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Original Article

Mortality among Older Adults Across Multimorbidity Categories and Lifestyle Patterns

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ABSTRACT: Multimorbidity is common in older adults, and certain combinations of chronic conditions may confer higher mortality risk. Unhealthy lifestyle behaviours are also linked to shorter life expectancy. This study examined whether lifestyle patterns (LPs) modify the association between multimorbidity configurations (MCs) and mortality. We analysed data from 20,853 adults aged 60 and older in the Northern Netherlands Lifelines cohort, followed for a mean of 12 years. Five LPs were previously identified via latent class analysis, based on diet, physical activity, substance use, sleep, social connection, and stress. Multimorbidity was defined both as a disease count (≥2 non-communicable diseases [NCDs]) and as five latent MCs reflecting distinct NCD combinations. All-cause mortality was estimated using Kaplan–Meier plots and Cox models, reporting hazard ratios (HRs) with 95% confidence intervals (CIs), stratified by LPs. Compared to having no NCDs, mortality risk differed across MCs, with associations varying by LPs. Among participants with a 'Healthy in a balanced way' lifestyle, the 'Complex-Treatment' (HR 3.18, 95%CI: 2.24–4.51) and 'CVD-&-Vascular' (HR 2.35, 95%CI: 1.97–2.79) configurations showed the highest risks. In the 'Unhealthy but no substance use' group, mortality risk across MCs was more heterogeneous, with larger effect sizes. In contrast, multimorbidity defined by disease count showed limited variation in effect sizes across other LPs. LPs shape the mortality risk associated with multimorbidity. Risk variability across MCs was more pronounced in healthier lifestyles. These findings support the value of considering specific multimorbidity profiles—beyond disease count—for prognostic assessment and targeted interventions in older adults.

Keywords: Multimorbidity, Lifestyle patterns, older adults, mortality risk, healthy ageing and chronic diseases.

INTRODUCTION

Life expectancy has steadily increased in recent decades, particularly in high-income countries [1, 2]. In Europe, the average life expectancy now exceeds 76 years, reaching approximately 81 years in the Netherlands (Retrieved from: World Health Organization (2025). *Life expectancy at birth (years)*. Available at: www.who.int/data/gho/data/indicators/indicator-details/GHO/life-expectancy-at-birth-(years). Accessed April 7, 2025). As a result, populations are ageing, and a growing proportion of older adults are living with chronic conditions such as diabetes, cardiovascular disease, hypertension, and cancer. This increasing burden is associated with reduced quality of life, functional decline, psychological distress, longer hospital stays, and increased healthcare costs [3].

Multimorbidity, defined as the coexistence of two or more chronic conditions within an individual, has become highly prevalent and is now recognized as a global public health concern [4, 5]. Its presence is consistently

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associated with elevated mortality risk, particularly among older adults [6–8]. Beyond the number of chronic conditions, recent studies have begun to examine multimorbidity patterns [9] and their potential as predictors of health outcomes, especially mortality risk [10–13].

The development of multimorbidity is complex and multifactorial [3]. Emerging evidence from genetic studies suggests that many diseases are genetically correlated, indicating the existence of shared biological pathways [14]. Numerous chronic conditions are linked through common mechanisms such as chronic inflammation and accelerated organ aging [15], both of which can be influenced by lifestyle factors[16]. Advances in genomics have further provided insights into the causal effects of modifiable lifestyle factors on a wide range of diseases. These findings offer valuable tools for identifying and prioritizing potential causal pathways that may be shared across multimorbid conditions [17]. Observational studies have consistently shown that a healthy lifestyle -characterized by optimal body mass index, non-smoking status, moderate alcohol intake, regular physical activity, and adherence to a balanced diet- is associated with a substantially lower risk of developing multimorbidity [16]. Lifestyle factors often co-occur, forming lifestyle patterns (LPs) that reflect the interplay of habitual behaviours and daily routines. The term 'lifestyle patterns' has been increasingly used in lifestyle medicine to describe the set of behaviours, routines, and decisions that collectively characterise how individuals or groups live[18]. However, limited studies have investigated the associations between LPs and multimorbidity.

Recent findings suggest that certain LPs may be linked to slower biological ageing and reduced mortality risk. A large prospective cohort study of over 500,000 UK Biobank participants found that individuals who adhered to an anti-inflammatory diet, engaged in at least moderate physical activity, and maintained healthy sleep habits showed a slower pace of physiological ageing (HR for slow physiological aging: 0.69) and a substantially lower risk of all-cause mortality (HR for All-Cause Premature Mortality: 0.49). These associations were particularly pronounced among individuals under 60 years of age and among women [19]. In another study involving 79,345 participants from the Lifelines cohort in the northern Netherlands, individuals with multimorbidity more often reported unhealthy behaviours, such as physical inactivity and chronic stress—both associated with increased mortality risk [20].

Importantly, several studies indicate that healthy lifestyles may mitigate the mortality risk associated with multimorbidity. Analyses of Chinese and UK populations reported that adherence to healthy lifestyle behaviours was associated with a 27% to 42% lower mortality risk among individuals with multimorbidity, and an 18% to 42% reduction among those without multimorbidity [21]. Findings from the NHANES cohort corroborated these results[22]. However, not all studies have been consistent. One study focusing solely on diet quality found a significant protective effect of healthier diets on mortality only among individuals free of type 2 diabetes or cardiometabolic diseases, but not among those with two or more chronic metabolic conditions [23]. In contrast, another study that examined multiple lifestyle factors reported that older adults with multimorbidity particularly benefited from adopting healthy lifestyles emphasizing nutrition, physical activity, sleep quality, and social engagement, which collectively reduced mortality risk [22].

Scientific evidence on the relationship between different multimorbidity patterns and mortality in older adults is heterogeneous across populations and warrants deeper examination. To date, most survival studies conceptualize multimorbidity as an accumulative phenomenon, without considering that specific combinations of diseases may confer distinct risks. Moreover, lifestyle factors are often included only as adjustment variables, without assessing how LPs—rather than isolated behaviors—may modify the risks associated with different accumulation patterns of non-communicable diseases (NCDs), or multimorbidity configurations (MCs) as referred to in this manuscript. Evaluating lifestyles as sets of co-occurring behaviors allows us to explore whether mortality risk varies across qualitative types of multimorbidity, even at the extremes in the gradient of what is considered healthy or unhealthy lifestyle profiles.

Considering the lack of research on LPs and inconsistency of findings, there raise a critical question: do LPs influence associated between multimorbidity and mortality risk, particularly across distinct multimorbidity categories and varying levels of disease severity? Addressing this question is essential for developing effective, targeted interventions to promote healthy aging and reduce premature mortality among individuals living with diverse multimorbidity categories [22]. Therefore, the primary aim of the study was to evaluate the impact of multimorbidity on mortality risk among Lifelines participants who share common LPs, with comparisons across distinct multimorbidity categories. An additional aim was to assess whether MCs provide more informative insights than the cumulative definition of multimorbidity (≥2 NCDs). Clarifying this association may help identify subgroups that could benefit most from lifestyle interventions and inform targeted strategies to promote healthy aging.

MATERIALS AND METHODS

Study design and population

This study is a prospective cohort survival analysis based on data from the Lifelines Cohort Study. "*Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics*". Lifelines covers the provinces of Drenthe, Friesland, and Groningen. Participants were enrolled between 2006 and 2013 for baseline assessments. Information on multimorbidity, lifestyle patterns, and covariates was obtained from baseline data. More detailed information about Lifelines has been published elsewhere [24, 25].

The current analysis included data on multimorbidity, LPs, and sociodemographic variables from the baseline (1A assessment). Participants were excluded if they were younger than 60 years (n=129,409), had unknown age (n=4), or had no mortality information available (n=108). A total of 20,853 subjects were included in the analysis (Fig. 1).

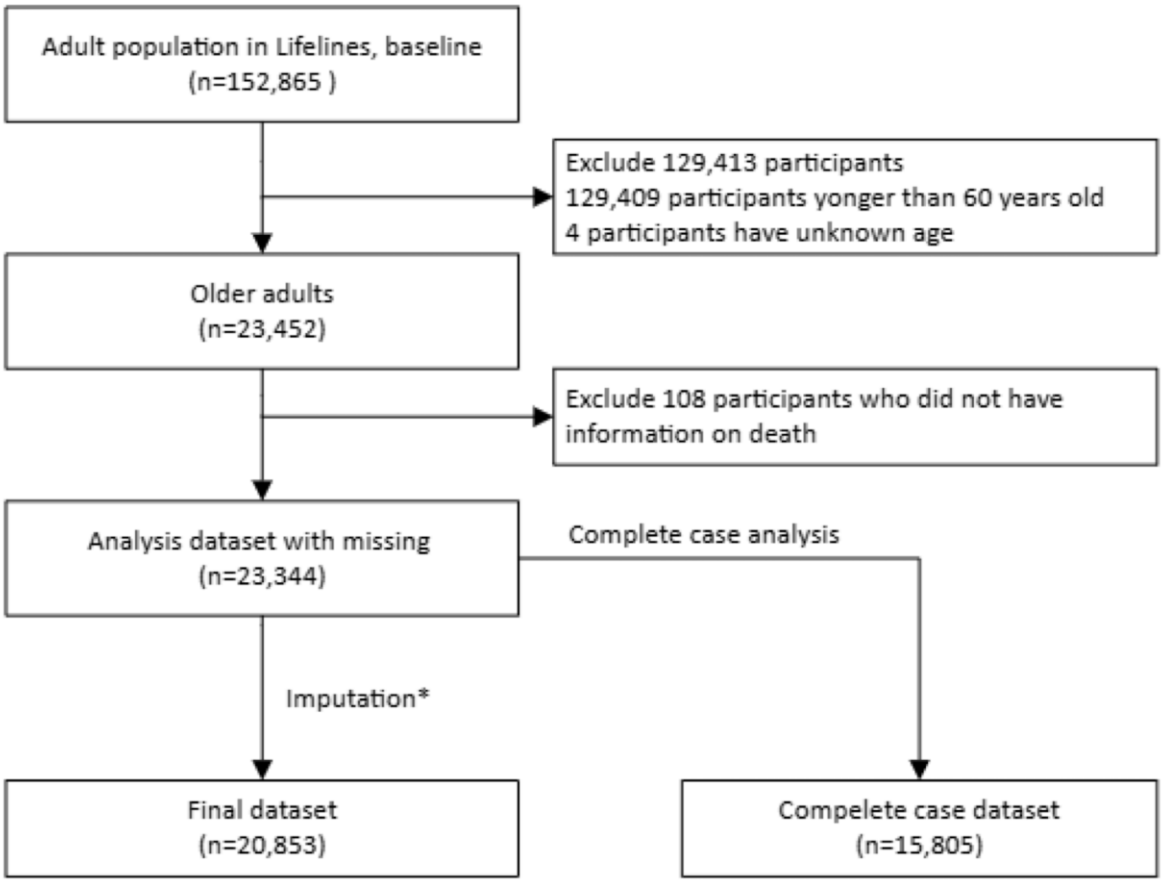

Figure 1. Flowchart of participants (inclusions and exclusions). For participants with information on at least two lifestyle factors.

All participants provided written informed consent prior to studying entry. The Lifelines Cohort Study was approved by the Medical Ethics Committee of the University Medical Center Groningen and is conducted in accordance with the Declaration of Helsinki and the UMCG research code. Additional details on the Lifelines protocol have been published previously.

Mortality follow-up

All-cause mortality data were obtained through linkage with Dutch municipal population registries, which record the vital status of residents. The date of death (month and year) was recorded up to February 2025. Mean follow-up time was 12.5 years (SD 2.6).

Procedures

Multimorbidity assessment

Multimorbidity was operationalized using two complementary approaches to capture both the cumulative burden of disease and the qualitative patterns of disease accumulation, allowing for a more objective and comprehensive estimation of mortality risk. First, we assessed cumulative multimorbidity [4], categorized as no NCDs, one NCD, or two or more NCDs. Second, we derived MCs using latent class analysis (LCA) among individuals with ⩾2 NCDs, a data-driven method that uncovered non-random latent patterns of disease clustering. Methodological details are published elsewhere [26]; however, a brief summary of the procedures used to derive MCs is provided below:

To derive MCs, we first grouped 45 NCDs into 14 clinically meaningful categories based on established frameworks from prior studies. Grouping criteria included shared pathophysiological mechanisms, clinical presentation, and affected organ systems. The categories included: 1) cancer (bone, brain, breast, prostate, lung, colon, and other types, excluding skin and cervical cancer) [27]; 2) major cardiovascular disease or CVD (myocardial infarction, heart failure, stroke, and heart surgery); 3) heart and peripheral vascular conditions or HPVC (atrial fibrillation, arrhythmia, valve disorders, claudication, aneurysm, atherosclerosis, thrombosis) [28, 29]; 4) hypertension or HTN (systolic/diastolic blood pressure ⩾140/90 mmHg); 5) arthritis; 6) osteoporosis; 7) digestive disorders (e.g., liver disease, ulcerative colitis, Crohn's disease); 8) respiratory diseases (asthma, breathing problems, COPD) [28, 29]; 9) thyroid disorders (hypo/hyperthyroidism and dysfunction); 10) neurological/degenerative diseases (Alzheimer's, dementia, Parkinson's, epilepsy, multiple sclerosis); 11) diabetes mellitus types 1 and 2; 12) kidney (chronic kidney disease, disturbed kidney, kidney disorders and renal failure) [30, 31]; 13) depression; and 14) obesity (BMI ⩾ 30 kg/m^2) (Retrieved from: World health Organization (WHO) (2025). Body mass index (BMI). Available at: www.who.int/data/gho/data/themes/topics/topic-details/GHO/body-mass-index?introPage=intro_3.html. Accessed 4 Oct 2025). Each condition was coded as present or absent.

To ensure diagnostic validity, classification was based on a multi-source approach at baseline (1A assessment), which included: (a) self-reported physician diagnoses (e.g., "Have you ever been diagnosed by a physician with...?"); (b) current use of prescribed medications or treatment for the condition; (c) clinical or laboratory diagnostic thresholds, based on serum, blood, or urine biomarkers; and (d) relevant surgical or medical history, such as organ transplantation, cardiac device implantation, coronary bypass, angioplasty, or dialysis. Where applicable, classification was further supported by clinical assessments, including spirometry (for respiratory diseases), blood pressure measurements (for HTN), electrocardiograms (for cardiovascular conditions), and anthropometric indicators (for obesity or metabolic risk) [24]. This multi-source approach ensured comprehensive case identification by integrating self-reported data, treatment records, and clinical biomarkers.

The 14-category NCD framework was analyzed using LCA to identify subgroups with similar disease patterns. Model selection was guided by the Bayesian Information Criterion, clinical interpretability, and parsimony. Participants were assigned to classes using an item-response probability threshold of ⩾0.3. A cut-off of ⩾2 NCDs was applied to define MCs. Five MCs were retained, each representing a latent disease profile characterized by distinct combinations of NCD categories.

Within each MC, diseases are listed in decreasing order of probability. Percentages indicate the proportion of the sample assigned to each configuration: 'Vascular' (23.0%): characterized by overall low NCD burden but most likely to include HTN, HPVC, and respiratory disease; 'Heart & Vascular' (10.4%): high probability of HPVC, HTN, and respiratory disease; 'Major CVD & Vascular' (7.3%): high probability of HPVC, CVD, and HTN; 'Metabolic' (14.2%): high probability of HTN, obesity (BMI ≥30), HPVC, and diabetes; and 'Complex Treatment' (1.4%): high probability of HTN, HPVC, obesity, diabetes, respiratory, kidney disease, CVD, and arthritis. Each was labeled according to the predominant disease profiles and etiological relevance.

These configurations represent profiles of elevated probability for the listed diseases, but not exclusivity. Participants without multimorbidity (<2 NCDs) served as the reference group. These MCs were later incorporated into the survival analyses.

Lifestyle patterns

LPs were identified using LCA among Dutch participants from the Lifelines cohort based on ten lifestyle factors from six domains: smoking, binge drinking, daily alcohol intake, diet quality, ultra-processed food consumption, long-term stress, physical activity, sleeping, TV watching time, and social connections. Five distinct patterns were identified. Percentages indicate the proportion of participants assigned to each pattern: 'Healthy but physically inactive' (13.7%); 'Healthy in a balanced way' (58.2%); 'Unhealthy but no substance use' (4.5%); 'Unhealthy but light drinking and never smoked' (14.9%);

and 'Unhealthy' (8.7%) [32]. Lifestyle factors within these patterns have been shown to be associated with health outcomes both individually and when considered jointly [33, 34].

The 'Healthy but physically inactive' pattern characterized as healthy in most lifestyle factors except for physical inactive. The 'Healthy in a balanced way' means most of lifestyle factors were mannered as a moderate level of healthiness. The 'Unhealthy but no substance use' were characterized as unhealthy in most lifestyle factors without smoking and drinking. The 'Unhealthy but light drinking and never smoked' representing most of lifestyle factors are unhealthy but no smoking and light drinking. The 'Unhealthy' pattern means most of lifestyle factors were unhealthy. Full methodological details are available elsewhere [32], and descriptive profiles are presented in Supplementary Figure 1.

Sociodemographic characteristics

Sociodemographic variables were collected via standardised self-report questionnaires and included age, sex, marital status, household income, educational attainment, and employment status. Marital status was categorised into: married/cohabiting, in a relationship but not cohabiting, no partner (including widows), and others. Household income (€) was normalised by dividing mid-category net household income (the midpoint of each participant's income category) by the square root of household size. Educational attainment was grouped into five categories: (1) elementary education (no education or primary education); (2) lower secondary education (lower or preparatory vocational education or lower general secondary education); (3) upper secondary education (intermediate vocational education, apprenticeship, higher general secondary education or pre-university secondary education); (4) tertiary education (higher vocational education or university); and (5) others. Employment status was categorized into six groups: full-time job, retired, housewife/husband, studying, part-time job and others (including individuals who are unemployed, looking for a job, unfit for work or on social assistance benefit).

Statistical analysis

Descriptive analyses were conducted across categories of cumulative multimorbidity and MCs. Variables were summarised using central tendency and dispersion measures as appropriate. Categorical variables are presented as counts (n) and percentages (%).

Missing data for sex, educational attainment, income, marital status, employment status, and LPs (Supplementary Table 1) were addressed through multiple imputation by chained equations, following assessment of missingness mechanisms[35, 36]. Imputation was restricted to cases with at least two informative lifestyle indicators. Pre- and post-imputation distributions were compared using chi-squared tests (Supplementary Table 2).

Time to all-cause mortality was assessed using Kaplan–Meier curves stratified by LPs and MCs (See Supplemental Figure 3 for Kaplan–Meier survival curves stratified by LPs and NCD accumulation), with log-rank tests used to assess between-group differences. Associations between MCs, LPs, and mortality risk were estimated using Cox proportional hazards models, with HRs and 95% CIs. Statistical significance was set at $P<0.05$[37].

Model building included potential confounders: age (continuous), sex, educational attainment, marital status, income, and employment status. Covariates were evaluated using backward elimination and retained based on statistical significance.

The proportional hazards assumption was tested using Schoenfeld residuals. A violation was detected for age, consistent with known age-related changes in mortality risk; age was therefore modelled as a time-varying covariate. Two sensitivity analyses were conducted in the pre-imputed dataset: one treating age as time-varying, and one as fixed (Supplementary Table 3).

Post-hoc analysis for interaction

An interaction term was added to the final adjusted Cox models as a post-hoc analysis to explore potential interactions between LPs and multimorbidity categories (LPs×MCs and LPs×NCDs accumulation), on mortality risk. The "Unhealthy" (LP) and "No multimorbidity" groups were used as reference categories (Supplementary Tables 4a and 4b).

Statistical significance was assessed using Wald tests (p for interaction < 0.05), both globally (Supplementary table 5) and for pairwise contrasts (Supplemental tables 6a and 6b). To account for multiple comparisons, p-values were adjusted using the Holm and Benjamini–Hochberg false discovery rate (FDR) procedures (Supplementary Table 7). Marginal predictions were derived from the exponentiated linear predictors of the extended Cox models, and 95% CIs were estimated for both global interaction terms and predicted values (Supplementary Tables 8a and 8b).

Interaction results were summarized in tables and visualized using marginal predictions to illustrate how mortality risk potentially varied across combinations of LPs and multimorbidity categories. These findings are further discussed in the Discussion section.

Imputation was performed in RStudio (version 4.2.2) using the *mice* package [36]; all other analyses were conducted in Stata/MP (version 18.0). Two-sided $P<0.05$ was considered statistically significant.

Role of the funding source

"There was no funding source for this study".

RESULTS

Of the 23,452 older adults initially included, 108 (0.5%) were excluded due to missing mortality data. Multiple imputation was performed on 5,048 cases, yielding a final analytical sample of 20,853 participants (Fig. 1). Distributional differences between pre- and post-imputation datasets are shown in Supplementary Table 2. Although group comparisons were statistically significant, subgroup proportions were highly similar, suggesting differences were mainly due to increased sample size following imputation.

Descriptive statistics and mortality outcomes are shown in Table 1. Overall, 54.8% of participants had ≥2 NCDs. The most frequent MC was the 'CVD & Vascular' configuration, observed in 23.9% of the sample. Mean follow-up was 12.5 years (SD 2.6; range 0.3–16.6). Age was comparable across subgroups defined by NCD count, while higher mean ages were observed in the 'Complex Treatment' (68.5 ± 6.1 years) and 'CVD & Vascular' (68.8 ± 6.1 years) groups, which also had the highest mortality rates. Participants with multimorbidity were, on average, older (67.6 ± 5.7 years), more often female (56.4%), more likely to have lower educational attainment (55.9%) and income (<€1,900 in 46.0%), be married (81.1%), and be retired (51.1%). They were also more frequently classified into the 'Healthy but physically inactive' or other unhealthy LPs.

Table 1. Descriptive analysis of all variables and deaths by diseases status (N=23,452).

	Accumulation of NCDs			Multimorbidity patterns				
	No NCD	One NCD	Two or more NCDs	Vascular	Heart & Vascular	CVD & Vascular	Metabolic	Complex treatment
Sample size [a]	4,191 (17.8%)	6,401 (27.3%)	12,860 (54.8%)	5,057 (23.9%)	2,208 (10.5%)	1,562 (7.4%)	2,808 (13.3%)	333 (1.6%)
Deaths [a]	501 (12.0%)	915 (14.3%)	2,771 (21.7%)	850 (16.9%)	425 (19.3%)	496 (31.9%)	486 (17.4%)	124 (37.5%)
Follow- up years [b]	12.7± 2.2	12.6± 2.4	12.3± 2.7	12.6± 2.4	12.5± 2.7	11.7± 3.2	12.6± 2.5	11.7± 3.2
Lost to follow-up [a]	17 (0.4%)	21 (0.3%)	70 (0.5%)	26 (0.5%)	<10 [c]	<10 [c]	14 (0.5%)	<10 [c]
Age [b]	66.8± 5.1	66.8± 5.3	67.6± 5.7	66.7± 5.1	67.6± 5.8	68.8±6.1	66.8±5.1	68.5±6.1
Sex, female [a]	2,037 (49.0%)	3,350 (52.3%)	7,256 (56.4%)	2,885 (57.1%)	1,708 (77.4%)	407 (26.1%)	1,608 (57.3%)	218 (65.5%)
Sex, missing [a]	102 (2.4%)	68 (1.1%)	65 (0.5%)	<10 [c]	-	<10 [c]	<10 [c]	-
Education attainment [a]								
Elementary	300 (7.2%)	484 (7.6%)	1,285 (10.0%)	343 (6.8%)	214 (9.7%)	147 (9.4%)	275 (9.8%)	48 (14.4%)
Lower secondary	1,865 (44.5%)	2,857 (44.6%)	5,901 (45.9%)	2,272 (44.9%)	1,058 (47.9%)	643 (41.2%)	1,397 (49.8%)	150 (45.1%)
Secondary	793 (18.9%)	1,320 (20.6%)	2,511 (19.5%)	1,046 (20.7%)	410 (18.6%)	335 (21.5%)	531 (18.9%)	77 (23.1%)
Tertiary	962 (23.0%)	1,392 (21.8%)	2,415 (18.8%)	1,117 (22.1%)	405 (18.3%)	339 (21.7%)	450 (16.0%)	45 (13.5%)
Others	144 (3.4%)	227 (3.6%)	498 (3.9%)	207 (4.1%)	88 (4.0%)	67 (4.3%)	98 (3.5%)	11 (3.3%)
Missing	127 (3.0%)	121 (1.9%)	250 (1.9%)	72 (1.4%)	33 (1.5%)	31 (2.0%)	57 (2.0%)	<10 [c]
Net income [a]								
(-1,100)	303 (7.2%)	516 (8.1%)	1,379 (10.7%)	483 (9.6%)	297 (13.5%)	177 (11.3%)	358 (12.8%)	57 (17.1%)
[1,100, 1,500)	535 (12.8%)	961 (15.0%)	2,413 (18.8%)	939 (18.3%)	492 (22.3%)	290 (18.6%)	614 (21.9%)	76 (22.8%)
[1,500, 1,900)	586 (14.0%)	1,022 (16.0%)	2,126 (16.5%)	941 (18.6%)	364 (16.5%)	288 (18.4%)	479 (17.1%)	50 (15.0%)
[1,900+)	1,275 (30.4%)	2,012 (31.4%)	3,623 (28.2%)	1,661 (32.9%)	610 (27.6%)	503 (32.2%)	771 (27.5%)	70 (21.0%)
I don't know this	154 (3.7%)	245 (3.8%)	559 (4.4%)	226 (4.5%)	134 (6.1%)	51 (3.3%)	129 (4.6%)	19 (5.7%)

I don't want to tell	451 (10.8%)	711 (11.1%)	1,502 (11.7%)	630 (12.5%)	262 (11.9%)	195 (12.5%)	365 (13.0%)	46 (13.8%)
Missing	887 (21.2%)	934 (14.6%)	1,258 (9.8%)	177 (3.5%)	49 (2.2%)	58 (3.7%)	92 (3.3%)	15 (4.5%)
Partner relationships [a]								
Married/cohabiting	3,513 (83.8%)	5,369 (83.9%)	10,423 (81.1%)	4,212 (83.3%)	1,689 (76.5%)	1,358 (87.0%)	2,309(82.2%)	251 (75.4%)
Have partner but no-cohabiting	<70 [d]	109 (1.7%)	234 (1.8%)	103 (2.0%)	<70 [d]	<70 [d]	<70 [d]	<10 [c]
No partner	506 (12.1%)	838 (13.1%)	2,101 (16.3%)	721 (14.3%)	473 (21.4%)	173 (11.1%)	436 (15.5%)	74 (22.2%)
Others	<10 [c]	14 (0.2%)	36 (0.3%)	15 (0.3%)	<10 [c]	<10 [c]	<10 [c]	<10 [c]
Missing	102 (2.4%)	71 (1.1%)	66 (0.5%)	<10 [c]	-	<10 [c]	<10 [c]	-
Employment statu [a]								
Full-time job	528 (12.6%)	719 (11.2%)	1,182 (9.2%)	565 (11.2%)	137 (6.2%)	145 (9.3%)	318 (11.3%)	15 (4.5%)
Retired	1,725 (41.2%)	2,944 (46.0%)	6,566 (51.1%)	2,691 (53.2%)	1,155 (52.3%)	1,018 (65.2%)	1,496 (53.3%)	188 (56.5%)
Housewife/husband	402 (9.6%)	751 (11.7%)	1,637 (12.7%)	681 (13.5%)	409 (18.5%)	91 (5.8%)	418 (14.9%)	37 (11.1%)
Part-time job	430 (10.3%)	697 (10.9%)	1,090 (8.5%)	562 (11.1%)	208 (9.4%)	80 (5.1%)	221 (7.9%)	18 (5.4%)
Others	132 (3.2%)	253 (4.0%)	877 (6.8%)	283 (5.6%)	192 (8.7%)	135 (8.6%)	212 (7.5%)	53 (15.9%)
Missing	974 (23.2%)	1,037 (16.2%)	1,508 (11.7%)	275 (5.4%)	107 (4.9%)	93 (6.0%)	143 (5.1%)	22 (6.6%)
Lifestyle patterns [a]								
Healthy in a balanced way	1,762 (42.0%)	2,827 (44.2%)	5,256 (40.9%)	2,382 (47.1%)	963 (43.6%)	671 (43.0%)	1,131 (40.3%)	104 (31.2%)
Healthy but physically inactive	294 (7.0%)	527 (8.2%)	1,558 (12.1%)	562 (11.1%)	350 (15.9%)	160 (10.2%)	423 (15.1%)	59 (17.7%)
Unhealthy but no substance use	84 (2.0%)	177 (2.8%)	521 (4.1%)	167 (3.3%)	92 (4.2%)	67 (4.3%)	158 (5.6%)	35 (10.5%)
Unhealthy but light drinking and never smoked	395 (9.4%)	685(10.7%)	1,397 (10.9%)	590 (11.7%)	231 (10.5%)	214 (13.7%)	322 (11.5%)	38 (11.4%)
Unhealthy	230 (5.5%)	383 (6.0%)	857 (6.7%)	354 (7.0%)	143 (6.5%)	119 (7.6%)	227 (8.1%)	14 (4.2%)
Missing	1,426 (34.0%)	1,802 (28.2%)	3,271 (25.4%)	1,002 (19.8%)	429 (19.4%)	331 (21.2%)	547 (19.5%)	83 (25.0%)

[a] n (%)
[b] means (SD)
[c] less than 10 participants. The sample size (n) was masked in accordance with Lifelines publication guidelines to prevent subject identification and protect participant privacy.
[d] less than 70 participants. The sample size (n) was masked in accordance with Lifelines publication guidelines to prevent subject identification and protect participant privacy.

During the 17-year follow-up, 4,187 deaths were recorded. Mortality rates varied across multimorbidity groups. Among participants with multimorbidity, 21.7% died, with the highest rates observed in the 'Complex Treatment' (37.5%) and 'CVD & Vascular' (31.9%) configurations (Table 1).

We then examined whether LPs influenced mortality across MCs. Kaplan–Meier survival curves by multimorbidity classification are shown in Figure 2. The 'Complex Treatment' and 'CVD & Vascular' groups exhibited the lowest survival probabilities and similar trajectories. In contrast, the 'Vascular', 'Heart & Vascular', and 'Metabolic' configurations showed overlapping curves, suggesting comparable survival outcomes.

In the 'Healthy in a balanced way' group (Fig. 2B), survival patterns closely mirrored the overall sample (Fig. 2A). In the 'Healthy but physically inactive' group (Fig. 2C), survival was higher overall and curves between MCs were more similar. In contrast, in the 'Unhealthy but no substance use' group (Fig. 2D), the 50% survival threshold was surpassed in both the 'CVD & Vascular' and 'Complex Treatment' configurations. In the remaining unhealthy lifestyle groups (Fig. 2E and 3F), this threshold was reached in only one MC—or not at all. Notably, the 'Unhealthy but light drinking and never smoked' group (Fig. 2E) showed the smallest survival differences among MCs, including the non-multimorbid group. All survival comparisons across multimorbidity and LPs were statistically significant (log-rank test,

p<0.001). Survival curves based on cumulative multimorbidity or stratified by LPs, are shown in Supplementary Figures 2 and 3.

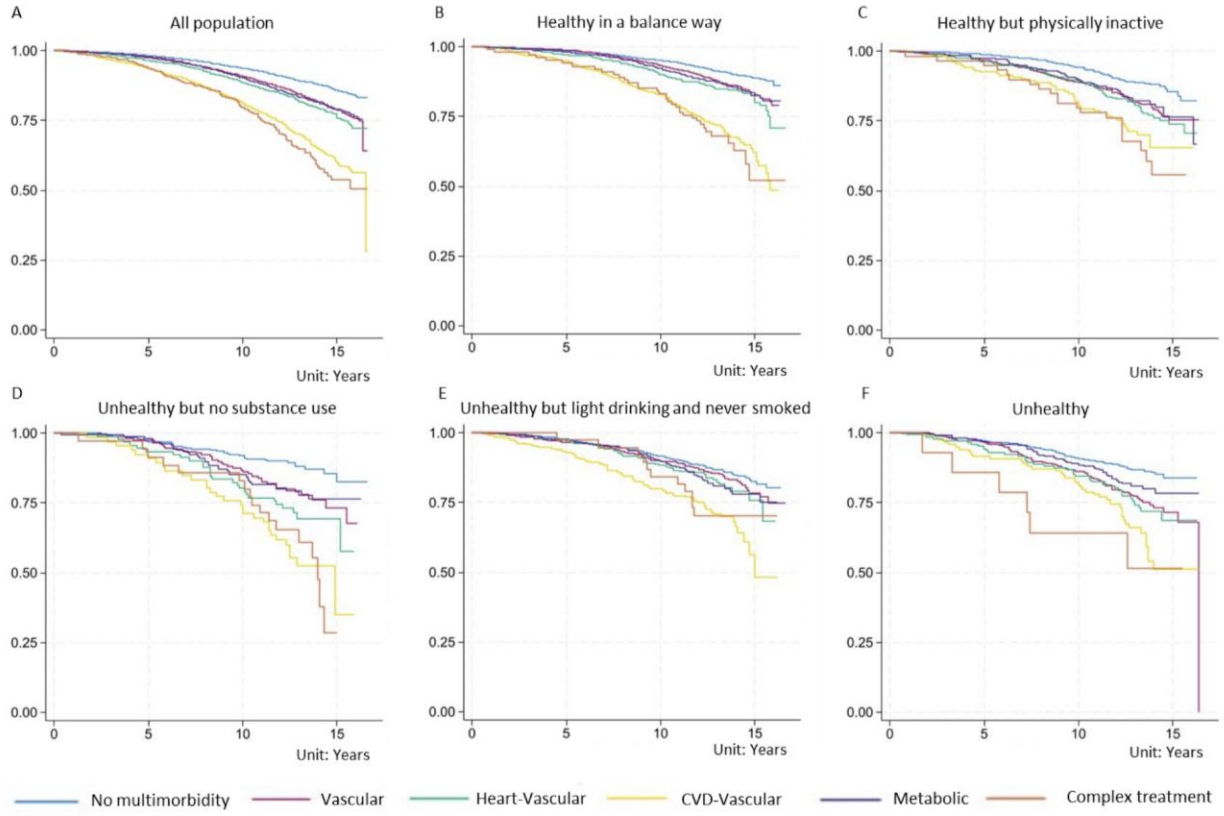

Figure 2. Kaplan-Meier survival plots with multimorbidity configurations by lifestyle patterns. (A) the whole population; **(B)** the "Healthy in a balance way" pattern group; **C:** the "Healthy but physically inactive" pattern group; **(D)** the "Unhealthy but no substance use" pattern group; **E:** the "Unhealthy but light drinking and never smoked" pattern group; **(F)** the "Unhealthy" pattern group. Kaplan–Meier survival plots showing survival probabilities by MCs, stratified by LPs. Each panel (A–F) represents a different LP group; panel A shows the overall population without stratification. The y-axis represents the proportion of surviving participants, and the x-axis shows follow-up time in years. Survival curves are color-coded by MC category: no multimorbidity, vascular, heart–vascular, CVD–vascular, metabolic, and complex treatment.

After adjustment for covariates, HRs for all-cause mortality by MCs were consistent with the survival trajectories observed in the Kaplan–Meier curves. Participants with ≥2 NCDs had a 78% higher risk of death compared to those with no NCDs (HR 1.78, 95% CI 1.58–2.00; p<0.001). However, risk estimates varied across MCs, suggesting added value beyond disease count. Compared with participants without multimorbidity, the highest HRs were observed in the 'CVD & Vascular' (HR 1.98, 95% CI 1.77–2.22; p<0.001) and 'Complex Treatment' (HR 2.97, 95% CI 2.45–3.59; p<0.001) groups (Table 2).

LPs were also associated with differential mortality risks. Compared with the 'Unhealthy' pattern, lower HRs were observed for: 'Healthy in a balanced way' (HR 0.63, 95% CI 0.57–0.71; p<0.001), 'Healthy but physically inactive' (HR 0.81, 95% CI 0.71–0.93; p=0.003), and 'Unhealthy but light drinking and never smoked' (HR 0.83, 95% CI 0.73–0.95; p=0.007). The 'Unhealthy but no substance use' group showed no significant difference (HR 1.02, 95% CI 0.86–1.21; p=0.796) (Table 2).

Figure 3A displays mortality HRs for each of the MCs across lifestyle patterns. The association between multimorbidity and mortality varied by LPs, with the exception of the 'Healthy in a balanced way' and 'Unhealthy but no substance use' groups. In contrast, mortality risk among participants with ≥2 NCDs was relatively consistent across LPs. Compared to the 'No NCD' group, the highest mortality risk in this category was observed in the 'Unhealthy but no substance use' group (HR 2.39, 95% CI 1.21–4.70), and the lowest in the 'Healthy but physically inactive' group (HR 1.82, 95% CI 1.25–2.66) (Fig. 3B).

Greater variability in mortality risk across MCs was found within the 'Healthy in a balanced way' and 'Unhealthy but no substance use' groups. In the latter, risk estimates spanned the widest range, suggesting that unhealthy behaviours excluding substance use may more clearly differentiate high-risk subgroups. Across nearly all LPs, the 'Complex Treatment' configuration consistently showed the highest mortality risk (HR >3), reinforcing its classification as a high-risk group regardless of lifestyle (Fig. 3).

Table 2. Mortality hazard ratios by accumulation of NCDs and multimorbidity configurations.

	Hazard ratio	95% CI	*P*-value
Accumulation of NCDs, N=20,853 [a]			
No NCD	1 (ref)	1 (ref)	-
One NCD	1.20	1.05-1.36	<0.01
Two or more NCDs	1.78	1.58-2.00	<0.001
Multimorbidity configurations, N=20,697 [b]			
No multimorbidity	1 (ref)	1 (ref)	-
Vascular	1.41	1.29-1.55	<0.001
Heart & vascular	1.58	1.40-1.78	<0.001
CVD & vascular	1.98	1.77-2.22	<0.001
Metabolic	1.45	1.30-1.62	<0.001
Complex treatment	2.97	2.45-3.59	<0.001
Lifestyle patterns, N=20,697 [c]			
Unhealthy	1 (ref)	1 (ref)	-
Healthy in a balanced way	0.63	0.57-0.71	<0.001
Healthy but physically inactive	0.81	0.71-0.93	0.003
Unhealthy but no substance use	1.02	0.86-1.21	0.796
Unhealthy but light drinking and never smoked	0.83	0.73-0.95	0.007

[a] Adjusted by age, sex, income, marital status, employment status and lifestyle patterns, defining age as a time-varying variable
[b] Adjusted by age, sex, marital status, employment status and lifestyle patterns, defining age as a time-varying variable
[c] Adjusted by age, sex, marital status, employment status and multimorbidity configurations, defining age as a time-varying variable

These findings underscore the relevance of both MCs and LPs in shaping mortality risk, with important variation across patterns. The discussion will explore why some LPs show limited differentiation between MCs, the added value of using MCs over disease count, and implications for clinical decision-making.

DISCUSSION

This study found that the prognostic value of MCs varies depending on LPs. Among individuals with unhealthy patterns, mortality risks were relatively uniform across MCs and comparable to those estimated by simple NCD accumulation. In contrast, within healthier lifestyle groups—particularly those classified as 'Healthy in a balanced way' or 'Unhealthy but no substance use'—mortality risk varied considerably by MCs, indicating that MCs provide more nuanced prognostic information than cumulative disease counts. Notably, the 'Complex treatment' configuration consistently showed the highest mortality risk across all LPs, suggesting an inherently high-risk profile that may reflect both disease burden and treatment complexity.

The severity of certain MCs in this study, particularly 'CVD & Vascular' and 'Complex treatment', may limit the protective effects of healthy LPs. These configurations likely reflect advanced physiological deterioration, where lifestyle modifications exert less influence on mortality. Conversely, very unhealthy LPs may reduce the ability to detect differences in mortality risk across MCs. This raises the question of whether higher baseline mortality risk is associated with lower relative variability across MCs. However, our findings do not support this hypothesis, as the 'Unhealthy but no substance use' and 'Unhealthy' LPs showed similarly high mortality risks yet differed markedly in how MCs stratified those risks.

Among all MCs, the 'Complex treatment' group exhibited the highest risk, reflecting discordant multimorbidity and complex care needs. Although LPs modified this risk to some extent—e.g., HR 1.88 in the 'Unhealthy but light drinking and never smoked' group vs HR 3.74 in the 'Unhealthy but no substance use' group, the elevated baseline risk persisted.

These findings align with previous evidence suggesting that individuals with complex disease profiles may require substantial behavioural changes to achieve health benefits[38], and that contextual barriers can further limit the protective role of lifestyle behaviours. In the Swedish National Study on Aging and Care, which included 2,931 older adults, the cognitive and sensory impairment cluster comprised the oldest individuals, with poor functional status and greater institutionalisation. The

heart disease cluster had the highest comorbidity and medication burden, along with elevated inflammation markers. The 'psychiatric and respiratory' cluster was associated with high alcohol use and neuroticism, while the 'unspecific' group included younger, healthier individuals with favourable cognitive and functional profiles [39]. Similarly, earlier work in the Lifelines cohort showed that MCs differ not only in disease burden but also in their sociodemographic and behavioural profiles [26], reinforcing the importance of considering both biological and contextual factors in risk stratification.

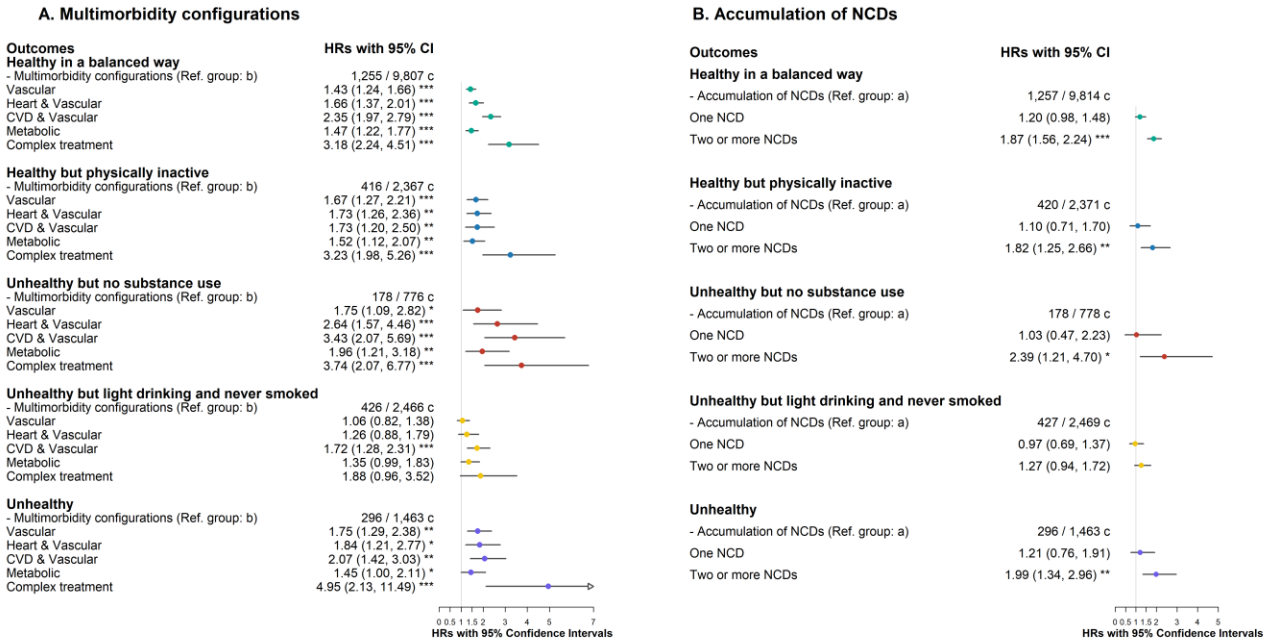

Figure 3. Mortality hazard ratios by accumulation of NCDs and multimorbidity patterns, across lifestyle patterns. (A) The reference group is "No NCD"; **(B)** The reference group is "No multimorbidity"; **(C)** Death/sample size. Forest plot for all-cause mortality according to multimorbidity definitions, stratified by LPs. Each LP is shown in bold on the left side, with multimorbidity subcategories listed beneath and divided into two panels: A) multimorbidity configurations and B) accumulation of NCDs. Stars in the figure denote levels of statistical significance: *P < 0.05; **P < 0.01; *P < 0.001. Numerical HRs with 95% CIs are presented in the central columns, and their graphical representation appears on the right (circles for HRs, horizontal lines for CIs). At the right of each multimorbidity definition, a code (a or b) indicates the reference group, as specified in the figure footnote. Sample size and number of deaths are reported for each stratum. Color coding was applied to LP categories to enhance visual distinction. Estimates for cumulative multimorbidity were adjusted for age, sex, income, marital status, and employment status, whereas estimates for multimorbidity configurations were adjusted for age, sex, marital status, and employment status. To save space, an arrow pointing to the right indicates that the CI extends beyond the plotted range (see 'Unhealthy LP and Complex treatment MC').

In the present study, sociodemographic variables were included as adjustment factors in all models. However, potential interactions between these factors, LPs, and MCs were not explored and may influence the interpretation of mortality risk estimates. A recent analysis of 38,011 NHANES participants reported that the protective effect of healthy lifestyles did not offset the elevated mortality risk associated with multimorbidity, and that socioeconomic status (SES) modified these associations, particularly among individuals with lower SES [40]. These findings support our observations, where LPs were insufficient to reduce mortality risk among individuals with severe MCs.

Scientific evidence underscores the significant impact of LPs or multimorbidity on mortality risk. Complex multimorbidity, defined as the presence of three or more chronic conditions affecting multiple organ systems, has been associated with reduced functional independence and increased mortality in older adults [41]. This burden may impair physiological resilience and hinder the adaptations required for healthy aging [42]. Although healthy behaviors are associated with increased longevity, their benefit may be constrained by advanced disease burden. Nonetheless, lifestyle indices combining multiple health behaviors have demonstrated strong cumulative protective effects. For instance, adherence to six or more healthy behaviors can reduce all-cause mortality risk by up to 50% [43].

Although extensive evidence links chronic diseases and lifestyle behaviors to adverse outcomes such as mortality, most evaluations have focused on single habits or individual conditions. In everyday life, however,

people rarely present only one health behavior or disease at a time. In this study, we integrated groups of chronic diseases and lifestyle factors into profiles that more closely reflect real-world patterns among older adults. By evaluating mortality risk across latent classes of NCDs within lifestyle profiles, we examined with greater precision how specific combinations of chronic conditions influence survival—even among individuals with a 'Healthy in a balanced way' lifestyle. This approach underscores that adverse outcomes may also be shaped by latent biological mechanisms or diminished physiological reserve beyond observable behaviors.

This study benefits from a large, well-characterized cohort with long-term follow-up, allowing robust estimation of mortality risk. The use of LCA to define MCs and LPs represents a novel approach and captures the multidimensional nature of chronic disease and health behaviors. Additionally, the study evaluates a broad range of lifestyle- related factors in relation to multimorbidity, offering valuable insights into the modifiable aspects of mortality risk. Although prevalence and distribution of LPs and MCs may vary across countries due to cultural practices and healthcare system priorities, the underlying biological mechanisms linking chronic disease clusters and mortality are likely generalizable. These findings contribute to the growing evidence supporting targeted interventions to reduce mortality and improve quality of life, especially in populations with high disease burden.

However, the study has some limitations. First, it is based on a population from a specific region, which may affect generalizability. Prior studies, including our own and a Spanish cohort study [32, 44], have shown that LPs vary across populations, which may influence their moderating role in the association between multimorbidity and mortality. Second, lifestyle behaviors were self-reported, which may have affected the classification into LPs, particularly for behaviors like diet and physical activity. Third, approximately 25–30% of participants had missing data on LPs, potentially introducing bias. To address this, we applied multiple imputation restricted to individuals with at least two single lifestyle indicators, to ensure that the imputed LPs are reliable. As shown in Supplementary Table 2, the distribution of LPs before and after imputation remained largely comparable. Finally, both multimorbidity and LPs may have changed during follow-up, though these changes were not accounted for. These differences highlight the importance of replicating analyses in diverse settings, while using comparable methodological approaches, to better evaluate the external validity and clinical relevance of MCs. Although both MCs and LPs have shown acceptable temporal stability in this population in previous evaluations [26, 32], we do not exclude the possibility that in other populations, changes in LPs may occur over time, together with transitions toward different multimorbidity profiles. It would therefore be important to explore the potential for reverse causation in such populations, as well as the evolution of both MCs and LPs across time. However, addressing these questions would require a broader age range (e.g., including participants aged >40 years), more than two repeated assessments, and follow-up intervals short enough to capture meaningful temporal changes.

Our findings support a shift from viewing multimorbidity as a static disease count toward a dynamic conceptualization based on disease patterns. This perspective underscores the importance of considering MCs as context-dependent constructs whose prognostic value may vary by outcome, such as mortality or functional decline. The MCs identified in this study may also provide a comparative framework for evaluating multimorbidity in other populations, facilitating assessments of generalizability and clinical relevance. Building on this, our results lay the groundwork for developing more refined, clinically actionable models of multimorbidity that integrate disease patterns with behavioral profiles. In the longer term, such models—potentially incorporated into AI-based tools leveraging electronic health records—could enhance individualized risk assessment and inform more precise preventive strategies for older adults.

Future studies should explore the dynamics of MCs and LPs over time, integrating repeated measures to account for behavioral and clinical changes. The influence of health system access, polypharmacy, and the interaction of multimorbidity with SES or quality of life are promising avenues. Experimental designs or longitudinal studies with targeted interventions could help determine which LPs are most modifiable and whether risk reductions can be achieved in complex MCs.

Based on the analyses presented in this study, it is of interest to further examine whether interaction occurs between lifestyle and multimorbidity groups. From a public health perspective, this question is particularly relevant, as it may help identify population segments that could benefit most from targeted interventions when specific lifestyle profiles coincide with particular multimorbidity categories.

The results of our exploratory post-hoc interaction analysis suggest that effect modification may be possible; however, under strict criteria, no statistical evidence of such modification was observed in the current Cox models. Nonetheless, interactions reaching statistical significance under exploratory analysis were identified between lifestyle and multimorbidity classifications in the predicted values derived from the interaction models (Supplementary Fig. 4 and 5). It is important to note that only multiplicative interaction was evaluated using the

reference groups defined in the main analysis. Additive interaction, which may be more informative for public health applications, was not tested and remains a valuable direction for future work.

While these analyses extend beyond the primary scope of this study, they highlight an important avenue for future research on potential effect modification, including the evaluation of alternative reference groups and greater attention to the compositional structure of both lifestyle and MCs.

Moreover, clinical studies are needed to explore mechanisms underlying the associations between specific MCs and mortality. Longer follow-up is required to capture potential failures in physiological systems and to clarify the sequence in which diseases emerge, shaping the trajectory of subsequent conditions. These insights are essential to better understand how lifestyle behaviors interact with disease progression. Shifting the focus from survival alone to broader indicators of healthy aging, including quality of life and functional independence, may be particularly valuable in populations with complex multimorbidity [45]. This broader perspective would support a more comprehensive understanding of how MCs and LPs interact to shape aging trajectories. Targeting lifestyle improvements in older adults remains a priority. Intervention-based evaluations stratified by LPs may help identify which profiles are most responsive to change and where resources should be focused to reduce mortality.

Taken together, these findings align with current understanding of ageing, in which the interplay between behavioural profiles and the biological complexity of disease shapes survival. The results are reasonable in light of evidence showing that lifestyle effects tend to be strongest when physiological reserve is preserved, whereas in more severe multimorbidity patterns, such as the CVD & Vascular and Complex Treatment groups, the underlying pathophysiological burden may overshadow behavioural influence. This study therefore helps clarify when lifestyle differences are likely to translate into meaningful variation in mortality risk. These insights also indicate concrete directions for future research, including the need to investigate how behavioural change, disease progression, and physiological decline interact over time, and to determine which combinations of lifestyle factors and disease patterns hold the greatest potential for targeted interventions. Furthermore, our findings support the notion that intrinsic capacity may play a key role in determining how physiological reserves are allocated when individuals face specific multimorbidity configurations, offering an additional dimension through which to understand heterogeneity in mortality risk.

Conclusions

Our findings suggest that MCs offer more refined mortality risk estimates than cumulative NCD counts, particularly within healthier LPs. While ≥2 NCDs may suffice to stratify risk in unhealthy or physically inactive LPs, MCs provided added value in 'Healthy in a balanced way' and 'Unhealthy but no substance use' profiles. Notably, the 'Complex treatment' group consistently showed the highest mortality risk across all LPs. These results underscore the importance of considering MCs in risk stratification, especially among individuals with healthier behaviors. A combined assessment of MCs and LPs enables a more nuanced understanding of mortality risk and may inform more targeted clinical and public health strategies.

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Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2025.1012.

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