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Review

Risk factors for multimorbidity in adulthood: A systematic review☆

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ABSTRACT

Background: Multimorbidity, the coexistence of multiple chronic diseases in an individual, is highly prevalent and challenging for healthcare systems. However, its risk factors remain poorly understood.
Objective: To systematically review studies reporting multimorbidity risk factors.
Methods: A PRISMA-compliant systematic review was conducted, searching electronic databases (MEDLINE, EMBASE, Web of Science, Scopus). Inclusion criteria were studies addressing multimorbidity transitions, trajectories, continuous disease counts, and specific patterns. Non-human studies and participants under 18 were excluded. Associations between risk factors and multimorbidity onset were reported.
Results: Of 20,806 identified studies, 68 were included, with participants aged 18–105 from 23 countries. Nine risk factor categories were identified, including demographic, socioeconomic, and behavioral factors. Older age, low education, obesity, hypertension, depression, low pysical function were generally positively associated with multimorbidity. Results for factors like smoking, alcohol consumption, and dietary patterns were inconsistent. Study quality was moderate, with 16.2% having low risk of bias.
Conclusions: Several risk factors seem to be consistently associated with an increased risk of accumulating chronic diseases over time. However, heterogeneity in settings, exposure and outcome, and baseline health of participants hampers robust conclusions.

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1. Background

Research on multimorbidity, the coexistence of two or more chronic diseases in the same individual, is growing exponentially, with 80% of papers on the subject being published post 2010[1]. Investigations into the epidemiology of multimorbidity have included its prevalence in different settings and populations, patterns of multimorbidity, clinical guidelines, and associated outcomes (Xu et al., 2017). Although the prevalence of multimorbidity varies across studies depending on the number of diseases evaluated, there is consensus that most community-dwelling older persons are affected by multiple chronic diseases (Calderon-Larranaga et al., 2017). Multimorbidity threatens healthcare systems sustainability; it has been associated with many adverse outcomes such as functional dependence (Rizzuto et al., 2017), poor quality of life (Makovski et al., 2019), and shorter life expectancy (Rizzuto et al., 2017). In terms of health inequities, multimorbidity is problematic; it is premature and overrepresented in younger adults living in areas with socio-economic deprivation, with some evidence of an expansion over time (Head et al., 2021). Multimorbidity is frequently associated with polypharmacy, drug-drug interactions, drug-disease interactions and, consequently, adverse drug reactions (Marengoni and Onder, 2015), making multimorbidity care and management a complex task for healthcare systems and professionals.

Identifying risk factors for multimorbidity is crucial to effectively tailor targeted interventions and management strategies. A diverse array of potential risk factors exists, spanning demographic elements, biological aging, socio-economic factors, and lifestyle aspects, among others.

The overall objective of this systematic review is to identify observational studies reporting data on risk factors for multimorbidity. The specific aims are: 1) to identify the association between risk factors and incident multimorbidity in adult persons affected by no or one chronic disease at baseline; 2) to identify the association between risk factors and an increase in the number of chronic conditions during follow-up in persons with baseline multimorbidity; and 3) to identify the association between risk factors and specific multimorbidity patterns.

2. Methods

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses (Liberati et al., 2009). The protocol of this review has been recorded in the International Prospective Register of Systematic Reviews (PROSPERO) (protocol number CRD42019123304).

2.1. Search strategy and selection criteria

We searched the following electronic bibliographic databases (until March 3rd 2022): MEDLINE, EMBASE, Web of Science, and Scopus, using the search string in Appendix A. Additional sources (i.e., references, supplementary files, and appendices) from selected articles were also considered for inclusion. Covidence (Veritas Health Innovation, 2022) was used for data management, and titles and/or abstracts of studies retrieved from the systematic literature search, and those from additional sources, were screened independently by two review authors to identify potentially eligible studies. The full texts of these studies were retrieved and independently assessed for eligibility by two review team members. Any disagreement regarding the inclusion of specific studies was resolved via discussion with a third senior reviewer.

2.2. Inclusion and exclusion criteria

Only longitudinal studies, either cohort or case-control, were included. Studies evaluating community-dwelling or institutionalized individuals were included.

Given that several definitions of multimorbidity have been proposed, we searched for multimorbidity, defined as the simultaneous presence of multiple chronic diseases in the same individual – irrespective of the cut-off used in the study (Calderon-Larranaga and Fratiglioni, 2019). Studies with one disease as an outcome were included if the participants already had at least one disease at baseline. Studies investigating specific multimorbidity patterns, continuous disease count, multimorbidity trajectories, and transitions from zero or one to two or more diseases were included.

Exclusion criteria were: non-human studies, those involving participants aged less than 18 years, experimental studies, randomized controlled trials, literature reviews, meta-analyses, case reports, editorials, abstracts, commentaries, and book chapters.

3. Data extraction and analysis

A standardized, pre-piloted form was used to extract data from the included studies. Two review authors independently extracted data and discrepancies were identified and resolved through discussion (with a third author where necessary).

Extracted information included:

- General information on the study (authors, year of publication, country, study design, analytical sample size, baseline health status inclusion and exclusion criteria)
- Information about participants (age and sex)
- Information about any possible risk factors (e.g., demographic, behavioural, socioeconomic, health status, mental health, cardiovascular risk factors, family history, childhood experiences etc.)
- Primary outcome
- Brief summary of study findings
- Information for assessing the risk of bias using the Newcastle-Ottawa Scale (NOS) (Stang, 2010)

3.1. Evaluation of the quality of the studies

The NOS was used to assess the quality of the included studies. The evaluation was carried out by two reviewers, independently. Any discrepancies were resolved by a third reviewer. The NOS consists of two different checklists: one for the evaluation of cohort studies, and one for case-control studies. Each of the two checklists includes scores for selection (maximum score 4), comparability (maximum score 2), and the outcome (maximum score 3), resulting in a total maximum score of 9. Scores$>$ 7 were considered low risk, 5–7 moderate risk, and $<$ 5 high risk of bias (Luchini et al., 2017; Wells et al., 2023).

4. Results

4.1. General description of the included studies

Fig. 1 displays a PRISMA flow chart of studies included in this systematic review, including the number of papers identified in PubMed, Web of Science, and Embase, as well as the number of, and reason for, study exclusion. Of the 20 806 abstracts identified in the search, 275 were selected for full-text reading. Reapplication of the eligibility criteria for full-text review resulted in 68 studies (Almas et al., 2019; Aminisani et al., 2019; Arias-de la Torre et al., 2021; Balogun et al., 2021; Bisquera et al., 2022; Blümel et al., 2020; Calderón-Larrañaga et al., 2019, 2020, 2021; Chau et al., 2021; Demirchyan et al., 2013; Dhalwani et al., 2016; Dibato et al., 2021; Fabbri et al., 2015a, 2015b, 2015c; Freisling et al., 2020; Gondek et al., 2021; Han et al., 2021; Henchoz et al., 2019; Hlaing-Hlaing et al., 2021; Humphreys et al., 2018; Hussin et al., 2019; Irshad and Dash, 2022; Jackson et al., 2015, 2016; Katikireddi et al., 2017; Khanolkar et al., 2021; Ki et al., 2017; Kivimäki et al., 2017; Li et al., 2021, 2022; Lin et al., 2021; Liu et al.,

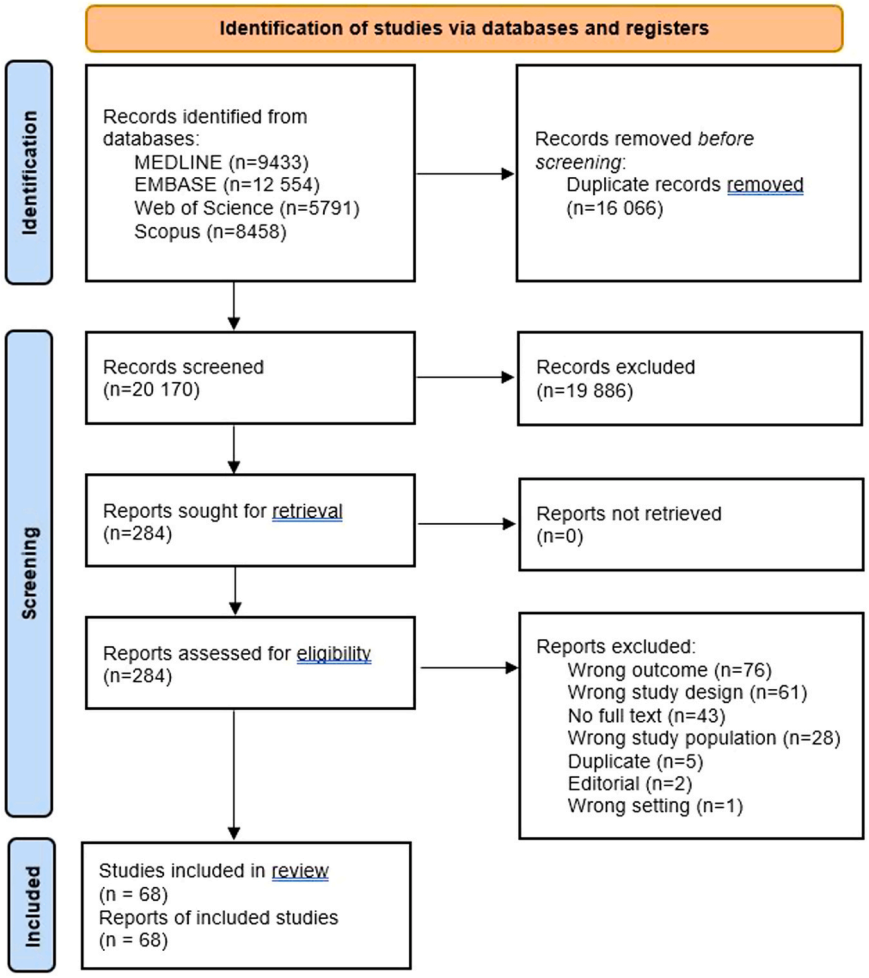

Fig. 1. PRISMA 2020 flow diagram.

2022; Lu et al., 2021; Melis et al., 2014; Moin et al., 2021; Mounce et al., 2018; Pérez et al., 2020; Petermann-Rocha et al., 2021; Peterson et al., 2021; Poole and Steptoe, 2018; Qiao et al., 2021, 2022; Quiñones et al., 2019; Rocca et al., 2017; Ryan et al., 2018; Schäfer et al., 2019; Schramm et al., 2022; Seo, 2019; Shang et al., 2020a, 2020b; Singh-Manoux et al., 2018; Sutin et al., 2013; Tajik et al., 2022; Tomasdottir et al., 2016; Vall Castelló and Tubianosa, 2020; van den Akker et al., 2000, 2001; Waller et al., 2010; Wikström et al., 2015; Willroth et al., 2021; Xu et al., 2018, 2019a, 2019b, 2020; Zhang et al., 2022; Zou et al., 2022) being included in this systematic review. Table 1 reports a summary of the associations (positive, negative, inconsistent, or no association) between the risk factors and multimorbidity. Detailed summaries of the results for each individual study are reported in Table S1.

4.2. Characteristics of the included studies

The studies were published between the years 2000 and 2022 in 23 different countries, 13 European and ten outside Europe. The number of study participants varied from 190 to 826,936. The age of the participants included in the studies ranged from 18 to 105 years. Nine studies only included women (Blümel et al., 2020; Hlaing-Hlaing et al., 2021; Jackson et al., 2015, 2016; Rocca et al., 2017; Xu et al., 2018, 2019a, 2019b, 2020). The included studies, beyond those looking at early-life exposures, had a maximum follow-up ranging from one point five to 33 years; in total, 34 studies had a follow-up $\geq$ 10 years.

4.3. Synthesis of the results

The majority of the articles included in this review took into consideration, either directly or indirectly, age as one of the possible risk factors for the development of multimorbidity. Bisquera et al (Bisquera et al., 2022). showed that persons aged 60–79 had almost 8 the hazard of developing multimorbidity in comparison with those aged 18–39. Similar results were also reported by others (Chau et al., 2021; Fabbri et al., 2015b; Irshad and Dash, 2022; Li et al., 2021; Moin et al., 2021; Mounce et al., 2018; Ryan et al., 2018; Schäfer et al., 2019; Seo, 2019; Vall Castelló and Tubianosa, 2020). Lu et al (Lu et al., 2021). reported that age was associated with an increased risk of developing another chronic condition among participant with one condition at baseline, but such association disappeared when considering persons without any chronic condition at the first assessment. The association between older age and multimorbidity was similarly inconsistent in the study by Peterson et al (Peterson et al., 2021).: age was consistently associated with an higher risk of the development of multiple chronic conditions in women, but not in men. Van den Akker et al (van den Akker et al., 2001). also found that only advanced age (70 +), in comparison with age 20–29, was associated with an increased risk of developing multimorbidity: no association was found for other age groups. A similar result was reported in another study by the same authors (van den Akker et al., 2001). However, other authors did not find any association between age and incident multimorbidity (Aminisani et al., 2019; Hussin et al., 2019). Finally, some authors used age or age groups to adjust or isolate the effect of other risk factors on the development of

Table 1
Characteristics and summary of main findings of the studies.

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
Almas et al. 2019	Cohort	Sweden	10,074	20–64	56	No MI, angina, or stroke	13 years	Incident CVD in those with 1 + diseases at baseline	Concurrent depression and non-CVD morbidity (HR = 2.0; 95% CI = 1.1–3.3), as well as depression (HR = 1.3; 95% CI = 1.0–2.0) and non-CVD morbidity (HR= 1.4; 95% CI = 1.0–2.0), alone, were associated with incident CVD.	8
(Aminisani et al., 2019)	Cohort	New Zealand	1673	55–70	52	No multimorbidity at baseline	10 years	2 + chronic diseases	Being separated/divorced/single/widowed (OR = 1.18; 95% CI = 1.01–1.37), having hypertension (OR = 1.23; 95% CI = 1.02–1.48), and having a chronic condition at baseline (OR = 2.92; 95% CI = 2.33–3.67) were significant risk factors for multimorbidity. The following variables were not found to be significant predictors of multimorbidity, and the results were not reported: age, sex, Māori ethnicity, education, income, smoking, alcohol consumption, physical activity, and body mass index.	6
Arias-de la Torre. 2021	Cohort	United Kingdom	15,845	23 +	49	Excluded those with current/past physical multimorbidity	3 decades	Physical multimorbidity (2 + self-reported long-term physical conditions)	Depressive symptoms were associated with physical multimorbidity development across adulthood, at ages: 34 years (RRR = 1.67; 95% CI = 1.50–1.87), 42 years (RRR = 1.63; 95% CI = 1.48–1.79), and 46 years (RRR = 1.58; 95% CI = 1.43–1.73). Analyses where multimorbidity was categorized as 2, 3, and 4 + diseases were also performed.	8
Balogun et al. 2021	Cohort	Australia	373	50 + , mean = 61	46	Excluded those with multimorbidity at baseline	10 years	2 + chronic diseases	BMI per kg/m^2 (RR = 1.05; 95% CI = 1.02–1.08) and total body fat mass per kg (RR = 1.03; 95% CI = 1.01–1.04) were associated with multimorbidity. Increases in 1000 steps/day in those with less than 10 000 steps/day (RR = 0.91; 95% CI = 0.85–0.97), relative lean muscle mass per 0.1 kg/kg/m2 (RR = 0.93; 95% CI = 0.88–0.98), and relative handgrip strength per 0.1 psi/kg/m2 (RR = 0.85; 95% CI = 0.77–0.94) were protective against multimorbidity. The following were not statistically significantly associated with multimorbidity: absolute lean muscle mass per kg (RR = 1.00; 95% CI = 0.98–1.02); increases in 1000 steps/day in those with 10,000 + steps/day (RR = 1.04; 95% CI = 0.93–1.09; and absolute handgrip strength per psi (RR = 0.97; 95% CI = 0.93–1.01).	7
(Bisquera et al., 2022)	Cohort	United Kingdom	826,936	18 + , mean = 34	52	N/A	Median 4.2	Transitioning from 1 to 2 conditions	Risk factors for transitioning from 1 to 2 conditions included: age 40–59 years (ref. = 18–39 years; HR = 1.87; 95% CI = 1.81–1.94); age 60–79 years (ref = 18–39 years: HR = 7.88; 95% CI = 6.72–9.24); female sex (HR = 1.17; 95% CI = 1.13–1.20); black ethnicity (ref = white ethnicity; HR = 1.25; 95% CI = 1.20–1.30); Asian ethnicity (ref = white ethnicity; HR = 1.2; 95% CI = 1.13–1.28); most socially/materially deprived (ref = least deprived; HR = 1.46; 95% CI = 1.30–1.64); at least one risk factor (hypertension, moderate obesity, high cholesterol, smoking, high alcohol consumption, psychoactive substance use; ref = no risk factors; HR = 1.69; 95% CI = 1.63–1.74); ever alcohol use (HR = 1.43; 95% CI = 1.23–1.68); ever moderate obesity (HR = 1.75; 95% CI = 1.69–1.81); resolved moderate obesity (HR = 1.16; ref = 1.09–1.23); ever smoking (HR = 1.40; 95% CI = 1.35–1.44); and resolved smoking (HR = 1.22; 95% CI = 1.17–1.26). Ever having high cholesterol (HR = 0.81; 95% CI = 0.79–0.84) was protective against transitions from 1 to 2 conditions. No significant association was found between resolved alcohol	8

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									consumption (HR = 2.00; 95% CI = 0.67–5.98) and transitioning from 1 to 2 conditions.	
Blümel et al. 2020	Cohort	Chile	1066	40–59	100	N/A	Mean 27.8 years	2 + chronic diseases	Obesity (OR = 2.48; 95% CI = 1.71–3.61), low-wage labor (OR = 2.18; 95% CI = 1.67–2.83), and high-density lipoprotein cholesterol (HDL-C) < 50 mg/dL (OR = 1.31; 95% CI = 1.02–1.68) were predictors of multimorbidity. Only significant predictors were reported. Correlations between pairwise combinations of diseases and multimorbidity were also reported.	7
Calderón-Larrañaga et al. 2019	Cohort	Sweden	2293	60 +	39	Excluded those with dementia/ questionable dementia diagnosis	9 years	Chronic disease accumulation	Among those without multimorbidity at baseline, high life satisfaction (β = −0.064; 95% CI = −0.116, −0.011) was protective against annual increases in the number of chronic diseases. The following factors showed non-statistically significant results in terms of annual increase in disease number: positive perceptions of future health (β = −0.065; 95% CI = −0.121, −0.008); high sense of resistance to illness (= 0.005; 95% CI = −0.055, 0.065); low tendency to accept sickness as a part of life: (β = −0.027; 95% CI = −0.079, 0.024); and low health worry (β = 0.014; 95% CI = −0.040, 0.068). The same analyses were also conducted and reported among the total sample, including those with multimorbidity at baseline.	8
Calderón-Larrañaga et al. 2020	Cohort	Sweden	1969	60 + , mean = 71	64	Excluded those with CVD at baseline	12 years	Rate of CVD multimorbidity development	The following rate of CVD accumulation was found according to baseline homocysteine: β = 0.023 per year (0.015, 0.030); baseline methionine: β = −0.007 per year (−0.013, −0.001); and baseline Methionine:homocysteine ratio: β = −0.017 per year (−0.023, −0.011). Methionine, homocysteine, and their ratio were also analysed as tertiles, and analyses stratified by MTHFR were also reported/ performed.	8
Calderón-Larrañaga et al. 2021	Cohort	Sweden	2189	60 + , mean = 72	63	N/A	12 years	Rate of chronic disease accumulation	Those with a fast-declining BMI trajectory (ref = stable BMI trajectory; β = 0.221; 95% CI = 0.221; 95% CI = 0.090, 0.352) had a significantly greater yearly rate of disease accumulation over the 12-year follow-up. No significant association was found for those with a slow-declining BMI trajectory (ref = stable BMI trajectory; β = 0.022; 95% CI = −0.024, 0.067). The authors also investigated and reported associations for yearly rate of CVD accumulation and neuropsychiatric disease accumulation. The analyses were repeated and reported using a joint model.	8
Chau et al. 2021	Cohort	Canada	166,665	18–105	52	Included those with 1 chronic disease at baseline	12 years	2, 3, and 4 chronic diseases	Those with a high continuity of care (HR = 0.92; 95% CI = 0.91–0.93) and those with little contact with physicians (HR = 0.73; 95% CI = 0.72–0.75) had lower hazards of transitioning from 1 to 2 diseases. Compared to those aged 18–24, those aged 25–29 years (HR = 1.09; 95% CI = 1.04–1.13) had increased hazards of transitioning from 1 to 2 diseases; the hazards increased with old age categories, as reported in the paper. Moreover, compared to those in the lowest income quintiles, those in the second lowest income quintile (HR = 0.96; 95% CI = 0.94–0.98) had reduced hazards of transitioning from 1 to 2 diseases; the hazards reduced more with increasing income quintile, as reported in the paper. In addition, those living in an urban residence (HR = 1.07; 95% CI = 1.05–1.09) had increased hazards of transitioning from 1 to 2 diseases. Compared to those not	7

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									enrolled in a primary care model, those enrolled in a family health group (HR = 1.12; 95% CI = 1.10–1.13) had increased hazards of transitioning from 1 to 2 diseases; no significant association was found for those in a family health network/organization (HR = 1.02; 95% CI = 1.00–1.04) or family health team (HR = 0.99; 95% CI = 0.96–1.02), and those in any other model (HR = 1.11; 95% CI = 1.06–1.16) had increased hazards of transitioning from 1 to 2 diseases. For every 5 outpatient general practice visits (HR = 1.02; 95% CI = 1.02–1.02) and every 5 outpatient specialist visits (HR = 1.02; 95% CI = 1.02–1.02), there was increased hazards of transitioning from 1 to 2 diseases; no association was found for every five inpatient general practice visits (HR = 1.01; 95% CI = 1.00–1.01) or every 5 inpatient specialist visits (HR = 1.00; 95% CI = 0.99–1.01). No association was found between female sex (HR = 1.01; 95% CI = 0.99–1.08) and transitioning from 1 to 2 diseases. The analyses were also repeated for the transition between 2 and 3 and 3–4 conditions. Analyses were also repeated, restricted to outpatient family physician and specialist visits, as well as inpatient and outpatient family physician and specialist visits excluding visits to anaesthesiologists, diagnostic radiologists, and pathologists.	
Demirchyan et al. 2013	Cohort	Armenia	725	39–90, mean = 58	68	Excluded those with multimorbidity at baseline from analyses on incident multimorbidity	22 years	2 + non-communicable health conditions	Perceived poor living standards in the 10 years post-earthquake (RR = 1.12; 95% CI = 1.03–1.22) and each additional stressful life event (RR = 1.03; 95% CI = 1.02–1.04) were associated with multimorbidity. No statistically significant association was found between each additional unit of baseline BMI (RR = 1.01; 95% CI = 1.00–1.02) and multimorbidity.	6
Dhalwani et al. 2016	Cohort	United Kingdom	5476	50 + , median = 61	53	Excluded those with multimorbidity at baseline	232,749 person-months	2 + chronic diseases	Physical inactivity (HR = 1.33; 95% CI = 1.03–1.73) was associated with multimorbidity development. Inadequate fruit and vegetable consumption was found to be associated with multimorbidity in in women (HR = 1.65; 95% CI = 1.17–2.34), but protective against multimorbidity in men (HR = 0.60; 0.43–0.86). No association with multimorbidity was detected for the following factors: smoking (HR = 1.21; 95% CI = 0.65–2.27); excess alcohol consumption (HR = 1.15; 95% CI = 0.92–1.43); and obesity (HR = 1.28; 95% CI = 0.85–1.91). Specific numbers of unhealthy lifestyle factors and combinations of unhealthy lifestyle factors were also investigated/reported in relation to multimorbidity development.	5
Dibato et al. 2021	Cohort	United States	606,440	18–70	44	All participants had type 2 diabetes	mean follow-up 5.3 years	2nd disease (after diabetes)	Compared to those with white ethnicity, those with African American ethnicity had increased risk of multimorbidity involving atherosclerotic cardiovascular diseases in the 18–39 years age group (HR = 1.17; 95% CI = 1.05–1.31), with no significant association in the 40–49 (HR = 1.02; 95% CI = 0.96–1.08), 50–59 (HR = 0.97; 95% CI = 0.93–1.01), and 60–70 (HR = 0.94; 95% CI = 0.90–1.01) years age groups. Those with African American ethnicity had higher hazards of multimorbidity involving major adverse cardiovascular events across all age groups: 18–39 years (HR = 1.63; 95% CI = 1.42–1.88), 40–49 years (HR = 1.48; 95% CI = 1.37–1.60), 50–59 years (HR = 1.37; 95% CI	7

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									= 1.31–1.44), and 60–70 years (HR = 1.11; 95% CI = 1.06–1.15). These analyses were repeated stratified by depression and by ethnicity.	
Fabbri et al. 2015 (A)	Cohort	United States	695	60–95, mean = 72	49	N/A	2–4 years	Disease count	Higher resting metabolic rate was associated with increased future number of diseases (β = 0.015, p = 0.034).	7
Fabbri et al. 2015 (B)	Cohort	Italy	1018	60 + , mean = 74	57	N/A	9 years	Disease count	People with higher baseline age (β = 0.008; p-value < 0.001) and baseline interleukin-6 ≥ 3.5 pg/mL (β = 0.06, p-value < 0.001) had higher average increases in disease count. β-values were not reported, but steeper increase of interleukin-6 over time was associated with steeper increase in disease number over time (p = 0.003)	7
Fabbri et al. 2015 (C)	Cohort	Italy	1025	60 + , mean = 74	56	N/A	4 years	Rate of change of multimorbidity	Obesity was associated with faster accumulation of chronic diseases compared to both normal weight (β = 0.044; p = 0.005) and overweight (β = 0.062; p < 0.001). No significant association was found between overweight and disease accumulation (β = −0.018; p = 0.18), with normal weight as the reference group. Analyses were also conducted examining the interaction between obesity and rate of change of BMI.	7
Freisling et al. 2020	Cohort	Italy, Spain, United Kingdom, Netherlands, Germany, Sweden, Denmark	291,778	51	64	Excluded those with cancer, CVD, Type 2 DM at baseline	10 years	Cancer-cardiometabolic multimorbidity (cancer, CVD, Type 2 DM)	BMI was a predictor of multimorbidity among those with cancer (HR = 1.63; 95% CI = 1.51–1.76), CVD (HR = 1.41; 95% CI = 1.30–1.53), and Type 2 DM (HR = 1.08; 95% CI = 1.01–1.16) at baseline. Smoking was also a risk factor among those with cancer (HR = 1.62; 95% CI = 1.36–1.92); cardiovascular disease (HR = 1.26; 95% CI = 1.06–1.49); and Type 2 DM (HR = 1.70; 95% CI = 1.44–2.01). Increases in healthy lifestyle index were protective against multimorbidity in those with cancer (HR = 0.75; 95% CI = 0.71–0.81); cardiovascular disease (HR = 0.84; 95% CI = 0.79–0.90); and Type 2 DM (HR = 0.82; 95% CI = 0.77–0.88). Mediterranean diet was protective against multimorbidity in those with cancer (HR = 0.89; 95% CI = 0.81–0.97), but no significant association was found in those with cardiovascular disease (HR = 0.95; 95% CI = 0.87–1.03) or Type 2 DM (HR = 0.96; 95% CI = 0.88–1.04).	6
Gondek et al. 2021	Cohort	Great Britain	7951	46–48	Not reported	N/A	From childhood to adulthood	2 + long-term health conditions (at least one must be a physical condition); multimorbidity clusters	The following factors were found to be associated with multimorbidity development: father's social class at birth (skilled non-manual/manual vs professional; RR = 1.30; 95% CI = 1.09–1.55); father's social class at birth (partly-skilled vs professional; RR = 1.43; 95% CI = 1.18–1.74); fathers social class at birth (unskilled vs professional; RR = 1.43; 95% CI = 1.15–1.77); higher BMI at age 10 (RR = 1.03; 95% CI = 1.01–1.05); and externalizing problems at age 16 (RR = 1.06; 95% CI = 1.03–1.09). An additional kg of birthweight (RR = 0.90; 95% CI = 0.84–0.96) was protective against multimorbidity development. The following factors were investigated but not found to be significantly associated with multimorbidity development: father's social class at birth (managerial and technical vs professional; RR = 1.14; 95% CI = 0.94–1.40); higher cognitive ability at age 10 (RR = 0.96; 95% CI = 0.91–1.00); and internalising problems at age 16 (RR = 1.04; 95% CI = 1.00–1.08). Factors associated with mental health and hypertension, as well as mental health and arthritis, multimorbidity clusters were also reported/investigated.	6

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
Han et al. 2021	Cohort	China	461,047	30–79, mean = 51	59	Excluded those with history of heart disease, stroke, cancer, or diabetes at baseline	Median 11.2 years	Cardiometabolic multimorbidity (2 + cardiometabolic diseases)	Smoking (HR = 1.16; 95% CI = 1.11–1.22); excessive alcohol consumption (HR = 1.16; 95% CI = 1.09–1.22); less healthy dietary habits, defined as infrequent vegetable/fruits/egg consumption and daily or less than weekly red meat consumption (HR = 1.18; 95% CI = 1.06–1.30); low physical activity (HR = 1.14; 95% = 1.10–1.18); and unhealthy body shape, defined as BMI < 18.5 or ≥ 28.0 kg/m^2 or waist circumference ≥ 90 cm in men or ≥ 85 cm in women (HR = 1.63; 95% CI = 1.57–1.68) were associated with incident cardiometabolic multimorbidity. Numbers of unhealthy lifestyle factors were also examined; a 1-factor increase (HR = 1.29; 95% CI = 1.27–1.32) was associated with cardiometabolic multimorbidity. Analyses were also repeated using multi-state models.	7
Henchoz et al. 2019	Cohort	Switzerland	4731	65–70, mean = 68	58	N/A	From childhood to adulthood	2 + chronic conditions	Serious illness or accident in childhood (OR = 1.45; OR = 1.18–1.79) and 2 + stressful life events in childhood (OR = 1.42; 95% CI = 1.15–1.74) were associated with multimorbidity incidence. The following childhood adversities were not significantly associated with multimorbidity incidence: premature birth (OR = 1.02; 95% CI = 0.71–1.48); food restrictions (OR = 1.13; 95% CI = 0.91–1.40); child labour (OR = 1.06; 95% CI = 0.86–1.30); poor family economic environment (OR = 0.94; OR = 0.74–1.19); and 1 stressful life event (OR = 1.13; 95% CI = 0.93–1.38). Multinomial logistic regression was also carried out examining the association between childhood adversity and 2, 3, and 4 + diseases.	4
Hlaing-Hlaing et al. 2021	Cohort	Australia	5350	50–55	100	Excluded those with non-communicable diseases	15 years	2 + noncommunicable diseases	Quintiles 5 versus 1 of three dietary indices (Healthy Eating Index for Australian Adults-2013 [HEIFA-2013], Mediterranean Diet Score [MDS], and Alternative Healthy Eating Index-2010 [AHEI-2010]) were examined in relation to multimorbidity development over 3, 6, 9, 12, and 15 years of follow-up. Those in the fifth versus 1st quintile of the HEIFA-2013 at 15 years (OR = 0.73; 95% CI = 0.55–0.96), the AHEI-2010 at 12 years (OR = 0.70; 95% CI = 0.51–0.96), and the AHEI-2010 at 15 years (OR = 0.75; HR = 0.57–0.99) had significantly higher odds of multimorbidity incidence.	6
Humphreys et al. 2018	Cohort	United Kingdom	2299	66	49	N/A	From childhood to adulthood	Chronic disease count	Number of childhood illnesses (OR = 1.15; 95% CI = 1.06–1.25) was significantly associated with number of chronic diseases in adulthood. The following childhood factors were not found to be significantly associated with chronic disease count in adulthood: Diphtheria immunized (OR = 0.96; 95% CI = 0.72–1.26), paternal social class (OR = 1.15; 95% CI = 0.93–1.43), maternal age at birth (OR = 1.00; 95% CI = 0.98–1.01), bottle fed (OR = 1.05; 95% CI = 0.78–1.40), bottle and breast fed (OR = 0.95; 95% CI = 0.79–1.14), birth weight (kg) (OR = 1.29; 95% CI = 0.58–2.89), weight at 1 year (kg) (OR = 0.52; 95% CI = 0.17–1.63), andconditional growth from 0 to 1 years (OR = 1.88; 95% CI = 0.61–5.74).	6
Hussin et al. 2019	Cohort	Malaysia	729	60 + , mean = 69	50	Excluded those with multimorbidity at baseline	1,5 years	2 + diseases	Among those with no diseases at baseline, smoking (OR = 3.26; 95% CI = 1.49–7.12) and irregular involvement in food preparation (OR = 2.36; 95% CI = 1.08–5.18) were associated with multimorbidity incidence. Male sex (OR =	5

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									0.30; 95% CI = 0.12–0.72) was protective against multimorbidity incidence. No significant association was found for the following factors: age (OR = 0.97; 95% CI = 0.92–1.02); having 6 or less years of education (OR = 1.40; 95% CI = 0.56–3.03), and cognitive function assessed through visual reproduction (OR = 0.99; 95% CI = 0.99–1.00). Analyses were also carried out and reported looking at multimorbidity incidence among those with one disease at baseline.	
(Irshad and Dash, 2022)	Cohort	India	10,218	60 + , mean = 66	52	Excluded those with chronic diseases at baseline	7 years	2 + chronic conditions	There was an association between being aged 80 + years (OR = 3.23; 95% CI = 1.63–6.41) and developing multimorbidity, with a reference age of 60–69 years; no significant association was found for those 70–79 years old (OR = 1.21; 95% CI = 0.93–1.56). Compared to the richest, the rich (OR = 0.65; 95% CI = 0.49–0.86) middle (OR = 0.57; 95% CI = 0.40–0.80), poor (OR = 0.36; 95% CI = 0.24–0.52) and poorest (OR = 0.48; 95% CI = 0.29–0.81) had reduced odds for multimorbidity development. Compared to those practicing Hinduism, those practicing Islam (OR = 0.29; 95% CI = 0.13–0.65) and other religions (OR = 0.24; 95% CI = 0.11–0.55) had reduced odds of multimorbidity; no association was found for Christianity (OR = 0.84; 95% CI = 0.39–1.82). There were mixed results for alcohol consumption, living arrangement, and caste, and non-significant results for sex, urban residence, education, marital status, smoking status, and chewing habits.	5
Jackson et al. 2015	Cohort	Australia	4865	47 + , mean = 50	100	Excluded those with chronic diseases at baseline	9 years	Multimorbidity trajectories	Five multimorbidity trajectories emerged: 1) no morbidity, constant; 2) low morbidity, constant; 3) moderate morbidity, constant; 4) no morbidity, increasing; and 5) low morbidity, increasing. One unit increases in BMI (RRR = 1.10; 95% CI = 1.07–1.16) were associated with increased risk of being in the low morbidity, increasing trajectory compared to the no morbidity, constant trajectory. Overweight (RRR = 2.57; 95% CI = 1.56–4.24) and obesity (RRR = 4.28; 95% CI = 2.41–7.60) were also associated with greater risk of being in this trajectory; no such association was found for underweight. Having middle (RRR = 2.20; 95% CI = 1.21–4.01) and low (RRR = 2.37; 95% CI = 1.12–5.04) education, compared to high education were also associated with greater risk of belonging to the low morbidity, increasing trajectory. Physical activity, smoking, alcohol intake, occupation, and income management did not confer significant risk of belonging to the low morbidity, increasing trajectory. Analyses were also conducted and reported assessing these factors in relation to the other three trajectories with no morbidity as the reference trajectory.	6
Jackson et al. 2016	Cohort	Australia	4896	47–52, mean = 50	100	Excluded those with MM at baseline	12 years	Multimorbidity patterns	Five multimorbidity patterns were identified: psychosomatic, musculoskeletal, cardiometabolic, cancer, and respiratory. Unit increases in BMI were significantly associated with the musculoskeletal (OR = 1.07; 95% CI = 1.06–1.09) and cardiometabolic (OR = 1.07; 95% CI = 1.06–1.09) patterns, but not the cancer (OR = 0.95; 95% CI = 0.93–0.96) pattern, with no significant association to the psychosomatic or respiratory patterns. Analyses were also presented with BMI as a categorical variable showing	6

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									similar trends in significance. Compared to those with high physical activity, those with low physical activity were only more likely to belong to the musculoskeletal (OR = 1.23; 95% CI = 1.02–1.48) pattern, and those with no physical activity were only more likely to belong to the psychosomatic (OR = 1.41; 95% CI = 1.13–1.76), musculoskeletal (OR = 1.39; 95% CI = 1.11–1.74), and cancer (OR = 1.35; 95% CI = 1.08–1.69) patterns. No significant association was found for those with moderate physical activity compared to high physical activity. Ex-smokers were only more likely to belong to the respiratory pattern (OR = 1.23; 95% CI = 1.04–1.45) and current smokers were more likely to belong to the musculoskeletal (OR = 1.24; 95% CI = 1.01–1.54) and respiratory (OR = 1.74; 95% CI = 1.42–2.13) patterns. Non-drinkers were only significantly associated with the cardiometabolic (OR = 1.18; 95% CI = 1.02–1.37) pattern and no association was found for risky/high risk alcohol intake. No association was found for middle compared to high education, and low compared to high education was significantly associated with the psychosomatic (OR = 1.34; 95% CI = 1.03–1.75) and musculoskeletal (OR = 1.43; 95% CI = 1.10–1.87) patterns. Sometimes difficult compared to easy income management was significantly associated with the psychosomatic (OR = 1.31; 95% CI = 1.11–1.54) pattern and impossible/always difficult income management was associated with the psychosomatic (OR = 1.73; 95% CI = 1.37–2.18) and musculoskeletal (OR = 1.38; 95% CI = 1.09–1.75) patterns. Occupation showed no significant associations to any pattern.	
Katikireddi et al. 2017	Cohort	Scotland	4338	18–75	54	N/A	20 years	2 + chronic conditions	Most (OR = 1.46; 95% CI = 1.26–1.68) and intermediate (OR = 1.28; 95% CI = 1.12–1.47), compared to low, area-based deprivation; former (OR = 1.35; 95% CI = 1.18–1.55) and current (OR = 1.57; 95% CI = 1.37–1.80) smoking; no alcohol consumption (OR = 1.49; 95% CI = 1.26–1.76), no fruit or vegetable consumption (OR = 1.45; 95% CI = 1.24–1.71); and being overweight (OR = 1.26; 95% CI = 1.12–1.41), obese (OR = 1.43; 95% CI = 1.21–1.68), and morbidly obese (OR = 1.98; 95% CI = 1.50–2.62) were associated with increased odds of developing multimorbidity. No significant associations were found for excessive alcohol consumption compared to normal alcohol consumption, eating fruit some days versus eating fruit every day, physical activity, or being underweight. Increased risk factors conferred greater odds of developing multimorbidity.	6
Khanolkar et al. 2021	Cohort	United Kingdom	3723	36	49	N/A	7–33 years	Multimorbidity trajectories	At age 69, there was an increased accumulation of chronic conditions in skilled manual (β = 0.39; 95% CI = 0.10–0.68) and partly skilled/unskilled (β = 0.39; 95% CI = 0.06, 0.72), compared to professional/intermediate, childhood social classes; a similar association was found at age 63, with no significant associations at age 36, 43, or 53. Similar associations were found for adulthood social classes at age 69 (skilled manual: β = 0.33; 95% CI = 0.03, 0.63, partly skilled/unskilled: β = 0.83; 95% CI = 0.45, 1.20) and age	7

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									63, with significant positive association for partly skilled/ unskilled also at ages 36, 43, and 53. Compared to those with a university degree, no educational attainment (β = 1.08; 95% CI = 0.67, 1.49) and having a GCE/leaving certificate (β = 0.35; 95% CI = 0.03, 0.67) were associated with accelerated multimorbidity accumulation; not having an education was also associated with accelerated multimorbidity accumulation at age 53 and 63, but no association were found at any other ages for the GCE/ leaving certificate. Women (β = −0.24; 95% CI = −0.46, −0.03) had lower rates of multimorbidity accumulation at age 69, higher rates at age 36 (β = 0.09; 95% CI = 0.02–0.15) and age 43 (β = 0.15; 95% CI = 0.06–0.24), and no significant association at ages 53 and 63.	
Ki et al. 2017	Cohort	South Korea	9971	30 + , mean = 53	54	N/A	3 years	Chronic disease count	Interactions between age (30 s, 40 s, 50 s, 60 s, 70 s, 80 s) and poverty, employment status, and educational attainment were examined in association with disease count. No risk factor was significantly associated across all ages. Significant increased risk of 2 diseases was found for poverty in one's 60 s (OR = 1.85; 95% CI = 1.08–3.17); not being employed in one's 40 s (OR = 1.82; 95% CI = 1.16–2.86) to 70 s (OR = 2.80; 95% CI = 1.27–6.17); and low education in one's 40 s (OR = 1.71; 95% CI = 1.03–2.84) to 60 s (OR = 1.90; 95% CI = 1.09–3.32). Analyses were also conducted with 3 + diseases and different disease groups as outcomes.	5
Kivimäki et al. 2017	Cohort	United States, Europe	120,813	35–103, mean = 51	59	Excluded those with diabetes, coronary heart disease, or stroke at or before study baseline	mean follow-up of 10·7 years	Cardiometabolic multimorbidity	Being overweight (OR = 2.0; 95% CI = 1.7–2.4), mildly obese (OR = 4.5; 95% CI = 3.5–5.8), and severely obese (OR = 14.5; 95% CI = 10.1–21.0) were each associated with increased cardiometabolic risk; being underweight was not a significant factor. Additional results by assessment of multimorbidity and assessment of BMI, as well as stratified by sex, age, and ethnicity, were reported.	7
Li et al. 2021	Cohort	Canada	29,838	18 +	51	Excluded those with physical illnesses	10 years	Two physical illnesses (among those with one physical illness)	Older age was associated with increased risk of multimorbidity development among women (i.e., 65 + vs 18–34 years: HR = 4.05; 95% CI = 3.45–4.76) and men (i.e., 65 + vs 18–34 years: HR = 5.93; 95% CI = 4.72–7.44). Compared to those with < $30,000 income, income between $50,000-$79,999 (HR = 0.87; 95% CI = 0.78–0.97) or ≥ $80,000 (HR = 0.88; 95% CI = 0.78–0.99) among women and income between $30,000-$49,999 (HR = 0.87; 95% CI = 0.76–0.99) among men was protective against multimorbidity development. Compared to normal weight, overweight (women: HR = 1.22; 95% CI = 1.12–1.34, men: HR = 1.24; 95% CI = 1.12–1.37) and obesity (women: HR = 1.37; 95% CI = 1.22–1.53, men: HR = 1.62; 95% CI = 1.44–1.83) were associated with multimorbidity development among men and women, but underweight was not. Underlying health status was associated with multimorbidity among men (HR = 1.27; 95% CI = 1.14–1.43) and women (HR = 1.43; 95% CI = 1.29–1.58). Among men, being an immigrant (HR = 1.15; 95% CI = 1.05–1.27) and smoking (HR = 1.25; 95% CI = 1.14–1.36) were associated with multimorbidity; this was not found among women.Depression was associated with	7

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									multimorbidity development among women (HR = 1.16; 95% CI = 1.02–1.33), but not men. No significant findings were detected among men or women for the association between marital status, alcohol use, physical activity, or having a regular medical doctor and incident multimorbidity.	
Li et al. 2022	Cohort	United Kingdom	State 1 (no cardiometabolic diseases at baseline): 357 433; stage 2 (one cardiometabolic disease at baseline): 35 034	37–73	Stage 1: 56; stage 2: 38	Excluded those with cardiometabolic multimorbidity, emphysema, asthma, or other chronic lung disease at baseline.	Median 11.2 years	Cardiometabolic multimorbidity (2 + cardiometabolic diseases)	In those without any cardiometabolic disease at baseline, compared to those with the lowest quartile of forced vital capacity (FVC), those with the highest quartile of FVC (HR = 0.541; 95% CI: 0.483–0.606) had protective hazards against cardiometabolic multimorbidity. Additional analyses for incidence of cardiometabolic multimorbidity were also carried out using multistate models and multinomial logistic regression (also by sex and age) with diabetes, stroke, and coronary heart disease as additional outcomes. All analyses were repeated and reported among those with one cardiometabolic disease at baseline.	8
Lin et al. 2021	Cross-sectional	China	9440	45 + , mean = 60	52	N/A	From childhood to adulthood	2 + diseases	Those with 2 (OR = 1.39; 95% CI = 1.19–1.62), 3 (OR = 1.71; 95% CI = 1.43–2.05), or 4 + (OR = 2.03; 95% CI = 1.70–2.41) adverse childhood events (physical abuse, emotional neglect, household substance abuse, household mental illness, domestic violence, incarcerated household member, parental separation or divorce, unsafe neighbourhood, bullying, parental death, sibling death, parental disability) had increased risk of multimorbidity; no significant association was found for 1 adverse childhood event. Subgroup analyses by age, sex, childhood economic hardship, educational attainment, and household expenditure were reported.	7
Liu et al. 2022	Cohort	United Kingdom	3977	50 +	51	Excluded participants with multimorbidity at baseline	median follow-up of 7.8 years	2 + chronic diseases	Low hand grip strength was associated with multimorbidity in women (HR = 1.19; 95% CI = 1.03–1.38) and men (HR = 1.20; 95% CI = 1.20; 1.03–1.40). Hand grip strength asymmetry was associated with multimorbidity in women (HR = 1.23; 95% CI = 1.07–1.41), but no statistically significant association was found in men (HR = 0.94; 95% CI = 0.81–1.09). Analyses were also carried out and reported with hand grip strength asymmetry dominance and categories of hand grip strength asymmetry as factors.	7
Lu et al. 2021	Cohort	China	Stage 1 (0 CVD at baseline): 8807; Stage 2 (1 CVD at baseline): 1714	45 +	Stage 1: 52; stage 2: 59	Excluded those with 2 + cardiometabolic diseases at baseline	4 years	2 + cardiometabolic diseases	For those with no diseases at baseline, high values of waist-to-height ratio (OR = 1.76; 95% CI = 1.05–2.97), waist circumference (OR = 2.06; 95% CI = 1.29–3.27), and waist divided by height^0.5 (OR = 1.81; 95% CI = 1.16–2.83), but not body mass index (OR = 1.48; 95% CI = 0.98–2.24) was associated with cardiometabolic multimorbidity incidence. Analyses were also conducted looking at cardiometabolic multimorbidity incidence in those with 1 disease at baseline.	7
Melis et al. 2014	Cohort	Sweden	390	78 +	75	Excluded those with 2 + chronic conditions	3 years	2 + chronic conditions	In those without chronic diseases at baseline, worse cognitive abilities (OR = 1.22; 95% CI = 1.00–1.48) were associated with multimorbidity development; this was not found in those with one chronic disease at baseline. Among those with one chronic disease at baseline, higher age (OR = 1.09; 95% CI = 1.01–1.17) was associated with multimorbidity development; this was not found in those with no chronic diseases at baseline. No significant associations between no or one chronic disease at baseline	7

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									with multimorbidity were found for the following factors: sex, education, number of disabilities, hemoglobin, erythrocyte sedimentation rate, white blood cell count, higher diastolic blood pressure, physical activity, depressive symptoms, smoking, alcohol consumption, and body mass index.	
Moin et al. 2021	Cohort	Canada	26,808	20–95	49	Excluded those with multimorbidity at baseline	16 years	2 + and 3 + chronic conditions	The following results were restricted to those aged 20–64 years. Female sex (HR = 1.12; 95% CI = 1.05–1.20) and older age i.e. age 35–49 vs 20–34 years (HR = 1.63; 95% CI = 1.50–1.76) were associated with increased hazards of multimorbidity. Compared to those with excellent self-perceived health, those with less than excellent i.e., poor (HR = 1.82; 95% CI = 1.32–2.51) self-perceived health had increased risk of multimorbidity. Compared to those in the most walkable neighbourhoods, those in the least walkable neighbourhoods (HR = 1.14; 95% CI = 1.02–1.28) had increased hazards of multimorbidity development. Higher education i.e. high school education (HR = 0.82; 95% CI = 0.69–0.98) was associated with reduced risk of multimorbidity compared to those with less than high school education. Those with income less than $20,000/year (HR = 0.85; 95% CI = 0.73–0.99) had reduced risk of multimorbidity compared to those with an income of $80,000 + /year, but no significant associations for the intermediate incomes. Non-significant results were obtained for marital status, smoking, physical activity, and life stress. Analyses were also conducted and reported for those aged 65–95 years, and stratified by neighborhood walkability quintiles and material deprivation.	7
Mounce et al. 2018	Cohort	England	4564	50 +	56	N/A	10 years	Multimorbidity (2 + conditions in those with no diseases at baseline), 1 + disease regardless of disease status at baseline	The following results are for incident multimorbidity in those with no conditions at baseline. Compared to those aged 50–54 years, those aged 55–59 years (HR = 1.44; 95% CI = 1.05–1.99), 60–64 years (HR = 1.85; 95% CI = 1.31–2.61), 65–69 years (HR = 2.93; 95% CI = 2.08–4.13), and ≥ 70 years (HR = 2.58; 95% CI = 1.83–3.64) had a higher risk of incident multimorbidity. Those with an external locus of control (HR = 1.41; 95% CI = 1.10–1.82) also had a higher risk for incident multimorbidity. Those in the lowest wealth quintile (ref = highest wealth quintile; HR = 2.19; 95% CI = 1.50–3.19) had a higher risk for incident multimorbidity, with no significant associations found for the middle three wealth quintiles. Obesity (HR = 1.92; 95% CI = 1.43–2.59) was a risk factor for multimorbidity, but overweight (HR = 1.15; 95% CI = 0.87–1.52) was not. No association was found for the following factors: female sex (HR = 1.14; 95% CI = 0.86–1.50), living alone (HR = 0.93; 95% CI = 0.71–1.21), intermediate education (ref = higher education; HR = 0.95; 95% CI = 0.73–1.23), no educational qualification (ref = higher education; HR = 0.73; 95% CI = 0.53–1.00), past smoking (HR = 1.12; 95% CI = 0.88–1.43) and current smoking (HR = 1.22; 95% CI = 0.87–1.70), medium physical activity (HR = 1.3; 95% CI = 1.00–1.70) and low physical activity (HR = 1.43; 95% CI = 1.02–2.00), and social isolation (HR = 1.16; 95% CI = 0.77–1.72). The same analyses were conducted and reported for those	7

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									starting with any number of conditions with an outcome of at least one new condition.	
Pérez et al. 2020	Cohort	Sweden	2596	60 + , mean = 73	61	N/A	6 years	Rate of multimorbidity development	Increased levels of baseline total serum glutathionine (ß = −0.144; p-value < 0.001) were associated with a lower rate of multimorbidity development.	7
Petermann-Rocha et al. 2021	Cohort	United Kingdom	316,980	37–73	53	Excluded those with cancer, CVD, and respiratory disease at baseline	Median 10.9 years	Sarcopenia + CVD, respiratory disease, or cancer	Sarcopenia and pre-frailty were significantly associated with cardiovascular disease (HR = 1.45; 95% CI = 1.24–1.71), respiratory disease (HR = 1.36; 95% CI = 1.20–1.54), and chronic obstructive pulmonary disease (HR = 1.76; 95% CI = 1.40–2.20), but not cancer. Sarcopenia and frailty were significantly associated with cardiovascular disease (HR = 1.68; 95% CI = 1.22–2.30), respiratory disease (HR = 1.77; 95% CI = 1.40–2.24), and chronic obstructive pulmonary disease (HR = 1.63; 95% CI = 1.10–2.43), but not cancer.	7
Peterson et al. 2021	Cohort	United States	12,618	51 +	61	N/A	8 years	2 + chronic diseases	Lower grip strength (per 0.05 unit) was associated with increased multimorbidity risk in men (OR = 1.14; 95% CI = 1.08–1.20) and women (OR = 1.14; 95% CI = 1.07–1.21). Compared to age < 65 years, age 65–79 (OR = 1.55; 95% CI = 1.27–1.88) and > 80 years (OR = 1.97; 95% CI = 1.32–2.93) were more associated with developing multimorbidity in women; only age 65–79 years (OR = 1.67; 95% CI = 1.32–2.10) was in men. Smoking was associated with multimorbidity in women (OR = 1.33; 95% CI = 1.01–1.75) but not men. Having a net worth in quartile 4 (OR = 0.70; 95% CI = 0.51–0.96) or quartile 3 (OR = 0.73; 95% CI = 0.54–0.99), but not quartile 2, compared to quartile 1 was protective against multimorbidity in women; no income quartiles were found to be significantly associated with multimorbidity development in men. Elevated high sensitivity C-reactive protein was associated with increased multimorbidity risk in women (OR = 1.60; 95% CI = 1.26–2.02), but not men. The following were not significant multimorbidity predictors in men or women: marital status, race, and education.	7
(Poole and Steptoe, 2018)	Cohort	England	2472	50 + , mean = 63	51	Excluded those with certain physical illnesses at baseline	10 years	Chronic disease count	Age (RR = 1.02; 95% CI = 1.01–1.02), BMI (RR = 1.03; 95% CI = 1.02–1.05), Hypertension (RR = 1.18; 95% CI = 1.06–1.32), and depressive symptoms (RR = 1.05; 95% CI = 1.02–1.08) predicted greater incident chronic disease burden. No association was found for the following factors: sex, ethnicity, living arrangement, wealth, smoking, alcohol consumption, physical activity, and cognitive function.	6
Qiao et al. 2021	Cohort	China, Europe	CHARLS: 7883; SHARE: 20558	CHARLS: 45 + , mean = 56; SHARE: 50 + , mean = 62	CHARLS: 49; SHARE: 55	No multimorbidity at baseline	4 years	2 + chronic physical conditions	Those impaired in activities of daily living (CHARLS: OR = 2.58; 95% CI = 1.97–3.38, SHARE: OR = 3.72; 95% CI = 2.82–4.91) and instrumental activities of daily living (CHARLS: OR = 1.46; 95% CI = 1.19–1.80, SHARE: OR = 2.44; 95% CI = 1.94–3.08) had increased risk of developing 2 chronic physical diseases. Results were also shown for 3 and 4 + diseases, and stratified by gender.	6
Qiao et al. 2022	Cohort	China	7056 (part one of study)	45 +	50	No multimorbidity at baseline	4 years	2 + chronic diseases	Depression was associated with increased risk of 2 diseases (RR = 1.64; 95% CI = 1.36–1.99). Analyses were also conducted looking at the incidence of 3 and 4 + diseases. Subgroup analyses by gender, age, obesity, smoking, and living place were reported.	7

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
Quiñones et al. 2019	Cohort	United States	8331	51–55, mean = 53	57	Excluded those with chronic diseases at baseline	16 years	Multimorbidity accumulation	Black participants (IRR = 0.99; 95% CI = 0.98–1.00) had slower chronic disease accumulation and Hispanic participants (IRR = 1.02; 95% CI 1.00–1.03) had faster chronic disease accumulation than white participants. Higher BMI (IRR = 1.01; 95% CI = 1.01–1.01) and female sex (IRR = 1.05; 95% CI = 1.00–1.09) were associated with greater accumulation of chronic diseases; educational attainment (IRR = 0.96; 95% CI = 0.94–0.95) was associated with slower chronic disease accumulation.	6
Rocca et al. 2017	Cohort	United States	1547	Median = 44	100	Excluded those with chronic conditions at baseline	Median of 14 years	Multimorbidity accumulation	Bilateral oophorectomy (HR = 1.18; 95% CI: 1.09–1.28) was associated with increased risk of multimorbidity accumulation. Analyses were also conducted by age strata and for single-year incidence rates of multimorbidity after bilateral oophorectomy. Analyses stratified by age at oophorectomy, estrogen therapy, surgical indication, calendar year, and smoking status were also conducted and reported.	7
Ryan et al. 2018	Cohort	Ireland	4823	50 +	54	N/A	2 years	2 + chronic conditions	Compared to those aged 50–59, those of older ages, i.e. 60–69 years (RR = 1.30; 95% CI = 1.11–1.52) had increased risk of multimorbidity. Compared to those with normal weight and underweight, obesity (RR = 1.26; 95% CI = 1.05–1.51) was associated with increased risk of multimorbidity, but no association was found for overweight. Stronger grip strength (RR = 0.98; 95% CI = 0.97–0.99) and faster gait speed (RR = 0.67; 95% CI = 0.49–0.90) were associated with reduced risk of multimorbidity. No relation between the following factors and multimorbidity incidence was detected: education, smoking, state support, and physical activity. Analyses were also conducted looking at worsening multimorbidity in those with multimorbidity at baseline.	8
Schäfer et al. 2019	Cohort	Germany	3189	65–85, mean = 74	59	Included those with 3 + diseases at baseline	5 years	Progression of multimorbidity severity	Age (β = 0.12; 95% CI = 0.09, 0.15) and smoking history in pack years (β = 0.011; 95% CI = 0.003, 0.018) were risk factors for progression of multimorbidity severity. Female sex (β = −0.92; 95% CI = −1.31, −0.53), medium education (ref = low education; β = −0.79; 95% CI = −1.18, −0.40), high education (ref = low education; β = −1.10; 95% CI = −1.66, −0.53), household disposable income (β = −0.57; 95% CI = −0.97, −0.17), physical activity (β = −0.31; 95% CI = −0.38, −0.24), alcohol consumption (β = −0.19; 95% CI = −0.28, −0.10), and perceived social support (β = −0.31; 95% CI = −0.56, −0.07) were protective factors against development of multimorbidity severity. The same analyses were also conducted and reported for multimorbidity severity specific to a cardiovascular and metabolic disorders multimorbidity cluster as well as a cluster including anxiety, depression, somatoform disorders, and pain-related disorders.	7
Schramm et al. 2022	Cohort	Denmark	102,818	32–56	48	Excluded those with multimorbidity at baseline	8 years	Multimorbidity patterns	Eight multimorbidity classes emerged: 1) few or no chronic conditions; 2) heart diseases, hypertension, high cholesterol; 3) musculoskeletal conditions; 4) diabetes, hypertension, high cholesterol; 5) asthma, allergy; 6) psychiatric conditions, epilepsy; and 7) many chronic conditions. Risk factors for belonging to the many chronic conditions pattern included: medium (OR = 2.02; 95% CI =	7

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									1.69–2.41) or short (OR = 3.52; 95% CI = 2.93–4.22) education, and medium (OR = 1.72; 95% CI = 1.34–2.19) or short (OR = 2.12; 95% CI = 1.65–2.70) parental education. Results were also presented for parental education, adjusted for individual education.	
Seo et al. 2019	Cohort	South Korea	6889	18 + , mean = 45	40	Excluded those with 2 + chronic diseases	Average of 3.6 years	2 + chronic diseases	Physical inactivity was associated with increased risk of multimorbidity in four different years (i.e. 2012) in men (OR = 2.66; 95% CI = 2.22–3.19) and women (OR = 2.31; 95% CI = 1.93–2.77). Compared to college or more, elementary (women: OR = 2.95; 95% CI = 2.12–4.12, men: OR = 1.69; 95% CI = 1.35–2.12) and high school education (women: OR = 2.53; 95% CI = 1.88–3.43, men: OR = 1.48; 95% CI = 1.26–2.38) were associated with higher multimorbidity incidence. Compared to those aged 55 + years, being aged 45–55 (women: OR = 0.42; 95% CI = 0.34–0.51, men: OR = 0.58; 95% CI = 0.49–0.68) and < 45 years (women: OR = 0.17; 95% CI = 0.13–0.22, men: OR = 0.30; 95% CI = 0.24–0.37) were associated with reduced multimorbidity incidence. Being in the mid 40% of income compared to the bottom 40% was protective against multimorbidity incidence in women (OR = 0.84; 95% CI = 0.74–0.97); this was not significant in men, and being in the top 20% was not significant for either gender. Being married was associated with increased multimorbidity incidence (OR = 1.85; 95% CI = 1.43–4.11), and currently smoking (OR = 0.74; 95% CI = 0.65–0.85) was protective against multimorbidity in men; no significant associations were found for either factor in women. Having unmet care needs (OR = 1.20; 95% CI = 1.06–1.40) was associated with multimorbidity incidence and not having health care needs (OR = 0.51; 95% CI = 0.30–0.84) was protective against multimorbidity in women; no significant associations were found for either factor in men. The following were not significant factors for multimorbidity incidence in men or women: having a standard employment-based job, non-autonomy at work, occupation type, and having school age children.	7
Shang et al. 2020 (A)	Cohort	Australia	98,958	45–64	55	Excluded those with cancer (except non-melanoma skin cancer), heart disease, stroke, depression, anxiety, dementia, and Parkinson's disease, severe diseases	Mean 8.9 years	Co-occurrence of cancer and mental disorders	Higher income; for instance, those with income an of 70,000 + AUD (HR = 0.71; 95% CI = 0.60–0.84) compared to those with < 20,000 AUD were at lower risk of multimorbidity. Education was also protective; high school (HR = 0.82; 95% CI = 0.71–0.95) and university (HR = 0.71; 95% CI = 0.60–0.84) conferred lower multimorbidity risk. Compared to excellent self-rated health and quality of life, lower levels, i.e. fair/poor self-rated health (HR=1.99; 95% CI = 1.64–2.41) and fair/poor self-rated quality of life (HR = 2.04; 95% CI = 1.68–2.49) were associated with increased multimorbidity risk. Compared to low psychological distress, increased levels, for instance high psychological distress (HR = 2.14; 95% CI: 1.77–2.59) were associated with increased multimorbidity risk. Hypertension (HR = 1.24; 95% CI = 1.12–1.37), arthritis (HR = 1.49; 95% CI = 1.25–1.77), diabetes (HR = 1.48; 95% CI = 1.26–1.75), asthma (HR = 1.29; 95% CI = 1.12–1.48), and family history of cancer (HR = 1.14; 95% CI = 1.05–1.24) and depression (HR = 1.20; 95% CI =	7

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									1.06–1.36) were also risk factors for multimorbidity. Former (HR = 1.29; 95% CI = 1.17–1.41) and current (HR = 1.69; 95% CI = 1.47–1.95) smoking, and obesity (HR = 1.17; 95% CI = 1.04–1.32), but not overweight (HR = 1.11; 95% CI = 1.00–1.24), were associated with increased multimorbidity risk. No association was found for sleep duration, physical activity, or vegetable, fruit, or chicken intake.	
Shang et al. 2020 (B)	Cohort	Australia	53,867	45–64	57	Excluded those with chronic diseases	9 years	2 + , 3 + , 4 + chronic diseases	Overweight (HR = 1.44; 95% CI = 1.35–1.53) and obesity (HR = 2.26; 95% CI = 2.10–2.43) were associated with 2 + diseases in men but not in women. An increasing number of health factors (including BMI between 18.5 and 24.9 kg/m^2, fruit intake≥2 servings/day, vegetable intake≥3 servings/day, red meat intake≤1 serving/week, chicken in- take≤1 serving/week, physical activity≥5 sessions/week, alcohol consumption between 1 and 4 drinks/week, never smoking, none-passive smoking, and sleep duration between 7 and 9 h/day) were protective against 2 + diseases in both men (HR = 0.86; 95% CI = 0.85–0.87) and women (HR = 0.84; 95% CI = 0.83–0.85). Factors associated with 3 + and 4 + diseases were also reported.	7
Singh-Manoux et al. 2018	Cohort	England	8270	Mean = 50	32	Excluded those with cardiometabolic disease before age 50	Mean 23.7 years	2 + cardiometabolic diseases	Alcohol abstention or heavy alcohol consumption (HR = 1.30; 95% CI = 1.09–1.56) and smoking (HR = 1.57; 95% CI = 1.28–1.92) were associated with increased risk of transitioning from 1 to 2 cardiometabolic diseases; no association was found for: physical inactivity,poor diet, hypertension, overweight/obesity, total cholesterol > 55 mmol/L, and family history of diabetes or CVD. Risk factors were also explored as aggregated measures. Lower occupational position (HR = 2.43; 95% CI = 1.75–3.37), unhealthy behaviour (smoking, alcohol abstention or heavy alcohol consumption, poor diet, physical inactivity; HR = 3.02; 95% CI = 2.13–4.29), and unhealthy clinical profile (hypertension, overweight/obesity, hypercholesterolemia, family history; HR = 3.68; 95% CI = 2.49–5.43) were each associated with increased risk of cardiometabolic multimorbidity.	8
Sutin et al. 2013	Cohort	United States	2008	19–96, mean = 57	49	N/A	21 years	Charlson Comorbidity Index	Among those living with disease at baseline, extraversion (OR = 1.26; 95% CI = 1.03–1.55), impulsivity (OR = 1.36; 95% CI = 1.08–1.71), warmth (OR = 1.29; 95% CI = 1.05–1.60), and positive emotions (OR = 1.24; 95% CI = 1.01–1.52) were associated with getting more ill over follow-up; conscientiousness (OR = 0.77; 95% CI = 0.62–0.96), order (OR = 0.77; 95% CI = 0.62–0.96), self-discipline (OR = 0.81; 95% CI = 0.67–0.98), and deliberation (OR = 0.78; 95% CI = 0.63–0.97) were associated with decreased risk of developing more disease.	6
Tajik et al. 2022	Cohort	Finland	1728	42, 48, 54, 60; mean = 54	0	Excluded those with a history of stroke, diabetes, and CHD at baseline	Mean of 22.4 years	Cardiometabolic multimorbidity subgroups: 1) CHD + stroke; 2) CHD + Type 2 DM; 3) Stroke + Type 2 DM; 4) CHD + stroke + Type 2 DM	Higher triglyceride (HR = 1.99; 95% CI = 1.12–3.53) and very-low-density lipoprotein-cholesterol (HR = 1.79; 95% CI = 1.04–3.11) were associated with increased risk of developing the coronary heart disease and type 2 diabetes cardiometabolic multimorbidity subgroup; no significant association was found for total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, non-high-density lipoprotein-cholesterol, apolipoprotein A1, or apolipoprotein B. None of the above	8

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									factors were significantly associated with developing the coronary heart disease and stroke; stroke and type 2 diabetes; or coronary heart disease, stroke, and type 2 diabetes cardiometabolic multimorbidity subgroups. Analyses were also presented examining different combinations of risk factors.	
Tomasdottir et al. 2016	Cohort	Norway	20,365	20–59, mean = 41	54	Excluded participants with multimorbidity at baseline	Mean 11 years	2 + chronic conditions	Life satisfaction below satisfied, i.e. somewhat satisfied (RR = 1.16; 95% CI = 1.10–1.23), compared to being satisfied, was associated with higher risk of multimorbidity. Not living a meaningful life (RR = 1.15; 95% C I = 1.06–1.25); not having enough friends (RR = 1.10; 95% CI = 1.03–1.18); sleeping problems affecting work (RR = 1.34; 95% CI = 1.22–1.46); not always feeling calm and good, i.e. never, (RR = 1.47; 95% CI = 1.06–2.05); and less than very good self-rated health, i.e. poor self-rated health (RR = 2.23; 95% CI = 1.50–3.23), were associated with multimorbidity development. Financial worries, i.e. often occurring (RR = 1.46; 95% CI = 1.25–1.70), were associated with increased risk of multimorbidity. Mixed results were obtained for positive self-opinion, distrusting neighbours, and enjoying work. No association was found between boiling with anger and multimorbidity incidence.	6
Vall Castelló et al. 2020	Cohort	Europe	167,698	50–80, mean = 65	56	N/A	6 years	Chronic cardiometabolic disorder accumulation	Adherence to the Mediterranean diet ($\beta = -0.0456$; $p < 0.05$), female sex ($\beta = -0.0862$; $p < 0.01$), tertiary education ($\beta = -0.2215$; $p < 0.01$), secondary education ($\beta = -0.1197$; $p < 0.01$), active sports ($\beta = -0.1715$; $p < 0.01$), never having smoked daily ($\beta = -0.0537$; $p < 0.01$), and being employed ($\beta = -0.1303$; $p < 0.01$) were protective factors against chronic metabolic disorders incidence. Age ($\beta = 0.0512$; $p < 0.01$) and Hispanic ethnicity ($\beta = 0.1007$; $p < 0.05$) were risk factors for chronic metabolic disorders incidence. Not living with a partner ($\beta = -0.0051$; $p > 0.1$) and household income ($\beta = -0.0000$; $p > 0.05$) were not found to be significant factors. Age and household income were also explored as quadratic terms.	6
van den Akker et al. 2000	Nested case-control	Netherlands	3745	20 + , mean = 53	49	N/A	3 years	New multimorbidity: 2 + new diseases, controls: no new diseases in selection period	Compared to those aged 20–29 years, those aged 70–79 (OR = 1.79; 95% CI = 1.12–2.84) and 80 + (OR = 1.87; 95% CI = 1.04–3.36) years, had increased risk of multimorbidity development; no association was found for those aged 30–39–60–69 years. Those with 2 + (OR = 1.49; 95% CI = 1.18–1.88), but not 1, baseline conditions; as well as 1 (OR = 1.37; 95% CI = 1.04–1.79), but not 2 + , long term difficulties had increased multimorbidity risk. Negative life events 2 years before study start (OR = 1.28; 95% CI = 1.02–1.62) were associated with increased multimorbidity risk; no association was found for positive events. Having an external locus of control (OR = 1.40; 95% CI = 1.12–1.75) was associated with increased multimorbidity risk. Compared to low blue collar, high white occupational class (OR = 1.48; 95% CI = 1.02–2.15) was associated with increased multimorbidity risk; no association was found for high blue, low white, or other classes. Having an active coping style (OR = 1.25; 95% CI = 1.01–1.55) was associated with increased multimorbidity risk. High (OR = 0.60; 95% CI = 0.41–0.88), but not secondary (OR = 0.81;	

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									95% CI = 0.64–1.03) education, and positive occupational status (OR = 0.63; 95% CI = 0.47–0.84), were protective against multimorbidity. No significant association was found for gender, type of health insurance, religion, body mass index, smoking, sports, family disease history, or social network.	
van den Akker et al. 2001	Cohort	Netherlands	3551	20 + , mean = 53	49	N/A	2 years	New multimorbidity (2 + new diseases), ref = (Xu et al., 2017) new disease	Compared to those aged 20–29 years, those aged 40 + years had increased odds for multimorbidity development (i.e. OR for age 40–49 = 3.67; 95% CI = 1.21–11.2), but no statistically significant association was found for those aged 30–39 years. Women (OR = 0.59; 95% CI = 0.45–0.77) had lower odds of multimorbidity development. No significant association was found for education level, insurance type, or disease count at baseline. Having an internal locus of control (OR = 0.73; 95% CI = 0.54–0.99) and a social network with 5 or more people (OR = 0.41; 95% CI = 0.21–0.83) were associated with reduced odds of multimorbidity development, and living alone (OR = 1.48; 95% CI = 1.03–2.13) was associated with increased odds of multimorbidity development. No association was detected for the remaining psychological characteristics: coping styles, positive and negative life events, external and chance loci of control, long-term difficulties, living with others, and social network below five.	7
Waller et al. 2010	Cohort	Finland	95 twin pairs	47–79, mean = 58	57	Excluded those with chronic diseases (except hypertension)	30 years	2 + chronic diseases	Physical activity was associated with reduced risk of multimorbidity among monozygotic twin pairs (OR = 0.14, p-value = 0.031), but not twin pairs in general (OR = 0.54; p-value = 0.19).	7
Wikström et al. 2015	Cohort	Finland	32,972	25–64	52	Excluded participants with multimorbidity at baseline	10 years	2 chronic conditions	Body mass index per kg/m2 increase (men: OR = 1.11; 95% CI = 1.08–1.14, women: OR = 1.08; 95% CI = 1.05–1.11), current smoking (men: OR = 2.68; 95% CI = 2.10–3.41, women: OR = 2.55; 95% CI = 1.76–3.71), and low physical activity (men: OR = 1.34; 95% CI = 1.03–1.73, women: OR = 1.62; 95% CI = 1.14–2.30) were associated with higher multimorbidity incidence. Blood pressure per 10 mm Hg increase (OR = 1.14; 95% CI = 1.07–1.20) and low education (OR = 1.40; 95% CI = 1.02–1.91) were only significant risk factors in men. Cholesterol and fruit and vegetable consumption were non-significant in both genders.	8
Willroth et al. 2021	Cohort	Japan, United States	3 cohorts: 1. Midlife in the U.S. (MIDUS) core sample (n = 2692), 2. MIDUS Milwaukee African American sample (n = 248), 3. Midlife in Japan (MIDJA) sample (n = 644)	MIDUS core sample: 30–84; MIDUS Milwaukee African American sample: 34–82; MIDJA sample: 30–79	MIDUS core sample: 55; MIDUS Milwaukee African American Sample: 51; MIDJA sample: 55	N/A	4–9 years	2 + chronic conditions	Higher sense of purpose levels and were associated with reduced chronic conditions in the MIDUS core sample (β = −0.10; 95% CI = −0.13, −0.06) and MIDJA sample (β = −0.13; 95% CI = −0.20, −0.05), as were higher change in sense of purpose levels (MIDUS: β = −0.10; 95% CI = −0.13, −0.06; MIDJA: β = −0.08; 95% CI = −0.15, −0.005). Significant associations were not detected for the MIDUS Milwaukee African American sample.	6
Xu et al. 2018	Cohort	Australia	11,941	45–50	100	Excluded those with prior history of	20 years	2 + cardiometabolic diseases	Being born outside of Australia (OR = 1.61; 95% CI = 1.26–2.05) and having hypertension (OR = 2.19; 95% CI = 1.74–2.75) were associated with increased multimorbidity	7

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Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
						cardiometabolic conditions			risk. Being separated/divorced/widowed (OR = 1.55; 95% CI = 1.21–1.98) was associated with increased multimorbidity risk; no association was found for never being married. Compared to university education, having no qualifications (OR = 1.45; 95% CI = 1.01–2.10) was associated with increased multimorbidity risk; no association was found for trade/apprenticeship/diploma or high school certificate. Finding it always difficult or impossible to manage one's income (OR = 1.72; 95% CI = 1.31–2.26) was associated with increased multimorbidity risk; no association was found for sometimes having difficulties with income management. Being overweight (OR = 1.77; 95% CI = 1.30–2.43) or obese (OR = 3.01; 95% CI = 2.21–4.08) was associated with increased multimorbidity risk; no association was found for being underweight. Being sedentary (OR = 1.38; 95% CI = 1.02–1.86) was associated with increased multimorbidity risk; no association was found for moderate or low, compared to high, physical activity. Current smoking (OR = 1.78; 95% CI = 1.31–2.42) was a multimorbidity risk factor; no association was found for past smoking. Depression/anxiety (OR = 1.46; 95% CI = 1.17–1.83), asthma (OR = 1.34; 95% CI = 1.04–1.72), cancer (OR = 1.49; 95% CI = 1.11–1.99), arthritis (OR = 1.45; 95% CI = 1.13–1.86), and osteoporosis (OR = 1.45; 95% CI = 1.07–1.96) were associated with increased multimorbidity risk; no association was found for COPD. No significant association with multimorbidity was found for age or area of residence.	
Xu et al. 2019 (A)	Cohort	Australia	7357	45–50	100	Excluded those with chronic diseases at baseline	20 years	0–2 diseases, 1–2 + diseases, 2 + to more diseases	Being overweight (OR = 1.27; 95% CI = 1.18–1.36), obese (OR = 1.64; 95% CI = 1.49–1.79), and very obese (OR = 1.81; 95% CI = 1.59–2.06) were each associated with multimorbidity accumulation; being underweight (OR = 0.78; 95% CI = 0.59–1.03) was not a significant risk factor; similar results were found when BMI categories were time-varying. High (>+5%) short term weight gain (OR = 1.24; 95% CI; 1.07–1.44) was a risk factor for multimorbidity accumulation; no association was found for other types of short-term weight gain. Analyses stratified by time-varying BMI categories were also presented.	7
Xu et al. 2019 (B)	Cohort	Australia	6013	18–23	100	Excluded women who had a chronic physical condition during 1996–2006	20 years	Chronic disease count	Compared to the high stable trajectory, women in the declining (OR = 1.50; 95% CI = 1.09–2.06) and low-stable (OR = 1.48; 95% CI = 1.08–2.01) mental health symptom trajectories had increased odds for developing chronic conditions; no association was found in the improving and declining-improving trajectories.	7
Xu et al. 2020	Cohort	Australia	5107	45–50	100	Excluded women with chronic conditions	20 years	2 + new conditions	Women with ≤ 40 years of age at natural menopause had increased odds of multimorbidity (OR = 3.03; 95% CI = 1.62–5.64) compared to those aged 50–51 years at natural menopause; no significant associations were found at ages 41–45, 46–49, 52–53, or 54 + years.	7
Zhang et al. 2022	Cohort	China	17,115	45 +	53	N/A	From childhood to adulthood	Comorbid CVD and diabetes	In terms of adverse childhood conditions, illiteracy of one's father (OR = 1.45; 95% CI = 1.03–2.03) and hunger (OR = 1.75; 95% CI = 1.18–2.60) were associated with comorbid cardiovascular diseases and diabetes; no significant association was found for the following exposures in	6

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Table 1 (*continued*)

Author and year	Study design	Country	Analytical sample size	Age (mean or range)	Sex female (%)	Baseline health status criteria	Time of follow-up	Outcome	Findings	NOS score
									childhood: early maternal death, early paternal death, father being a farmer, economic hardship, loneliness, neighbourhood, poor family relations, abuse from mother, abuse from father, and poor self-rated health.	
Zou et al. 2022	Cohort	China	6037	45 +	51	Excluded participants with multimorbidity at baseline	4 years	2 + chronic conditions	Compared to 6–8 h per night, short sleep durations of ≤ 5 h (RR = 1.33; 95% CI = 1.15–1.55) or 5–6 h/night (RR = 1.24; 95% CI = 1.06–1.46) were associated with increased risk of multimorbidity; no association was found for those sleeping 8–9 h or > 9 h per night. Sleep restlessness, i.e. 1–2 times per week (RR = 1.46; 95% CI = 1.24–1.73), was also associated with multimorbidity development. Stratified analyses by age, sex, and presence of a baseline chronic condition were also conducted and reported.	7

Notes: NOS = Newcastle-Ottawa Scale, MI = myocardial infarction, CVD = cardiovascular disease, HR = hazard ratio, CI = confidence interval, OR = odds ratio, RRR = relative risk ratio, BMI = body mass index, kg/m^2 = kilograms/$meters^2$, RR = relative risk, N/A = not applicable, mg/dL = milligrams/deciliter, MTHFR = methylenetetrahydrofolate reductase, pg/mL = picograms/milliliter, DM = diabetes mellitus, vs = versus, kg = kilogram, cm = centimeters, GCE = general certificate of education, CHARLS = China Health and Retirement Longitudinal Study, SHARE = Survey of Health, Ageing and Retirement in Europe, AUD = Australian dollars, mmol/L = millimoles/liter, CHD = coronary heart disease, mm Hg = millimeter of mercury, n = number.

multimorbidity: for example, Ki et al (Ki et al., 2017). looked at the role of the interaction between age groups and different socio-economic variables on the development of multiple chronic conditions, without finding a factor that was consistently associated with multimorbidity.

Sex and gender were also evaluated in some of the included studies. Female sex was found to be associated with an increased risk of developing multimorbidity in 4 studies (Bisquera et al., 2022; Hussin et al., 2019; Moin et al., 2021; Quinones et al., 2016), whereas others (Schäfer et al., 2019; Vall Castelló and Tubianosa, 2020) found female sex was protective. No association between sex and multimorbidity was found by other authors (Chau et al., 2021; Irshad and Dash, 2022; Melis et al., 2014; Mounce et al., 2018; Poole and Steptoe, 2018; van den Akker et al., 2000).

Smoking and alcohol were also considered by some authors as potential risk factors. A form of association between these risk factors and incident multimorbidity was highlighted by some authors (Bisquera et al., 2022; Freisling et al., 2020; Han et al., 2021; Hussin et al., 2019; Jackson et al., 2016; Katikireddi et al., 2017; Li et al., 2021; Peterson et al., 2021; Schäfer et al., 2019; Shang et al., 2020a, 2020b; Singh-Manoux et al., 2018; Vall Castelló and Tubianosa, 2020; Wikström et al., 2015; Xu et al., 2018), whereas others did not found any or even found a protective association (Aminisani et al., 2019; Dhalwani et al., 2016; Irshad and Dash, 2022; Jackson et al., 2015; Melis et al., 2014; Mounce et al., 2018; Poole and Steptoe, 2018; Ryan et al., 2018; Seo, 2019; van den Akker et al., 2000). In particular, the association between small alcohol consumption or without taking into consideration the amount of alcohol consumed was mostly found inconsistent or found to be protective in most studies. Among risk factors for chronic conditions, hypertension (Bisquera et al., 2022; Poole and Steptoe, 2018; Shang et al., 2020b; Singh-Manoux et al., 2018; Wikström et al., 2015; Xu et al., 2018) and high cholesterol (Bisquera et al., 2022; Blümel et al., 2020; Singh-Manoux et al., 2018; Tajik et al., 2022; Wikström et al., 2015) were also evaluated by a number of studies. In the majority of these studies, hypertension and cholesterol were found to be associated with the risk of incident multimorbidity.

Nineteen studies (Aminisani et al., 2019; Hussin et al., 2019; Jackson et al., 2015, 2016; Katikireddi et al., 2017; Khanolkar et al., 2021; Ki et al., 2017; Li et al., 2021; Melis et al., 2014; Moin et al., 2021; Mounce et al., 2018; Ryan et al., 2018; Schäfer et al., 2019; Schramm et al., 2022; Seo, 2019; Shang et al., 2020b; Vall Castelló and Tubianosa, 2020; Wikström et al., 2015; Xu et al., 2018) investigated the relationship between education and the development of multiple chronic conditions: the majority of these studies found either a protective effect of higher education. Jackson *e al (*Jackson et al., 2016*)* found that low education, in comparison with high education was associated only with the development of psychosomatic or musculoskeletal multimorbidity, but the association disappeared when considering other multimorbidity patterns.

Income or other proxies of wealth were also evaluated by various authors: some authors (Bisquera et al., 2022; Chau et al., 2021; Ki et al., 2017; Mounce et al., 2018; Schäfer et al., 2019; Seo, 2019) found that higher socio-economic status was protective against the development of multimorbidity. On the contrary, van den Akker (van den Akker et al., 2000) et al. and Irshad et al (Irshad and Dash, 2022). found that being in the upper socio-economical class increased the risk of accruing chronic conditions.

Few studies (Balogun et al., 2021; Liu et al., 2022; Peterson et al., 2021; Qiao et al., 2021; Ryan et al., 2018; Petermann-Rocha et al., 2020) evaluated physical performance measures (hand grip strength, walking speed), disability (in basic and/or instrumental activities of daily living), or frailty/sarcopenia as risk factors and for incident multimorbidity or the accumulation of chronic conditions: in these studies, low physical function was consistently associated with an increased risk of developing chronic diseases.

Obesity or high body mass index (BMI) were found as risk factors for incident multimorbidity in a significant number of studies (Balogun

et al., 2021; Bisquera et al., 2022; Blümel et al., 2020; Fabbri et al., 2015c; Freisling et al., 2020; Gondek et al., 2021; Han et al., 2021; Jackson et al., 2015, 2016; Katikireddi et al., 2017; Kivimäki et al., 2017; Li et al., 2021; Lu et al., 2021; Mounce et al., 2018; Poole and Steptoe, 2018; Shang et al., 2020a, 2020b; Wikström et al., 2015; Xu et al., 2018, 2019a; Quinones et al., 2016). The association was generally stronger for obesity rather than for simple overweight. However, Calderón-Larrañaga et al (Calderón-Larrañaga et al., 2021). found an association between the loss of body weight and malnutrition and the incident accrual of chronic conditions.

Physical activity, evaluated by several authors (Aminisani et al., 2019; Balogun et al., 2021; Dhalwani et al., 2016; Fabbri et al., 2015a; Han et al., 2021; Jackson et al., 2015, 2016; Katikireddi et al., 2017; Moin et al., 2021; Mounce et al., 2018; Poole and Steptoe, 2018; Ryan et al., 2018; Schäfer et al., 2019; Seo, 2019; Vall Castelló and Tubianosa, 2020; van den Akker et al., 2000; Waller et al., 2010; Wikström et al., 2015; Xu et al., 2018), was identified as a protective factor for incident multimorbidity in the majority of the studies, although some authors found no- or inconsistent associations. Some other authors (Dhalwani et al., 2016; Freisling et al., 2020; Han et al., 2021; Hlaing-Hlaing et al., 2021; Hussin et al., 2019; Katikireddi et al., 2017; Shang et al., 2020b; Vall Castelló and Tubianosa, 2020) also evaluated the association between diet and the risk of developing multimorbidity: in general poor diet, low adherence to the Mediterranean diet, or a low Healthy eating index were found to be associated with an increased risk of chronic conditions accrual.

Mental health and depression were also found to be strong risk factors for incident multimorbidity as shown by some of the studies included (Arias-de la Torre et al., 2021; Calderón-Larrañaga et al., 2019; Demirchyan et al., 2013; Poole and Steptoe, 2018; Qiao et al., 2022; Sutin et al., 2013; Tomasdottir et al., 2016; Willroth et al., 2021; Xu et al., 2019b), although a high degree of variability in the definition of mental health was found among the studies.

Lastly, some authors (Gondek et al., 2021; Henchoz et al., 2019; Lin et al., 2021; Zhang et al., 2022) evaluated the possible impact of childhood traumatic events or stress on the risk of developing multiple chronic conditions lather in life. Although the majority of studies reported some possible associations, the variability in the definition of childhood events from abuse to economic difficulties, to hunger) was found to be high.

Table 1 reports the main characteristics and findings of the 68 included studies, including baseline health status of the participants as well as outcome measures. Only results from the most adjusted models are reported.

4.4. Quality of the included studies

On average, the risk of bias in the included studies was moderate (mean NOS score = 6.75). The risk of bias was low (NOS score > 7) in 11 (16.2%) studies, moderate (5 < NOS score < 7) in 56 (82.3%) studies, and high (NOS score < 5) in 1 (1.5%) study.

5. Discussion

This systematic review of the literature shows that a wide range of risk factors for multimorbidity have been identified to date, with different level of evidence on their actual role. A previous systematic review on multimorbidity identified very few prospective studies evaluating the incidence of risk or protective factors for multimorbidity defined as the co-occurrence of two or more chronic diseases (Marengoni et al., 2011). Although we included more studies in the present review, they are extremely heterogeneous in terms of setting, demographic and clinical characteristics of the participants, outcomes, and measurement of specific risk factors.

Participants exhibited various health statuses at baseline in the included studies, from no existing chronic disease to having one or more chronic diseases. However, it has been shown that the accumulation of chronic diseases over time depends on the presence of baseline conditions (Melis et al., 2014). In our systematic review, several baseline conditions, such as diabetes, hypertension, and depression, were found to be associated with a higher risk of developing other diseases over time. This association may occur through a variety of mechanisms, including direct pathophysiological links (e.g., hypertension and ischemic heart disease), shared risk factors (e.g., obesity and low physical activity among those with diabetes and stroke), or the development of new risk factors (e.g., depression leading to reduced physical activity and social isolation, which increase the risk of dementia). The complex interplay of these mechanisms contributes to the grouping of chronic diseases and highlights the importance of studying them as clusters or patterns of diseases rather than isolated conditions. This approach is thought to offer new insights into patient-centered prevention, diagnoses, and treatment strategies (Prados-Torres et al., 2014).

Our systematic review not only confirms the well-known heterogeneity in the operationalization of multimorbidity, but also a significant variation in the way certain risk factors are assessed. For instance, physical activity has been evaluated in various ways, ranging from a single question on the frequency of vigorous activity in the previous week (Aminisani et al., 2019) to comprehensive (Dhalwani et al., 2016; Han et al., 2021) or validated (Freisling et al., 2020; Singh-Manoux et al., 2018) questionnaires. Moreover, evaluating certain risk factors through self-reported information can result in low-to-moderate reproducibility and under- or over-estimation (when compared with an objective measurement); this is the case for diet (Rimm et al., 1992; Poppitt et al., 1998) and physical, itself. Diet and, in particular, physical activity may be targeted by clinical interventions and policies (Kettle et al., 2022) that greatly reduce the risk of developing chronic conditions and multimorbidity. As such, increasing the uniformity and reproducibility of their assessments ought to be considered pivotal goals for future research (Arvidsson et al., 2019; England et al., 2015).

Our study also shows that among the evaluated risk factors related to childhood, only a few (i.e.: low parental education and serious illness or accident in childhood) were consistently associated with developing multimorbidity in adulthood. It is worth noting, however, that the assessment of such risk factors may be hindered by recall bias, lack of trustworthy sources, and survival bias.

Most of the included studies evaluated risk factors using a single-time assessment, typically at baseline. It is likely, however, that risk factors, as well as their impact on the accrual of multiple chronic conditions, change over time. For example, a recent metanalysis focused on overweight and obesity and the risk of multimorbidity; overall, the authors observed an increased risk of multimorbidity among subjects with overweight and obesity compared to normal weight (Delpino et al., 2023). Similarly, in our review, several studies (Balogun et al., 2021; Blümel et al., 2020; Fabbri et al., 2015c; Freisling et al., 2020; Jackson et al., 2015, 2016; Kivimäki et al., 2017; Xu et al., 2018, 2019a) confirmed that being overweight or obese is associated with an increased risk of accumulating chronic diseases. On the other hand, the work of Calderón-Larrañaga A et al (Calderón-Larrañaga et al., 2021). shows that the rate of accumulation of chronic conditions is considerably faster among participants presenting with a rapidly decreasing BMI, compared to those with a mildly decreasing BMI trajectory. These results are important, as unintentional weight loss has been shown to be strongly associated with poor health-related outcomes in older persons (Alharbi et al., 2021) differently from elevated BMI, which is a well-known risk factor for cardiovascular diseases in early- and mid-adulthood (Flegal et al., 2013). It is likely that, among selected populations (e.g., older adults), investigating risk factors as dynamic elements that change over time may promote the implementation of preventive measures based on follow-ups and trajectory descriptions, which more closely resembles the actual experience of care-seeking persons, rather than static and generalized cut-offs.

Special attention needs the association between socioeconomic factors and multimorbidity. Social determinats of health (SDH) have gained increasing attention by the World Health Organization because of their important influence on health inequities (Braveman et al., 2011). SDH are the non-medical factors that influence health outcomes, such as income, education, unemployment, early childhood development, and others. A systematic review investigating social determinants of patterns of multimorbidity showed that cardiometabolic multimorbidity profiles were common among men with low SES (Álvarez-Gálvez et al., 2023). In our review, the majority of studies evaluating SDH reported a positive association between deprivation and multimorbidity. SES may have a direct influence on health, for example it is well-known that low education increases the risk of dementia (Wang et al., 2022). However, the association between SES and multimorbidity may also be mediated by unhealthy lifestyles frequent in persons with low SES, such as smoking, sedentarism, and low quality of diet. Finally, upstreaming controls may also have a role, such as policies on environment and pollution. Interestingly, several studies on childhood adversities and future development of multimorbidity reported no or inconsistent associations, probably due to recall biases or uncontrolled confounders during the lifespan.

The etiology of multimorbidity is complex and involves multiple contributing factors, making it challenging to isolate individual factors. To address this issue, some authors (Dhalwani et al., 2016; Freisling et al., 2020; Singh-Manoux et al., 2018) have created composite scores to evaluate the combined impact of several risk factors, such as diet, smoking, alcohol consumption, physical activity, and anthropometric measures. Dhalwani et al (Dhalwani et al., 2016). found that the combination of multiple factors increases the risk of developing multimorbidity beyond that of the sum of the risks of individual factors considered in isolation (although the confidence intervals for these analyses were large). Freisling et al (Freisling et al., 2020). showed that the magnitude of risk associated with individual factors varies depending on the first disease developed, but this heterogeneity was reduced when using a composite score of unhealthy lifestyles as the exposure variable. These studies suggest that risk factors tend to co-occur and interact with each other and are also likely to be associated with broader social, cultural, and psychological elements. Multimorbidity prevention likely requires a comprehensive evaluation of multiple risk factors and specific interventions targeting those that can be modified. This approach aligns with the comprehensive management strategy suggested for individuals affected by multiple chronic conditions (Onder et al., 2022; Palmer et al., 2018).

Management of the risk factors identified in this systematic review is highly variable in both public health and clinical settings. While smoking is widely recognized as a risk factor for cardiovascular diseases and has been the target of numerous public health policies (Hopkins et al., 2010), the identification and management of other risk factors, such as low physical activity or poor dietary patterns, are less standardized and may vary among health professionals (Thornton et al., 2016; Little et al., 2022). Furthermore, mental health, specifically depression, is often overlooked in the prevention of somatic diseases, despite findings on their link with multimorbidity, as highlighted by several studies (Proper and van Oostrom, 2019; Sarris et al., 2014) in our systematic review. Given the high incidence of multimorbidity, it is crucial to develop an approach that comprehensively addresses the majority of its risk factors, involving collaboration between healthcare professionals and public health policymakers.

5.1. *Strengths, limitations, and future directions*

This systematic review aimed to assess many risk factors for multimorbidity; however, the comprehensiveness of the review depends on that of the primary research conducted in this field. For instance, studies on biomarkers, metabolomics, epigenetics and multimorbidity onset are still lacking.

This work should be interpreted with its limitations in consideration. First, owing to the significant heterogeneity across studies, it was not possible to run a meta-analysis of the results. In addition, most studies implemented definitions of chronic diseases based on pre-defined lists of conditions – a method that is likely to underestimate the real prevalence or incidence of the diseases. Lastly, some studies only reported significant results and, therefore, some information regarding inconsistent or absent associations between risk factors and multimorbidity may be missing.

6. Conclusion

Several risk factors (i.e., age, obesity, depression, low education) seem to be consistently associated with an increased risk of accumulating chronic conditions over time. The current literature, however, is characterized by a significant heterogeneity in both the definition of multimorbidity, and in the assessment of its risk factors hampering robust conclusions.

Authors' contribution

Conception and design of the study: CT, AM, GT, NV; Literature search strategy conception: GT, DS, JD; Article screening: CT, JD, LS, DS, DSR, CB, SB, GG; Conflict resolution: AZ, AM; Quality assessment: AZ, AM; Data extraction and synthesis: CT, DLV; Drafting of the manuscript: CT, AZ, DLV, AM; Critical revision and approval of the manuscript: all authors.

Declaration of Competing Interest

All authors declare that there are no conflicts of interest.

Data Availability

Data will be made available on request.

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Appendix A. : Search strategy

TITLE-ABS-KEY ((multimorbidity OR multi-morbidity OR "multiple.
diseases" OR "multiple morbidities" OR "multiple chronic.
conditions") AND (risk OR prognos* OR determin* OR predict* OR pattern*)).
(TS=((multimorbidity OR multi-morbidity OR "multiple diseases" OR "multiple.
morbidities" OR "multiple chronic conditions") AND (risk OR prognos* OR determin*.

OR predict* OR pattern*))) OR (TI=((multimorbidity OR multi-morbidity OR "multiple. diseases" OR "multiple morbidities" OR "multiple chronic conditions") AND (risk OR. prognos* OR determin* OR predict* OR pattern*))).
TS: Topic; TI: Title.
MESH terms: Comorbidity; Comorbidity[Trends]; Multimorbidity; Multiple chronic conditions.

First author(s) surname	Year of publication	Country	Study design	Total sample	Age (mean and SD)	Sex (% Female)	Baseline status	Outome	Summary of main results

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2023.102039.

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