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ORIGINAL INVESTIGATION

Lifestyle factors and incident multimorbidity related to chronic disease: a population-based cohort study

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Abstract

Background: Multimorbidity is linked to poor quality of life, and increased healthcare costs, and multimorbidity risk is potentially mitigated by a healthy lifestyle. This study evaluated the individual and joint contributions of an extensive set of lifestyle factors to the development of multimorbidity. Methods: A prospective study of 133,719 adults (age 45.2 ± 12.9, range 18–93 years) from the Dutch Lifelines cohort assessed the influence of lifestyle factors on multimorbidity, defined as having at least two of four major chronic diseases, using Cox regression models and population attributable fractions (PAFs). Lifestyle-related factors included diet quality, physical activity, TV watching, substance use (alcohol, smoking), sleep (duration, medication), stress (acute, chronic) and social connectedness (social contacts, marital status). Results: Over a median follow-up of 3.4 years, 3687 (12.5%) of the 29,545 participants with a chronic disease at baseline developed multimorbidity, compared to 434 (0.4%) of the 104,174 without a chronic disease. Key lifestyle factors linked to multimorbidity included smoking, prolonged TV watching, and stress, with hazard ratios indicating a higher risk in both groups. Additionally, high alcohol consumption and inadequate sleep duration were found to increase multimorbidity risk specifically in those with a chronic disease. Lifestyle factors jointly accounted for 34.4% (PAF, 95%CI 28.8%–73.5%) (with baseline morbidity) and 55.6% (95%CI 17.2%–48.5%) (without) of multimorbidity cases, with smoking as the primary contributor. Conclusions: Lifestyle factors, particularly smoking, alcohol consumption, TV watching, stress, and sleep, significantly contribute to the development of multimorbidity. The study underscores the importance of targeted prevention in public health and healthcare settings to manage and prevent multimorbidity.

Keywords Lifestyle factors · Chronic disease · Multimorbidity · Cohort · TV watching · Chronic stress

Introduction

Greater longevity has increased the likelihood of chronic disease (Scott 2021), with cardiovascular disease (CVD), cancer, chronic respiratory disease (CRD), and type 2 diabetes (T2D) now accounting for over 80% of premature deaths worldwide (Noncommunicable diseases. 2024). In 2019, CVD affected 523 million individuals and resulted in 18.6 million deaths, contributing to 34.4 million disability-adjusted life years (DALYs) (Roth et al. 2020). That same year, cancer accounted for approximately 23.6 million new cases and 10 million deaths, leading to around 250 million DALYs (Kocarnik et al. 2022). CRDs were responsible for a prevalence of 454.6 million cases and 4 million deaths (Momtazmanesh et al. 2019). In 2021, diabetes affected 529 million people, contributing to 79.2 million DALYs, primarily T2D (Ong et al. 2023). As populations age, the burden of

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these diseases is projected to rise further by 2050 (Vollset et al. 2024).

The co-existence of two or more chronic diseases, known as multimorbidity, is a growing global health challenge (Nagel et al. 2024) affecting an estimated 37.2% of adults worldwide, with over half (51.0%) of individuals aged 60 and older experiencing multimorbidity (Chowdhury et al. 2023). This condition can increase disability and decrease quality of life and life expectancy (Hanlon et al. 2022; Arokiasamy et al. 2015), and impose a significant economic burden on healthcare systems and society (Tran et al. 2022). The WHO action plan, 'The Decade of Healthy Ageing 2020–2030', seeks to promote well-being at older ages (Rudnicka et al. 2020). To achieve this goal, identifying and targeting modifiable risk factors for multimorbidity, particularly those related to CVD, cancer, CRD, and T2D, is crucial given the substantial burden these diseases impose.

Lifestyle medicine highlights the role of healthy lifestyles in preventing, managing, and even reversing chronic diseases, emphasizing prevention over cure (Lippman et al. 2024). Studies suggest that up to 80% of chronic diseases could be prevented through actions like smoking cessation, healthy eating, physical activity, and weight management (Ford et al. 2009). In lifestyle medicine, six key lifestyle domains have been identified for chronic disease prevention: nutrition, physical activity, stress management, sleep, social connectedness, and substance use (College and of Lifestyle Medicine | American College of Lifestyle Medicine. 2022). Poor lifestyle habits are linked to not only individual diseases but also to the co-occurrence of multiple chronic conditions (i.e., multimorbidity) (Mounce et al. 2018; Wikström et al. 2015; Dhalwani et al. 2017; Shang et al. 2020; Xu et al. 2018; Katikireddi et al. 2017; Aminisani et al. 2020; Melis et al. 2014), due to their broad impact on various organ systems. Multimorbidity is essentially a heterogeneous phenotype, as it can include people with random accumulation of multiple diseases, as well as people developing complications instigated by a pre-existing chronic condition, like the development of CVD in patients with type 2 diabetes (Harrison et al. 2021). Despite this heterogeneity, different configurations of multimorbidity may share common lifestyle-related risk factors (Skou et al. 2022).

Current research has mostly focused on limited lifestyle factors, highlighting the need for a more comprehensive approach to inform policy and prioritize prevention strategies at the population level. Additionally, given the rising prevalence of obesity and chronic diseases, it is crucial to examine these risk factors not only in healthy individuals but also in those with a (pre-)existing chronic condition.

In this study, we aimed to investigate the association between a comprehensive set of lifestyle factors and the development of multimorbidity involving major chronic diseases in a large cohort of healthy adults and individuals with a pre-existing chronic disease. Since multimorbidity represents a heterogeneous aggregation of various types of diseases, we further explored whether this association varies by the type of baseline disease. Furthermore, while the transition from a single disease to multimorbidity requires only the acquisition of one additional disease, healthy individuals need to acquire two incident diseases to reach the same state. We therefore investigated the contribution of acquiring a single additional disease in people without any chronic disease at baseline compared this those with pre-existing disease. Finally, to translate these findings into a measure of societal relevance, we identified the primary lifestyle-related drivers of incident multimorbidity by quantifying the population attributable fractions (PAFs).

Methods

Study design and population

We used data from Lifelines, a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviors of 167 729 persons living in the North of the Netherlands with a unique three-generation design. The design involved recruitment through general practitioners, followed by invitations to family members (including partners, parents, parents-in-law, and children). Additionally, adults had the option to self-register. It employs a broad range of investigative procedures for assessing the biomedical, socio-demographic, behavioral, physical and psychological factors that contribute to health and disease in the general population, with a special focus on multimorbidity and complex genetics (Sijtsma et al. 2021). The current study included data for 152 728 participants collected at baseline (2006–2013), the first (2011–2014) and second (2012–2015) follow-ups, and a second full assessment (2014–2018). We included adults (age $\geq$ 18 years) with no or one chronic disease at baseline and excluded participants with multimorbidity or missing information about relevant diagnoses at baseline and during follow-up (Fig. 1). The medical ethics review committee of the University Medical Centre Groningen approved the study protocol (UMCG METC 2007/152) and all participants gave their written informed consent.

Baseline and follow-up measurements

The exact criteria for defining lifestyle factors, socio-demographic factors, anthropometric measurements and the four chronic diseases are presented in Supplement Box 1 and Table S1.

Lifestyle data were collected by self-reported questionnaires. We assessed a comprehensive set of eleven lifestyle

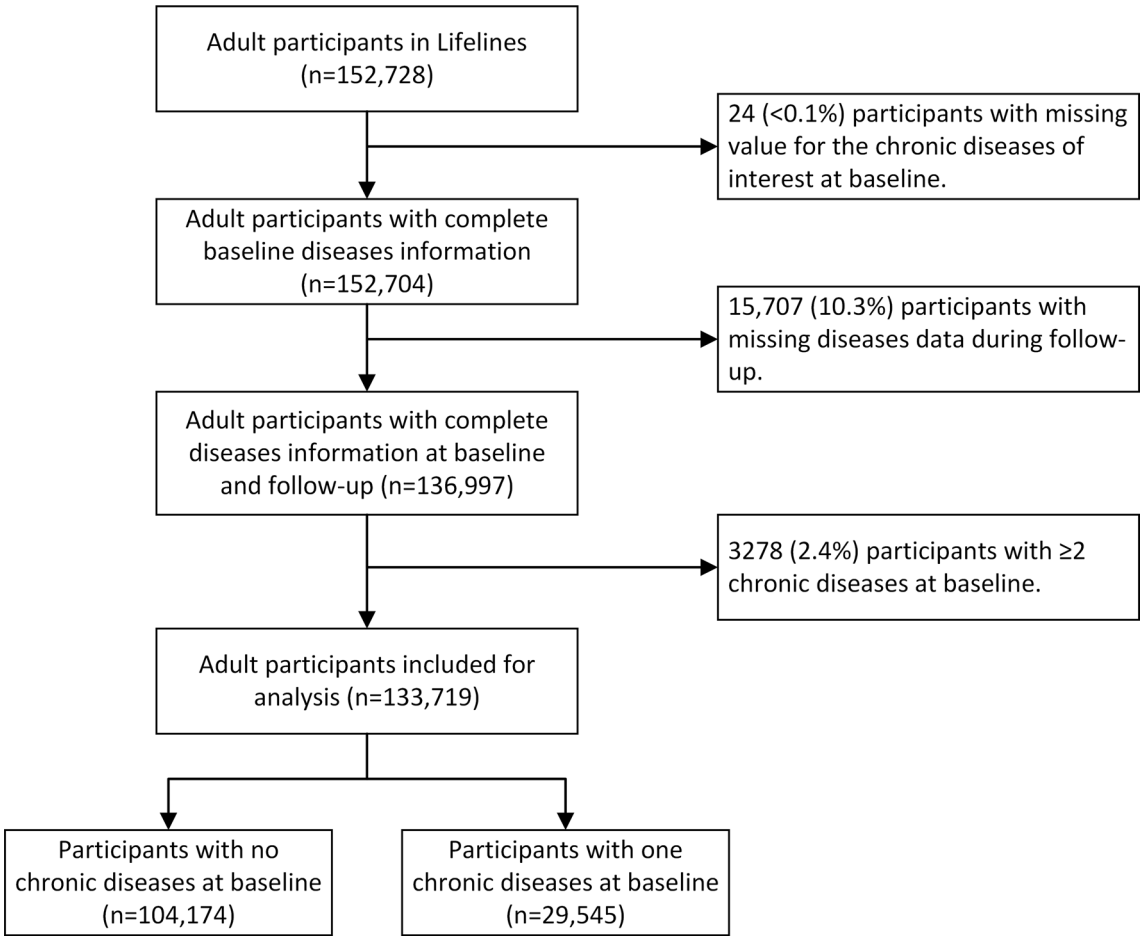

Fig. 1 Flowchart of participant selection

factors from the six domains included in the definition of lifestyle medicine (i.e., nutrition, physical activity, stress, substance use, sleep quality, and social connection). These factors included diet quality (Vinke et al. 2018), physical activity (Wendel-Vos et al. 2003; WHO guidelines on physical activity and sedentary behavior 2022), TV watching (Ekelund et al. 2016), acute and chronic stress (Rosmalen et al. 2012), alcohol consumption (Guidelines for good nutrition 2015; Wood et al. 2018), smoking status, sleep duration (Hirshkowitz et al. 2015), sleep treatment, number of social contacts and marital status.

Baseline socio-demographic factors included age, sex, and educational level collected through self-administered questionnaires. Objective height and weight measurements were collected at the research site to calculate body mass index (BMI).

Four chronic diseases were selected for this study: CVD, which includes myocardial infarction, stroke, heart failure and other forms treated with balloon angioplasty and/or bypass surgery); cancer, encompassing solid tumors, bone and soft tissue cancers, hematological cancers, and central nervous system cancers (excluding primary skin cancer); CRD, which includes chronic bronchitis, asthma, and airflow obstruction; and T2D. These outcomes were determined based on self-reported questionnaires and objectively measurements (i.e., lung function test and laboratory determinants including fasting plasma glucose and hemoglobin A1c) at the different follow-up assessment rounds. Participants could enter the study with either no chronic disease or a single chronic disease (i.e., baseline cases). Both groups could then develop a chronic disease during the study (i.e., incidence cases).

The outcome of interest was the development of multimorbidity, defined as the co-occurrence of two or more of the four identified chronic diseases in the same individual during follow-up. People with no chronic disease at baseline therefore had to develop at least two chronic diseases, whereas those with a single chronic disease at baseline had to develop at least one chronic disease.

Statistical analysis

All analyses were conducted separately for subjects with no or one chronic disease at baseline. We described the baseline socio-demographics and lifestyle factors (mean ± standard deviation or frequency with percentage) and calculated the incidence rate (per 1000 person-years) for both multimorbidity and the four chronic diseases. Missing socio-demographic and lifestyle factors at baseline were accounted for by multiple imputation using the MICE package in R, assuming missing at random (Buuren and Groothuis-Oudshoorn 2011). Missing data were imputed ten times and results from regression analyses were pooled into a single estimate using Rubin's rule.

We used Cox regression models to analyze the association between lifestyle factors at baseline and the development of morbidity during follow-up. For subjects without a chronic disease at baseline, two models were fitted separately to evaluate the associations between lifestyle factors and the development of either one or more chronic diseases. For subjects with one chronic disease at baseline, a model was fitted to assess lifestyle factors and the development of an additional chronic disease (i.e., multimorbidity). All models were adjusted for age, sex, educational level, and BMI at baseline. All lifestyle factors were entered simultaneously so that their estimates were mutually adjusted. The follow-up time was defined as the duration from the baseline assessment to the time of reporting a subsequent second event (occurrence of multimorbidity) during follow-up assessments, the date of the most recent follow-up assessment, or the date of death, whichever occurred first. Deaths were censored and not modeled as a separate outcome. Hazard ratios (HR) and 95% confidence intervals (95%CI) were reported. All analyses were conducted using R (version 4.0.2).

We estimated the population attributive fractions (PAF) for the contribution of individual and combined lifestyle factors that were associated to the development of multimorbidity with the prevalence of an unhealthy lifestyle and the adjusted HR using the equations in Supplement Box 2. The 95%CI of the HR for each risk factor was used to calculate upper and lower limits of PAFs (Steenland and Armstrong 2006).

To evaluate the effect of missing values in lifestyle factors on the effect estimate of lifestyle factors and multimorbidity, we performed complete case analyses to compare the estimates with those obtained using imputed datasets. Because we only knew if the incident disease occurred within a time period, without the exact diagnosis date, we also applied accelerated time failure models to evaluate the association between lifestyle factors and multimorbidity.

Results

Participant characteristics at baseline

Among the 133 719 included participants (females, 59.1%; age, 45.2 ± 12.9 years; age range, 18—93 years), 29 545 (22.1%) had one chronic disease at baseline (Fig. 1). Table S2 shows that the baseline group with one chronic disease tended to be older, more often male, obese and have higher BMIs and lower educational attainments than the baseline group without disease. Their lifestyles more often included watching TV for > 5 h/day, having high acute stress, being ex- or current smokers, having inadequate sleep and not having a partner. The included participants tended to be older, female, and have higher educational attainment than those who dropped out during follow-up ($N = 15\,707$, 10.5%) (Table S3).

Incidence of multimorbidity

During a median follow-up of 3.4 years (IQR, 2.2–4.3 years; range, 0.08–11.1 years), the baseline group without chronic disease had incident morbidities of 4.7 (1655 cases), 3.4 (1197 cases), 12.9 (4559 cases), 4.6 (1617 cases), and 1.2 (434 cases) per 1000 person-years for CVD, cancer, CRD, T2D and multimorbidity, respectively; among participants with one chronic disease at baseline, the corresponding rates were 6.7 (659 cases), 3.9 (385 cases), 23.0 (2265 cases), 6.1 (601 cases), and 37.5 (3687 cases) per 1000 person-years. Generally, a higher incidence was observed in groups of more hours watching TV, more acute stress, any smoking history, and inadequate sleep (Table S4). Incidence of multimorbidity and cluster of diseases by baseline disease are presented in Table 1.

Lifestyle factors associated with the development of multimorbidity

Several established lifestyle risk factors were related to incident multimorbidity in healthy adults from the general population, namely prolonged TV watching, former smoking and current smoking. In addition, both chronic stress -based on long-term life difficulties- as well as high acute stress -based on impactful life events- were related to incident multimorbidity (Fig. 2**,** Table S5).

In people living with a major chronic disease, also prolonged TV watching, former smoking and current smoking were related to incident multimorbidity, as well as acute stress and chronic stress. In addition, high alcohol

Table 1 Incident multimorbidity of specific diseases cluster by baseline disease

	No prevalent disease at baseline (*N* = 104,174)	One prevalent disease at baseline (N = 29,545)			
		CVD (*N* = 2554)	Cancer (*N* = 2742)	CRD (*N* = 21,626)	T2D (*N* = 2623)
Incident disease during follow-up					
CVD	1414	–	85	330	127
Cancer	1054	58	–	202	62
CRD	4275	138	133	1679	157
T2D	1383	121	57	331	–
CVD + Cancer	42	0	0	11	7
CVD + CRD	100	0	12	44	10
CVD + T2D	74	0	1	17	0
Cancer + CRD	52	8	0	18	1
Cancer + T2D	34	2	0	9	0
CRD + T2D	102	11	4	36	0
CVD + Cancer + CRD	6	0	0	3	1
CVD + Cancer + T2D	0	0	0	2	0
CVD + CRD + T2D	15	0	0	9	0
Cancer + CRD + T2D	5	1	0	0	0
CVD + Cancer + CRD + T2D	4	0	0	0	0

CVD cardiovascular disease, *CRD* chronic respiratory disease, *T2D* type 2 diabetes. Data were reported as frequency

consumption and inadequate sleep were associated with incident multimorbidity (Fig. 2, Table S5).

Since in people living with a major chronic disease, multimorbidity is acquired with the incidence of one major chronic disease added to the pre-existing disease, this was compared to incident single disease in those without disease at baseline (Fig. 3, Table S5). Apart from diet quality and social connectedness, the associations were comparable in terms of effect size, indicating that the lifestyle-related risk for acquiring an additional major chronic disease, be it a first disease or a comorbidity, is comparable. This includes prolonged TV watching, high alcohol consumption, former smoking and current smoking, inadequate sleep, acute stress and chronic stress.

Lifestyle factors and risk of multimorbidity by type of baseline disease

The association between smoking and multimorbidity was significant for any baseline disease and presents as the most universal lifestyle risk factor (Table 2). Some factors however do not see a risk factor overall, but may be relevant for specific patients groups, i.e., poor diet quality (cancer), alcohol intake (cancer, CRD) and chronic stress (CVD, CRD).

PAF of lifestyle factors to multimorbidity

Overall, and assuming relevant causal links, 34.4% (17.2–48.5%) and 55.6% (28.8–73.5%) of the incident multimorbidity was attributable to the lifestyle factors evaluated in the baseline groups with and without a chronic disease. Among these, (ex-)smoking and chronic stress accounted for most cases of multimorbidity in both groups (Fig. 4, Table S6).

Sensitivity analysis

In the complete case analyses, greater uncertainty in the estimates generally existed compared with the primary analyses due to the smaller sample size. The estimate changed for low physical activity in the baseline group without chronic disease, from 1.23 (0.97–1.57) in the primary analysis to 1.37 (1.04–1.79) in the complete case analysis. The estimate also changed for high alcohol consumption in the baseline group with one chronic disease, from 1.27 (1.15–1.41) in the primary analysis to 0.98 (0.87–1.11) in the complete case analysis. Applying the accelerated time failure model to the imputed datasets produced HRs similar to those in the primary analysis (Table S7).

Discussion

Smoking is the major lifestyle-related risk factor for multimorbidity based on associations with incident multimorbidity and population attributable risk in people with and without a major chronic disease. In addition, TV watching, high alcohol consumption and inadequate sleep are modifiable

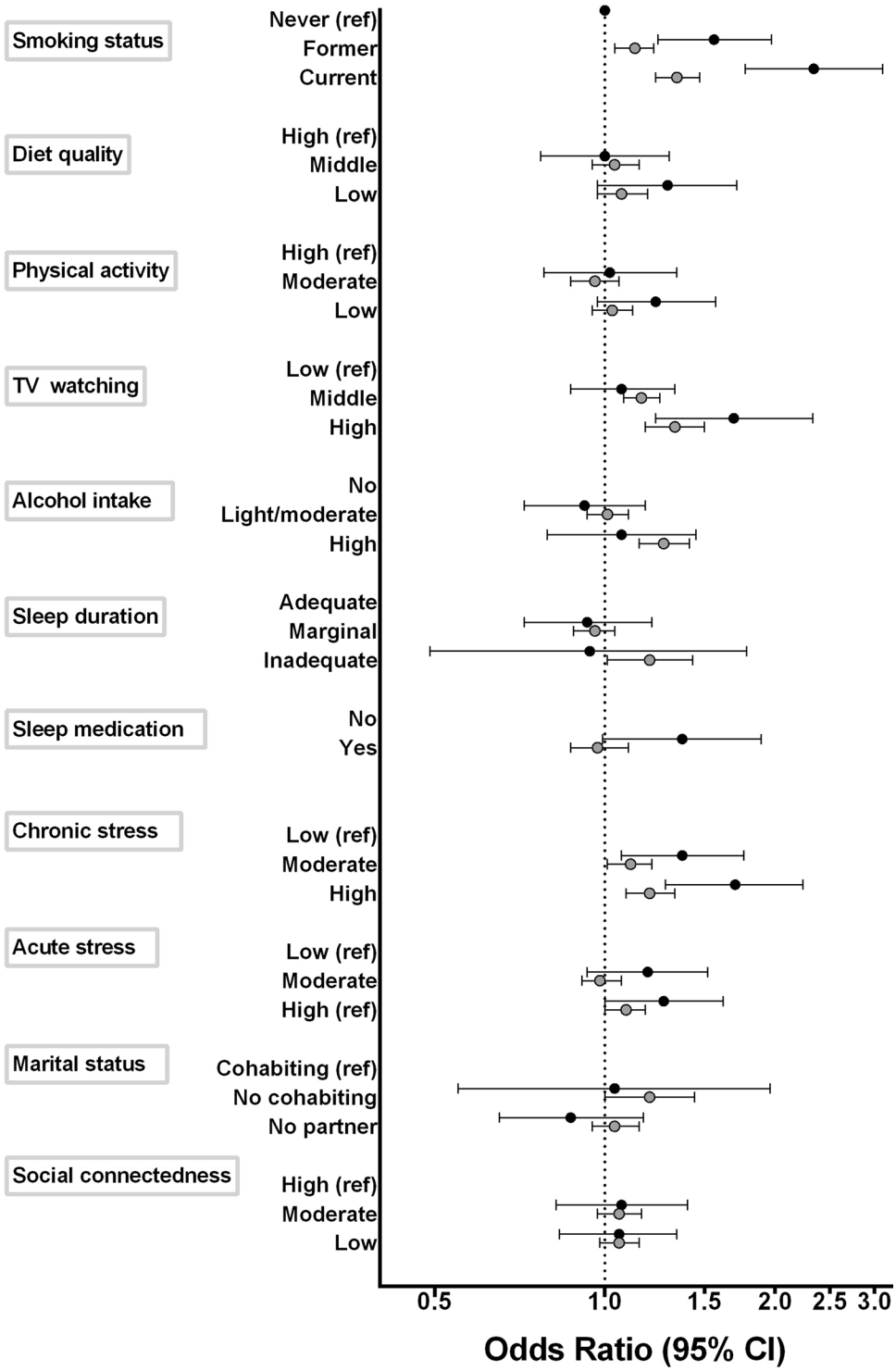

Fig. 2 Associations between lifestyle factors and incidence of multimorbidity in those with and without a disease at baseline. Black circles represent multimorbidity incidence in those with no disease at baseline, gray circles indicate incidence of multimorbidity in those who already live with a disease. Models were adjusted for age, sex, educational level, BMI and mutually adjusted for all evaluated lifestyle factors. The exact estimates are presented in Table S5

risk factors for multimorbidity, and both acute and chronic stress are important lifestyle-related risk factors. For some lifestyle risk factors, like diet, alcohol intake and chronic stress, the associations may be more relevant for specific patient groups than for people with a chronic disease in general. Importantly, lifestyle factors exert comparable risk on acquiring an additional disease, either as the first acquired major chronic disease or as a comorbidity for those already living with one disease.

Smoking is the lifestyle factor that is most related to the incidence of multimorbidity. This is in line with previous studies assessing multiple lifestyle factors for common chronic diseases. They have found smoking to be the most detrimental factor (Wikström et al. 2015; Fortin et al. 2014).

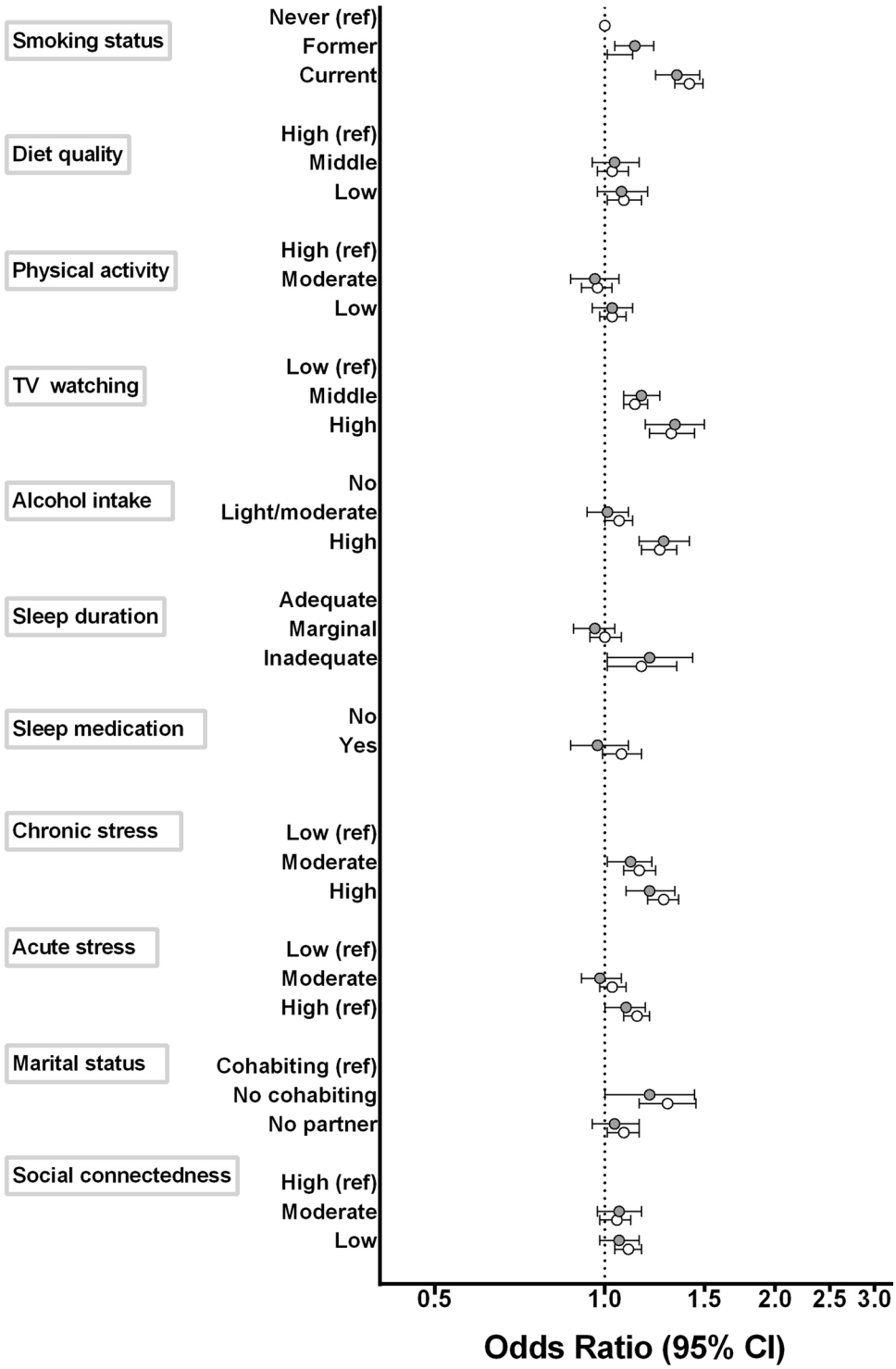

Fig. 3 Associations between lifestyle factors and incidence of acquiring one additional disease in those with and without a disease at baseline. Gray circles indicate incidence of multimorbidity in those who already live with a disease, and open circles represent incidence of 1 disease in those with no disease at baseline. Models were adjusted for age, sex, educational level, BMI and mutually adjusted for all evaluated lifestyle factors. The exact estimates are presented in Table S5

For example, a study of 32 972 disease-free participants aged 25–64 years indicated that current smoking was associated with 2.68- and 2.55-fold increased risks of multimorbidity in men and women, respectively (Wikström et al. 2015). In a cross-sectional study of men aged ≥ 45 years, with multimorbidity defined as ≥ 3 chronic diseases, current or former smoking was associated with a 3.16-fold increased risk of multimorbidity (Fortin et al. 2014). The only prospective study of lifestyle factors in people with baseline disease suggested that current smokers had a 1.21-fold increased risk of developing at least one new disease (Mounce et al. 2018). These findings underline the importance of smoking cessation for risk reduction in people with and without a chronic disease.

Table 2 Lifestyle factors and risk of multimorbidity by type of baseline disease

Lifestyle factors	Baseline CVD	Baseline Cancer	Baseline CRD	Baseline T2D
Diet quality (LLDS)				
High (T3, score 28–46)	Ref	Ref	Ref	Ref
Moderate (T2, score 22–27)	1.16 (0.94 – 1.44)	1.15 (0.92 – 1.44)	0.99 (0.90 – 1.09)	1.04 (0.84 – 1.28)
Low (T1, score 1–21)	0.97 (0.75 – 1.27)	**1.32 (1.02 – 1.72)**	1.04 (0.94 – 1.15)	0.83 (0.65 – 1.07)
Physical activity				
High (≥ 300 min/week)	Ref	Ref	Ref	Ref
Moderate (150–299 min/week)	0.86 (0.67 – 1.12)	1.17 (0.90 – 1.54)	0.92 (0.83 – 1.02)	0.98 (0.77 – 1.25)
Low (< 150 min/week)	1.01 (0.81 – 1.25)	1.22 (0.97 – 1.53)	1.00 (0.92 – 1.09)	1.00 (0.81 – 1.24)
TV watching time				
Low (≤ 2 h/day)	Ref	Ref	Ref	Ref
Moderate (3–4 h/day)	1.17 (0.96 – 1.42)	1.05 (0.86 – 1.29)	**1.17 (1.08 – 1.26)**	**1.23 (1.01 – 1.49)**
High (≥ 5 h/day)	1.19 (0.90 – 1.59)	1.06 (0.78 – 1.46)	**1.43 (1.26 – 1.63)**	1.29 (0.99 – 1.69)
Acute stress				
Low (0 event)	Ref	Ref	Ref	Ref
Moderate (1 event)	1.20 (0.95 – 1.51)	1.03 (0.82 – 1.31)	0.95 (0.87 – 1.05)	1.06 (0.85 – 1.32)
High (≥ 2 events)	1.18 (0.95 – 1.48)	0.99 (0.79 – 1.24)	1.09 (1.00 – 1.19)	1.17 (0.95 – 1.43)
Chronic stress				
Low (0 factor)	Ref	Ref	Ref	Ref
Moderate (1 or 2 factors)	**1.26 (1.01 – 1.57)**	1.08 (0.85 – 1.36)	1.05 (0.95 – 1.16)	1.21 (0.99 – 1.49)
High (≥ 3 factors)	1.01 (0.76 – 1.34)	1.09 (0.82 – 1.44)	**1.15 (1.04 – 1.28)**	1.08 (0.84 – 1.38)
Alcohol consumption				
No	Ref	Ref	Ref	Ref
Light/moderate	0.96 (0.76 – 1.21)	**1.27 (1.01 – 1.61)**	1.03 (0.94 – 1.13)	0.94 (0.76 – 1.15)
High	1.12 (0.85 – 1.47)	1.23 (0.91 – 1.66)	**1.25 (1.12 – 1.40)**	1.19 (0.91 – 1.56)
Smoking status				
Never smoker	Ref	Ref	Ref	Ref
Former smoker	**1.32 (1.05 – 1.65)**	**1.38 (1.11 – 1.72)**	**1.11 (1.01 – 1.21)**	**1.35 (1.11 – 1.65)**
Current smoker	**1.67 (1.27 – 2.20)**	**1.85 (1.39 – 2.47)**	**1.22 (1.11 – 1.34)**	**1.53 (1.18 – 2.00)**
Sleep duration				
Adequate	Ref	Ref	Ref	Ref
Marginally too short/long	1.07 (0.87 – 1.33)	0.95 (0.74 – 1.23)	0.98 (0.89 – 1.08)	0.98 (0.79 – 1.21)
Inadequate (too short/long)	1.24 (0.82 – 1.87)	1.44 (0.90 – 2.31)	1.08 (0.88 – 1.33)	1.35 (0.92 – 1.99)
Sleep medication use				
No	Ref	Ref	Ref	Ref
Yes	1.14 (0.83 – 1.56)	1.15 (0.85 – 1.56)	0.98 (0.86 – 1.11)	1.04 (0.74 – 1.48)
Number of social contacts				
High (> 20)	Ref	Ref	Ref	Ref
Moderate (11–20)	1.19 (0.93 – 1.52)	1.11 (0.86 – 1.42)	1.07 (0.97 – 1.18)	0.93 (0.74 – 1.16)
Low (≤ 10)	1.11 (0.89 – 1.39)	0.96 (0.75 – 1.22)	1.03 (0.95 – 1.13)	0.90 (0.73 – 1.11)
Marital status				
Relationship with cohabiting	Ref	Ref	Ref	Ref
Relationship with no cohabiting	1.20 (0.69 – 2.08)	0.96 (0.50 – 1.84)	1.12 (0.92 – 1.36)	1.18 (0.70 – 2.00)
No partner	0.91 (0.71 – 1.16)	0.98 (0.76 – 1.26)	1.01 (0.92 – 1.12)	**0.79 (0.62 – 1.00)**

Data were reported as aHR (95%CI), *aHR* adjusted hazard ratio from cox regression model adjusting for all the socio-demographics and lifestyle factors

Bold values indicate statistical significance at $P < 0.05$

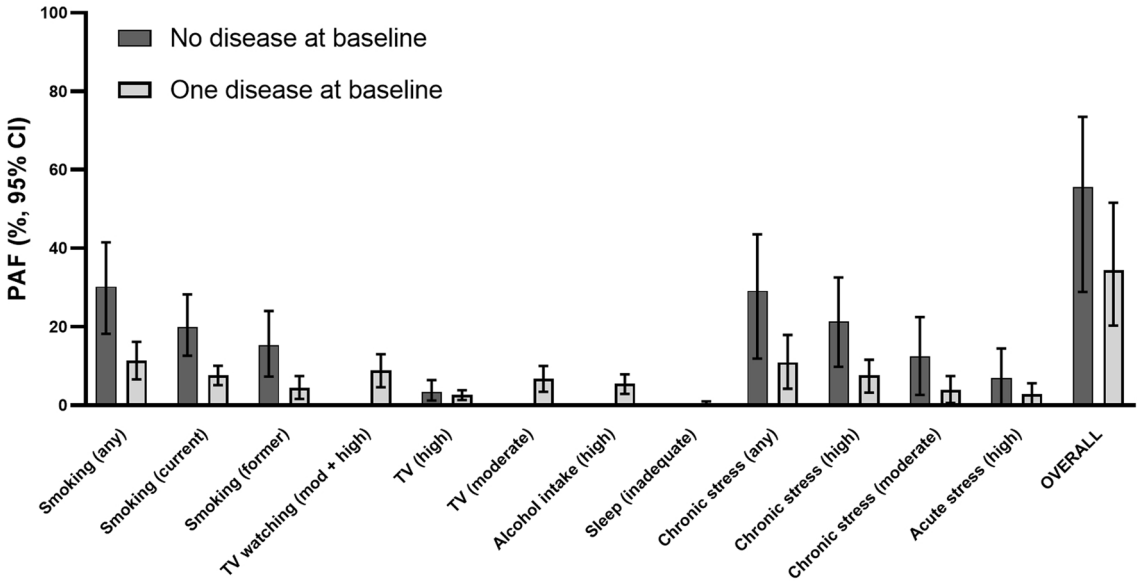

Fig. 4 Population attributable fraction of the established lifestyle factors for multimorbidity. *PAF* Population attributable fraction

In addition to smoking, other relevant and significant factors include television watching, alcohol consumption, sleep and chronic stress. Although comprehensively evaluated for the risk of developing individual chronic diseases (Patterson et al. 2018; Schmid and Leitzmann 2014), prolonged TV watching has received less attention for multimorbidity. A cross-sectional study has also shown that watching TV for ≥ 6 h/day is associated with an increased odds of multimorbidity compared with < 2 h/day (odds ratio, 1.57; 95% CI, 1.40–1.76) (Barboza et al. 2022). Weaker but significant associations existed between TV watching and multimorbidity among people with one chronic disease for 3–4 h/day (HR, 1.16; 95%CI, 1.08–1.24) and ≥ 5 h/day (HR, 1.33; 95%CI, 1.18–1.50). These associations could reflect disease severity but can also be explained as sedentary lifestyles that impair skeletal muscle function and mass, lead to low-grade systemic inflammation and reduce insulin sensitivity, thereby promoting cardiometabolic disease (Young et al. 2016) and carcinogenesis (Schmid and Leitzmann 2014). Additionally, alcohol consumption and inadequate sleep contributed as significant risk factors for multimorbidity in individuals with pre-existing conditions. Prospective studies show that excessive alcohol consumption or past drinking is associated with a higher risk of multimorbidity than never or non-excessive drinking (Singh-Manoux et al. 2018; Han et al. 2021). Some show that not drinking or having stopped drinking increases the risk of multimorbidity compared with drinking within accepted limits (Katikireddi et al. 2017). This potential protective effect may reflect reverse causation because non-drinkers may not drink due to a medical problem or medication. Indeed, a Mendelian randomization study has shown that the observed protective effect of alcohol intake on certain types of cardiovascular disease is unlikely to be causal (Millwood et al. 2019). Although the causal effect of light-to-moderate alcohol intake remains inconclusive for cardiovascular disease and diabetes (Luitgaarden et al. 2022), we demonstrated that excessive alcohol intake and binge drinking were associated with a 5.5% attributable risk for multimorbidity in patients with a pre-existing disease. Furthermore, sleep can affect growth, recovery from illness and the immune system (Besedovsky et al. 2019). Inadequate sleep (too long or too short) was identified as a significant risk factor for multimorbidity. This is consistent with a recent prospective study of 7864 UK participants followed over 25 years, with data showing that short sleeping (≤ 5 h) at age 50 years was associated with a higher risk of developing a first chronic disease (HR, 1.20; 95%CI, 1.06–1.35) and subsequent multimorbidity (i.e., ≥ 2 of 13 chronic diseases) (HR, 1.21; 95%CI, 1.03–1.42) (Sabia et al. 2022). We found no association between sleep inadequacy and multimorbidity in people without baseline disease due to the low number of events (multimorbidity in 11 of 1750 cases with inadequate sleep).

Notably, a pronounced association has been observed between both chronic and acute stress and the development of multimorbidity. Several cross-sectional, but no prospective, studies are known to have reported an association between stress and multimorbidity (Sakakibara et al. 2019; Stubbs et al. 2018; Vancampfort et al. 2017; Swartz and Jantz 2014). For example, among 110 455 adults in the US, psychological distress due to stressful events increased the probability of medical multimorbidity (OR, 1.98; 95%CI, 1.84–2.14) (Swartz and Jantz 2014). The PAFs indicate that stress reduction efforts could reduce the incidence of

multimorbidity by as much as 11–29%. All in all, from the six key lifestyle domains in lifestyle medicine, four have been identified to be relevant to multimorbidity: substance use, sleep, being physically inactive and stress management. Considering that stress is a significant risk factor alongside smoking, excessive television watching, poor sleep, and alcohol consumption, it underscores the necessity of evaluating healthy lifestyles from a comprehensive perspective. It is important to include stress management in lifestyle programs. These programs should encourage effective stress management techniques and promote relaxation through healthy lifestyle practices, rather than relying on less beneficial coping strategies such as smoking or television viewing.

The mechanisms underlying the development of multimorbidity are complicated (Skou et al. 2022). Many diseases share common pathophysiologies, such as inflammation and accelerated aging of organ systems (Masoudkabir et al. 2017), This processes can be affected by various lifestyle factors explored in this analysis. Conversely, some diseases may have unrelated pathophysiologies but share risk factors (e.g., smoking). Additionally, having one chronic disease can create a domino effect, increasing susceptibility to others. For instance, diabetes can damage blood vessels, raising the risk of heart disease, and stroke. Last, some medications used to treat chronic diseases can have side effects that increase the risk of developing other conditions. For instance, inhaled corticosteroids used for the treatment of respiratory disease could raise blood sugar levels, increasing the risk of diabetes (Suissa et al. 2010).

The healthfulness of lifestyle behaviors and lifestyle-related factors may also reflect social, psychosocial, and behavioral elements of health, being associated with both health literacy and self-management skills. This observational study precludes making causal inferences, but it does provide leverage points that may improve lifestyle and self-management programmes by expanding the focus beyond smoking, diet, and physical activity to include both relaxation and sleep.

A main strength of this study is the use of a comprehensive set of lifestyle factors, which allowed the identification of all relevant lifestyle domain as suggested by the American College of Lifestyle Medicine and adopted by Lifestyle Medicine organizations internationally (Leefstijlroer | Vereniging Arts en Leefstijl. 2024). Furthermore, our study provides estimates of single lifestyle factors after mutual adjustment for other lifestyle factors. It is also one of the largest prospective studies on the association between lifestyle factors and multimorbidity in people with chronic disease. Several limitations also warrant consideration. First, by studying multimorbidity as the outcome, people without baseline disease needed to acquire at least two diseases, whereas those with a pre-existing disease only needed to develop one. This explains the larger HRs in the healthy population. However, the HRs were broadly comparable when comparing incident single diseases (Table S5). Second, including a large set of determinants resulted in considerable missing values (e.g., $\leq 9.4\%$ for physical activity and $\leq 12.7\%$ for diet) and the need to impute data. In the complete analysis of the baseline group with one chronic disease, the associations for alcohol consumption and incident multimorbidity changed considerably due to the exclusion of participants who reported their alcohol intake but had missing data for physical activity and diet. Therefore, we can justify the use of imputed data in our main analysis. Third, we only know if incident cases developed a chronic disease within the interval between assessment waves, rather than the exact diagnosis time, which could have led to overestimation of the time to event. However, completing follow-up questionnaires every 1.5–2.5 years will have limited this effect, as verified by the sensitivity analysis using an accelerated time failure model. Fourth, cancer and CVD were mainly self-reported, which may have introduced misclassification and survival bias, though we assume that these will have had limited effects on the results. Finally, lack of data meant that we could not assess the influence of medication on the association between lifestyle factors and incident multimorbidity for the baseline group with one chronic disease.

In conclusion, our results indicate that current smoking, chronic and acute stress, prolonged TV watching and high alcohol consumption represent major risk factors for developing multimorbidity. These lifestyle factors have a similar impact on acquiring a new chronic disease, whether it's the first one someone develops or an additional condition alongside an existing one. Promoting healthy lifestyles could reduce up to 56% and 34% of the incident multimorbidity in people with no or one chronic disease, respectively. Notably, some lifestyle factors, like diet and stress, the impact on multimorbidity risk might be more pronounced in specific patient groups compared to the group with either chronic disease. Interventions must target preventing the spectrum of unhealthy lifestyle factors among both healthy adults and those with a pre-existing chronic disease, especially in care settings.

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Availability of data and materials For access to the data that support the findings of this study, the Lifelines research office can be contacted via www.lifelines.nl/researcher.

Declarations

Ethics approval and consent to participate The Lifelines Cohort Study was approved by the medical ethics committee of the University Medical Center Groningen, the Netherlands. All participants signed the informed consent form.

Competing interests The authors declare no competing interests.

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