care trajectories according to the first diagnosis. Moreover, the way multimorbidity was defined in the current work may under-represent its full spectrum. The absence of other diseases, such as chronic respiratory diseases or mental health disorders, could prevent a more comprehensive assessment of the outcome. However, since cancer, T2D and CVD are among the most prevalent NCDs,[3] the operational definition adopted provides a focused yet relevant framework for the study. A related aspect was the absence of information on treatment following the initial NCD diagnosis, that might have influenced the possible progression of ensuing multimorbidity. Some treatments, for instance, for T2D might reduce the cardiovascular risk and perhaps some types of cancer.[37] On the other hand, it is well known that systemic cancer therapies can be cardiotoxic, inducing a large set of cardiovascular side effects.[38] In countries where universal health coverage is guaranteed,

inequalities in treatment according to SEP are less likely, although some disparities may still persist.[39] An additional aspect regards the response rate that seemed to vary by level of SEP. Even if the EPIC study sampling is done from the general population, people with low SEP usually have a lower response rate,[40] and that could determine a selection bias due to differential response rates. Also, an associated limitation is the use of RII as a proxy of SEP, in particular for women. While access to education has become more equal between the sexes today, the EPIC data were collected in the 1990s from an older cohort who had been educated in earlier decades. In this context, education may not be the most appropriate indicator of SEP for women, who were more commonly dependent on their husbands' SEP compared with more recent years. Other SEP indicators, such as occupation or household income, could have provided a more comprehensive view. However, educational level offers several advantages, as it is established early in life and remains stable over time, reducing the risk of reverse causality. Furthermore, it can serve as a proxy for health awareness and the ability to seek medical advice and navigate the healthcare system and is correlated with other metrics such as income in adulthood. Finally, although a careful evaluation of the theoretical causal model was conducted, the possibility of residual confounding remains likely and represents a limitation, which is nonetheless inherent to all observational epidemiologic studies.

In conclusion, this work demonstrates that, among modifiable risk factors that are involved in the co-occurrence of more than one NCD, lifestyle behaviours played a significant role in driving inequalities in the risk of developing multimorbidity of cancer and cardiometabolic diseases, leading to different trajectories in distinct socioeconomic layers.

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