

The incidence of multimorbidity and patterns in accumulation of chronic conditions: A systematic review

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Abstract

Multimorbidity, the presence of I+ chronic condition in an individual, remains one of the greatest challenges to health on a global scale. Although the prevalence of multimorbidity has been well-established, its incidence is not fully understood. This systematic review determined the incidence of multimorbidity across the lifespan; the order in which chronic conditions accumulate to result in multimorbidity; and cataloged methods used to determine and report accumulation of chronic conditions resulting in multimorbidity. Studies were identified by searching MEDLINE, Embase, CINAHL, and Cochrane electronic databases. Two independent reviewers evaluated studies for inclusion and performed quality assessments. Of 36 included studies, there was high heterogeneity in study design and operational definitions of multimorbidity. Studies reporting incidence (n = 32) reported a median incidence rate of 30.7 per 1,000 person-years (IQR 39.5 per 1,000 person-years) and a median cumulative incidence of 2.8% (IQR 28.7%). Incidence was notably higher for persons with older age and I+ chronic conditions at baseline. Studies reporting patterns in accumulation of chronic conditions (n = 5) reported hypertensive and heart diseases, and diabetes, as among the common starting conditions resulting in later multimorbidity. Methods used to discern patterns were highly heterogenous, ranging from the use of latent growth trajectories to divisive cluster analyses, and presentation using alluvial plots to cluster trajectories. Studies reporting the incidence of multimorbidity and patterns in accumulation of chronic conditions vary greatly in study designs and definitions used. To allow for more accurate estimations and comparison, studies must be transparent and consistent in operational definitions of multimorbidity applied.

Keywords

Multimorbidity, systematic review, incidence, epidemiology, accumulation

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Introduction

Multimorbidity continues to increase world-wide, presenting one of today's biggest challenges to individual and population health, and to health systems.^{1,2} Multimorbidity results in poorer patient outcomes^{3,4} and excess mortality.^{5–20} Patients with multimorbidity also present with unique medical care needs; while specialized treatment approaches are appropriate for single diseases, patients with multimorbidity require complex and structured care plans.²¹ This poses substantial impacts on disease management, healthcare utilization, and costs.^{22–24} The study of multimorbidity, and its epidemiology, may help in better understanding its development; determine reasons for variations in patient outcomes; and design targeted interventions to manage adverse outcomes of multimorbidity.^{25–27}

Existing literature on the epidemiology of multimorbidity has increased substantially, moving from a nascent body of evidence in the 1970s to a now well-established and distinct field of research. Consistent with a growing area of study, the epidemiological research was concerned first with defining multimorbidity and summarizing studies concerning its prevalence.^{26,28} Determining prevalence has permitted us to quantify the burden of multimorbidity in populations and health care systems. However, prevalence is limited in its ability to tell us when and why people accumulate multimorbidity. In order to better understand the etiology of multimorbidity and to project the healthcare needs of patients with multimorbidity, we must turn our attention to determining its incidence.

The incidence of multimorbidity is, by definition, the incidence of multiple chronic conditions that are accumulated in a particular order. Therefore, it is important to study both the incidence of multimorbidity and the accumulation of its component chronic conditions. Currently, there is a growing body of research addressing incidence of multimorbidity. As well, there is emerging literature using innovative and heterogeneous methods to describe the accumulation of chronic conditions in multimorbidity. Our goal was to summarize available evidence on the incidence of multimorbidity across the lifespan. More specifically, our objectives were: 1. to determine the incidence of multimorbidity overall and by age groups, including children; 2. to determine the order in which people accumulate the component chronic conditions leading to multimorbidity; and 3. to catalog the methods used to assess and report accumulation.

Methods

We conducted a systematic review (registered in PROSPERO, reference no. CRD42020191876) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist (Supplementary Table S1).²⁹ An a priori review process was established and followed; this protocol was not

published. As this was a systematic review of literature, Research Ethics Board review or approval was not required. There were no participants or patients enrolled and so no consent was needed for participation, or for patient information and images to be published.

Literature search strategy

Following the recommendation from Chapter 4: Searching for and Selecting Studies in the Cochrane Handbook for Systematic Reviews of Interventions,³⁰ searches of the health-related bibliographic databases, MEDLINE, Embase, CINAHL, and The Cochrane Library were undertaken by the Health & Medicine Librarian (MS1), utilizing both free-text and subject headings (MeSH) to identify an initial batch of relevant and eligible studies reporting incidence of multimorbidity and/or patterns in accumulation of chronic conditions. Databases were searched from inception to May 26, 2020.

Search terms used in the database query for multimorbidity, with its various spelling, were “multimorbidity,” “multimorbidity,” “multimorbidities,” “multi-morbidities,” “multiple morbidities,” “multiple-morbidities,” “multiple chronic diseases” and “multiple chronic conditions.” We searched for incidence and accumulation and their different meanings, using “inciden*,” “accumulat*,” “trajector*,” “longitudinal,” “acquire,” “acquisition,” “predict*,” “cohort,” and “epidemiology.” The full search strategy is provided in Supplementary Table S2.

Study selection

After removing duplicates, titles and abstracts of initial search results were screened by the two reviewers (PK, BS) independently for eligibility. Reviewers initially screened two sets of 10 articles and discussed decisions with the senior study coordinator (BLR) to ensure consistency in applying selection criteria. Eligible articles included peer-reviewed studies using primary or secondary quantitative analyses, including mixed methods studies, published in English and/or French language. Studies with participants of all ages, including children, and specifically reporting 1. incidence of multimorbidity and/or 2. patterns in accumulation of chronic conditions as primary or secondary outcomes, were included. Conference presentations, books, letters, editorials, non-human literatures, and abstract-only studies were excluded. Articles deemed suitable for full-text review were identified and full-texts were then reviewed to confirm eligibility criteria by the two reviewers first independently and then collaboratively to reach consensus. Studies which still satisfied inclusion and exclusion criteria upon full-text review were selected for data extraction. Disagreements were initially discussed by reviewers for resolution. The study coordinator worked with reviewers to resolve any disagreement through consensus. Within the articles identified for review, reference

lists were hand-searched for additional articles meeting our criteria.

Quality assessment

The two reviewers independently performed quality assessment using the Newcastle-Ottawa Scale (NOS) for assessing study methodology of non-randomized studies.³¹ NOS assessment guidelines were followed and, where dictated by NOS guidelines, some assessment criteria were further defined by study authors as described in Supplementary Table S3. Randomized controlled trials (RCTs) were assessed for study methodology and risk of bias (RoB) using the Cochrane Collaboration's RoB tool.³² Of the 36 included studies, 35 observational studies and one RCT underwent quality and risk of bias assessment (Supplementary Table S4). Individual NOS ratings were converted to Agency for Healthcare Research and Quality (AHRQ) standards as one of three levels: Good, Fair, and Poor. A priori scores to exclude studies of low quality were not established in order to include the entire landscape of literature in this review; as such, studies of all scores were included.

Data extraction

The two reviewers independently extracted data from eligible studies following full-text review. A comprehensive data extraction sheet was developed to collect data pertaining to: study characteristics (authors, date of publication, study design, geographic locations, data collection period, follow-up period, data sources, sample size, populations of interest); sample demographics (ages, sex and/or gender, race and/or ethnicity, body mass index (BMI), education levels, smoking status, alcohol consumption levels, physical activity levels, and marital statuses); definitions of multimorbidity; number and selection of conditions included in definitions of multimorbidity; incidence rates and/or cumulative incidences of multimorbidity; patterns in accumulation of chronic conditions; methods used in accumulation studies; and risk factors for multimorbidity. The sheet was pilot tested using three studies. The two reviewers then reconciled any differences, consulting the senior study coordinator as required. Study authors were contacted by email for further information as needed for clarification.

Incidence data were recorded in separate tables for studies reporting incidence rates (IRs) and for studies reporting cumulative incidence. IRs were extracted as the number of incident cases per 1,000 person-years. Results from studies not already reporting per 1,000 person-years were adjusted to meet this format. Cumulative incidence was extracted as a percentage. Results from studies not providing percentages were standardized to meet this format by dividing the incident cases by the number of baseline participants without multimorbidity and multiplying by 100. When multiple IRs were reported, overall IRs across the population were reported in tables if available; additional IRs were not

reported; however, in the tables, the availability of additional IRs is noted. If overall IR or cumulative incidence was not available, incidences provided by study authors were presented in the following priority, as available: by age, sex and/or gender, other demographics.

Results

Overview of studies

The process used for study selection is reported in the PRISMA flow diagram (Figure 1) and PRISMA checklist³³ (Supplementary Table S1). We identified 4,579 studies from the initial database searches; all were published between 1976 and 2020. After removing duplicates and non-original articles, 2,926 studies were identified, of which 109 were retained for full-text screening. A total of 73 articles were excluded following full-text review or qualitative synthesis,^{34–106} with reasons; the majority of excluded studies were those that did not report incidence of multimorbidity; reported incidence of specific chronic conditions and not of multimorbidity; and/or did not account for temporal components when determining patterns in accumulation of chronic conditions, amongst other reasons. Of the articles that underwent full-text review, 36 studies were included in further synthesis. No additional articles meeting our inclusion criteria were identified during hand-searches of study reference lists.

Study quality and characteristics

Of the 35 observational studies, most studies ($n = 26$) were rated as Good quality according to AHRQ standards. Nine studies were ranked as Poor quality due to their omission of information regarding: representativeness of their data, ascertainment of exposure, controlled factors, assessment of outcome, adequacy of follow-up duration, case definition(s), case representativeness, selection strategy(ies), and/or non-response rate(s).^{107–115} RoB assessment for the one RCT¹¹⁶ yielded low risk (Supplementary Table S5).

Of the 36 included studies, one examined both incidence and accumulation¹¹⁷; 31 studies reported only the incidence; and four studies reported only the accumulation of chronic conditions resulting in multimorbidity. Multimorbidity was defined as the presence of 2+ chronic conditions in all but six studies. Of these six, one study¹⁰⁷ defined multimorbidity as the co-occurrence of 3+ conditions and four^{111,116,118,119} did not specify a definition (Supplementary Table S6). However, all authors referenced consideration of 2+ conditions in their prose and/or tables. The number of chronic conditions used to identify multimorbidity varied extensively, ranging between 3 and 506. At the extremes, in one study of accumulation,¹¹⁷ three conditions were included (cancer, diabetes, and cardiovascular diseases); whereas, in another,¹¹⁸ 132 clusters of chronic conditions were included.

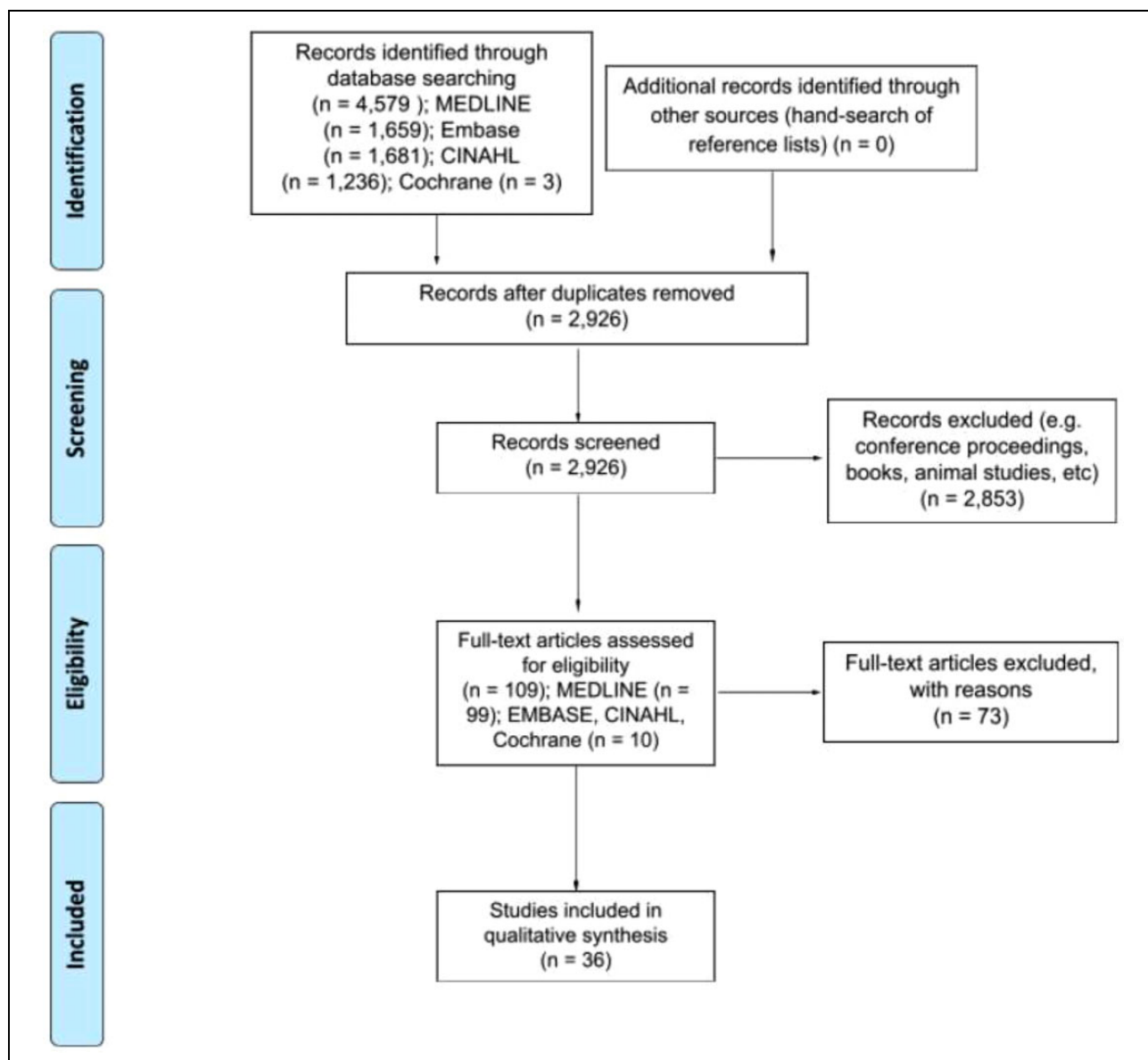


Figure 1. PRISMA flow diagram for study selection.

Table 1 reports the characteristics of the 32 studies that reported incidence of multimorbidity: 14 reported IR and 18 reported cumulative incidence. Studies were heterogeneous across all descriptive variables, including geographical location of study, data collection and follow-up periods, data sources, sample size and population, and demographics. The majority of studies reported either national or local incidence in high income (HIC) ($n = 30$) or middle income countries^{108,120} (MIC) ($n = 2$). The majority of studies sourced data from a combination of sources,^{108,109,112–114,117,119–128} and sampled general populations,^{109,110,112–117,120,122,124,126,128–135} with the remainder focused on specific patient populations.^{25,107,108,119–121,136–138} Samples were generally larger for studies examining general populations. All

except two^{115,130} studies included different age groups across the lifespan. The majority of studies did not report race and/or ethnicity ($n = 16/36$), and, of those that did, there was heterogeneity in the terminology used to describe race and/or ethnicities.

Table 2 reports characteristics of the five studies reporting patterns in accumulation of chronic conditions resulting in multimorbidity. Similar to studies reporting incidence of multimorbidity, accumulation studies were heterogeneous across all descriptive variables, including geographical location of study; data collection and follow-up period; sample population and size; and demographics. The majority of studies reported either national or local patterns in accumulation of chronic conditions in HICs.^{25,107,111,118} Most accumulation studies sampled general populations

Table 1. Baseline characteristics for studies reporting incidence of multimorbidity (n = 32).

Study, year of publication	Country	Data collection period	Follow-up period ^a	Data source	Sample size ^b	Population	Age, years (range) ^c	Female, n (%)	Ethnicity ^d
Studies reporting incidence rates (n = 14)									
Aminisani et al., 2019	New Zealand	2006–2016	10.0 years	Self-report (questionnaire)	1,673	General population	55–70	868 (52)	Māori, Non-Māori (European, Asian, Pacific persons, Other)
Bjur et al., 2019	USA	1999–2014	5.0 years	Medical records	1999 cohort: 31,390, 2004 cohort: 32,490, 2009 cohort: 32,942	General population	0–17	1999 cohort: 15,200 (48) ^f , 2004 cohort: 15,814 (49) ^f , 2009 cohort: 16,058 (49) ^f	Non-Hispanic white, Other (African-American, Asian-American, Hispanic, Other and/or Unknown)
Castilho et al., 2019	Brazil	2003–2014	3.9 years	Medical records, laboratory values	6,121	Persons with HIV receiving ART	36.9 (median) ^e	2,027 (33)	White, Mixed Black or Black, Other/Unknown/ Missing
Castilho et al., 2020	USA	1998–2015	No mood disorder at baseline: 4.9 years (mean), Mood disorder at baseline: 5.1 years (mean)	Medical records	No mood disorder: 2,487, Mood disorder: 725	Persons with HIV	No mood disorder at baseline: 38.7 (median) ^e , Mood disorder at baseline: 40.1 (median) ^e	953 (23) ^f	White, Black, Other
Chan et al., 2019	United Kingdom	2001–2010	5.5 years (mean)	Medical records	844,838	Primary care	≥45 ^e	595,176 (53) ^f	Not specified
Dhalwani et al., 2016	United Kingdom	2008–2013	232,749 person-months	Self-report (survey), clinical evaluation	5,476	General population	≥50	2,901 (53)	White, Non-White
Dugravot et al., 2020	United Kingdom	1985–2017	23.6 years (median)	Self-report (questionnaire), clinical evaluation	6,425	British civil servants	35–55 ^e	1,848 (29)	White, Other
Freisling et al., 2020	Denmark, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom	1992–2010	11.0 years (median)	Self-report (questionnaire), medical records, health insurance records	291,778	General population	43–58 (median)	186,564 (64)	Not specified
Hussin et al., 2019	Malaysia	2014–2016	1.5 years	Self-report (interviews)	729	General population	≥60	363 (49)	Malay, Chinese, Indian
Kivimäki et al., 2017	USA, United Kingdom, Finland, France, Sweden, Austria, Belgium, Germany, Denmark, Spain, Italy, Netherlands, Israel	1995–2014	10.7 years (mean)	Self-report (survey), medical records	120,813	Persons with overweight and/or obesity	35–103	71,445 (59)	White, Non-White
Lau et al., 2019	Malaysia	2012–2016	3.0 years	Self-report (questionnaire), interview	738	General population	≥60 ^e	813 (52) ^f	Malay, Chinese, Indian, Others
Licher et al., 2019	Netherlands	1989–2012	75,354 person-years	Medical records, interview	9,061	General population	45–107	5,458 (60)	Not specified
Meis et al., 2014	Sweden	1991–1993	3.0 years	Medical records	390	General population	≥78	292 (75)	White
St Sauver et al., 2015	USA	2000–2013	14.0 years	Medical records	106,061	General population	All ages	53,582 (43)	White, Black, Asian

(continued)

Table 1. (continued)

Study, year of publication	Country	Data collection period	Follow-up period ^a	Data source	Sample size ^b	Population	Age, years (range) ^c	Female, n (%)	Ethnicity ^d
Studies reporting cumulative incidence (n = 18)									
Demirchyan et al., 2013	Armenia	1990–2012	22.0 years	Self-report (survey), clinical evaluation	597	Survivors of the 1988 Armenian earthquake	39–90 ^e	491 (68) ^f	Not specified
Guaraldi et al., 2015	Italy	2003–2014	8,206 person-years	Medical records, clinical evaluation, laboratory values	2,383	Persons with HIV	46 (mean) ^e	867 (32) ^f	Not specified
Hohmann et al., 2019	Sweden, Netherlands, Germany	Not specified	4–20 years following birth	Self-report (questionnaire)	18,451	General population from 5 birth cohorts	4–20	9,040 (49)	Not specified
Marengoni et al., 2018	Finland	2009–2011	2.0 years	Self-report (questionnaire)	489	General population	60–77 ^e	499 (47) ^f	Not specified
Mounce et al., 2018	United Kingdom	2002–2013	10.1 years (mean)	Self-report (interview), clinical evaluation	3,011	General population	≥50	1,593 (53)	Not specified
Niedzwiedz et al., 2019	USA	2008–2014	6.0 years	Self-report (questionnaire), laboratory values	1,989	General population	50–100 ^e	1,173 (59)	Non-Hispanic White, Non-Hispanic Black, Hispanic, Other
Ryan et al., 2018	Ireland	2010–2012	2.0 years	Self-report (questionnaire), clinical evaluation	2,235	General population	≥50	1,120 (50)	Not specified
Salloum et al., 2019	USA, Canada	1970–1999	15.0 years	Medical records, self-report	997	Survivors of childhood cancer (medulloblastoma)	0–21	389 (39)	Non-Hispanic White, Non-Hispanic Black, Hispanic, Other
Singh-Manoux et al., 2018	United Kingdom	1985–2002	23.7 years (mean)	Medical records, clinical examination, laboratory values, self-report	8,270	General population	50	2,720 (33)	White, Non-White
Tomasdottir et al., 2016	Norway	1995–2008	11.0 years (mean)	Self-report (questionnaire), clinical evaluation, laboratory values	20,365	General population	20–59	10,938 (54)	Not specified
Ungrasert et al., 2017	USA	1976–2013	Cases: 12.9 years (median), Comparators: 15.6 years (median)	Medical records	690	Persons diagnosed with sarcoidosis	Cases: 45.6 (mean), Comparators: 45.4 (mean)	345 (50)	Caucasian, African-American, Asian, Native American, Other
van den Akker et al., 1998	Netherlands	1993–1994	1.0 years	Medical records	60,857	General population	All ages	31,227 (51)	Not specified
Wikström et al., 2015	Finland	1982–2002	10 years	Self-reporting (questionnaire), clinical evaluations, laboratory values	32,972	General population	25–64	17,068 (52)	Not specified
Wilson-Genderson et al., 2017	USA	2006–2014	8 years	Self-report (questionnaire)	3,396	General population	50–74	2,080 (61)	White, African-American

(continued)

Table 1. (continued)

Study, year of publication	Country	Data collection period	Follow-up period^a	Data source	Sample size^b	Population	Age, years (range)^c	Female, n (%)	Ethnicity^d
Xu et al., 2018	Australia	1996–2016	20 years	Self-report (survey)	11,941	Women	45–50	11,941 (100)	Not specified
Xu et al., 2019	Australia	1996–2016	20 years	Self-report (survey)	7,357	Women	45–50	7,357 (100)	Not specified
Xu et al., 2020	Australia	2010–2016	6 years	Self-report (survey)	5,107	Women reporting premature ANM	45–50	5,107 (100)	Not specified
Xu, Mishra & Jones, 2019	Australia	1996–2016	20 years	Self-report (survey)	6,398	Women	45–50	6,398 (100)	Not specified

ANM, age at natural menopause; ART, antiretroviral therapy; HIV, human immunodeficiency virus; IR, incidence rate.

^aAs provided by study authors as either mean or median years, or person-years. Group-specific mean (or median) follow-up periods are included for studies which did not report an overall mean or median follow-up period.

^bWithout multimorbidity at baseline, as defined by study author(s).

^cAge at baseline; reported as range or mean or median if an exact range was not reported.

^dEthnicity is reported using terminology directly reported by study authors. Elaboration of ethnicities included in groups is provided where reported.

^eThis age refers to the age of participants at baseline among all study participants irrespective of multimorbidity status as the age specific to participants without multimorbidity at baseline was not provided by authors.

^fThis proportion of females refers to the proportion at baseline among all study participants irrespective of multimorbidity status as the proportion of females specific to participants without multimorbidity at baseline was not provided by authors.

Table 2. Baseline characteristics of studies and participants reporting accumulation of chronic conditions (n = 5).

Study, year of publication	Country	Data collection period	Follow-up period ^a	Data source	Sample size	Population	Age, years (range) ^b	Female, n (%)	Ethnicity
Ashworth et al., 2019	United Kingdom	2004–2018	Not specified	Medical records	332,353	Primary care	≥ 18	164,487 (49)	Black, South Asian, Mixed, Other, Unknown
Freisling et al., 2020	Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom	1992–2010	11.0 years (mean)	Self-report (questionnaire), medical records, health insurance records	291,778	General population	43–58 (median)	186,564 (64)	Not specified
Haug et al., 2020	Austria	2003–2014	12.0 years	Medical records	5,112,811	General population	All ages	Not specified	Not specified
Jørgensen et al., 2020	Denmark	1994–2016	Not specified	Medical records	73,213	Persons with AD and VaD	AD: 80.32 (mean), VaD: 79.12 (mean)	44,786 (61)	Not specified
Strauss et al., 2014	United Kingdom	2003–2005	3.0 years	Medical records	9,160	Primary care	50–75	5,166 (56)	Not specified

AD: Alzheimer's disease; VaD: Vascular dementia.

^aAs provided by study authors as either mean or median years. Group-specific mean (or median) follow-up periods are included for studies which did not report an overall mean or median follow-up period.^bAt baseline.

and sample sizes ranged from 9,160 and approximately 5 million. Comparable to studies reporting incidence of multimorbidity, study population ages ranged across the lifespan with most studying older adults only. One study reported race and ethnicity,¹⁰⁷ and data were most commonly sourced from medical records.

Incidence of multimorbidity

The incidence of multimorbidity for the 32 incidence studies are reported in *Table 3*.

Among the 14 studies reporting IRs, rates were highly heterogeneous. Only five of the 14 studies reported an overall IR in addition to group-specific rates.^{109,121,123,126,132} Across studies reporting incidence, the median (unadjusted) incidence rate was 30.7 per 1,000 person-years (IQR 39.5 per 1,000 person-years) and the median (unadjusted) cumulative incidence was 2.8% (IQR 28.7%). Incidence rates ranged from 1.26 to 342 per 1,000 person-years. Of all incidence studies, two adjusted incidence for age, sex, and/or ethnicity.^{129,130} IRs across the lifespan increased with age, with studies of middle-aged to older participants (50+ years of age) reporting higher IRs than those consisting of younger and adult populations (0–40 years of age). Most studies did not stratify IRs by sex, with only one reporting IRs among male and female participants separately¹³⁰; this study reported a higher IR among women than in men. Of the 11 studies reporting race and/or ethnicity, five reported incidence rate(s) stratified by race and/or ethnicity,^{109,112,123,129,132} one adjusted incidence rates for race and/or ethnicity,¹³⁶ and two presented both adjusted overall and stratified incidence rate(s) by race and/or ethnicity.^{129,130} Two studies consisting solely of South and East Asian ethnicities (Malay, Chinese, and Indian)^{110,112} reported higher IRs than the remaining studies reporting IRs in White, Non-White, Black/African-American, Hispanic, and Māori populations.

Cumulative incidences of multimorbidity are presented in *Table 3*. Of the 18 studies reporting cumulative incidence, 10 studies reported overall unadjusted cumulative incidence ranging from 1.3% to 61.0%. Group-specific values ranged between 0% of participants developing multimorbidity (expressed in a European study as development of four chronic conditions over 2-year follow-up)¹¹⁶ and 76.8% of participants developing multimorbidity (defined in an Australian study of women as development of two or more chronic conditions over 20-year follow-up).¹³⁹ Amongst five studies of specific patient populations, three had higher cumulative incidence^{108,137,138} compared to those conducted in general populations.

Across studies reporting either incidence rate or cumulative incidence, studies of older (45+ years of age) populations reported higher cumulative incidence than those which included younger population (<21 years of age).^{119,133} Additionally, in studies which presented incidence stratified by baseline disease counts, persons with

one chronic condition at baseline had higher incidence of multimorbidity by the end of study follow-up, compared to those with zero at baseline.^{110,113,116,128,134,137,139} With the exception of one,¹¹² studies including nine or more chronic conditions in their definition of multimorbidity reported higher incidence than those including fewer conditions.

Patterns in accumulation of chronic conditions

The five articles that studied the accumulation of chronic conditions varied in the methods used to determine patterns, format of reporting, and in the component chronic conditions making up multimorbidity (*Table 4*). Four studies reported overall pattern(s) in accumulation^{25,107,111,118} and, of these, only one reported additional patterns by demographic subgroups¹⁰⁷ and one reported patterns in accumulation by starting condition among participants.¹¹⁷ Three studies characterized the order of component chronic conditions as trajectories,^{25,111,118} one as transitions,¹¹⁷ and one as pathways.¹⁰⁷ All but two studies^{25,107} reported patterns in accumulation of chronic conditions in populations of individuals with specific underlying diseases.

As reported by Ashworth et al.,¹⁰⁷ starting conditions varied by age, social deprivation, and ethnicity. For example, depression was more common as a starting condition in individuals under 65 years of age, while diabetes and CHD were more common in those 65+ years of age.¹⁰⁷ Four studies reported hypertensive and heart diseases as among the common starting conditions resulting in later multimorbidity^{25,111,117,118} and two reported diabetes as the most common starting condition.^{107,111} Second and third conditions contributing to multimorbidity were highly variable amongst reported patterns; two studies indicated cerebrovascular diseases and mental health illness (i.e. mood disorders) as common second conditions resulting in multimorbidity status.^{111,118} This is in contrast to one study reporting a mental health illness (depression) as a common overall starting condition.¹⁰⁷ Additional second- and third-component conditions reported include chronic pain, osteoarthritis, cancer, diabetes, and hypercholesterolemia.^{25,107,117}

Methods in determining patterns in accumulation of chronic conditions

There were diverse methods used by the five studies to determine and report the accumulation of component chronic conditions leading to multimorbidity; despite this diversity, each study reported their results diagrammatically.

Ashworth et al.¹⁰⁷ employed alluvial plots,¹⁴⁰ whereby the chronic conditions in the accumulation sequence are assigned to vertical axes. Bar heights of the vertical axes were used to represent the number of persons with a particular chronic condition, and the widths of “streams” joining bars were used to represent the number of persons in each adjoining pair of chronic conditions. Freisling et al.¹¹⁷ identified chronic conditions and calculated hazard ratios

Table 3. Incidence of multimorbidity by study (n = 32).

Study, year of publication	Group	Incidence	Adjustment
Studies reporting incidence rates (n = 14)			
Aminisani et al., 2019 ^a	Overall	68.5 per 1,000 person-years	Unadjusted
Bjur et al., 2019 ^a	1999 cohort	2.56 per 1,000 person-years	Adjusted for age, sex, and ethnicity
Bjur et al., 2019 ^a	2004 cohort	3.00 per 1,000 person-years	Adjusted for age, sex, and ethnicity
Bjur et al., 2019 ^a	2009 cohort	3.35 per 1,000 person-years	Adjusted for age, sex, and ethnicity
Castilho et al., 2019 ^a	Multiple	Varied between 11.87–14.97 per 1,000 person-years by age and length of follow-up period (1 to 11 years from study entry)	Unadjusted
Castilho et al., 2020 ^a	Multiple	Varied between 24.0–51.5 per 1,000 person-years by age group (30 to 70+ years)	Unadjusted
Chan et al., 2019 ^a	Multiple	Varied between 17.4–160.9 per 1,000 person-years by age group (45 to 85+ years)	Unadjusted
Dhalwani et al., 2016 ^a	Overall	59 per 1,000 person-years	Unadjusted
Dugravot et al., 2020 ^a	Overall	13.87 per 1,000 person-years	Unadjusted
Freisling et al., 2020 ^a	Cancer to multimorbidity	13 per 1,000 person-years	Unadjusted
Freisling et al., 2020 ^a	CVD to multimorbidity	31.3 per 1,000 person-years	Unadjusted
Freisling et al., 2020 ^a	T2D to multimorbidity	25.0 per 1,000 person-years	Unadjusted
Hussin et al., 2019 ^a	Zero conditions at baseline	137 per 1,000 person-years	Unadjusted
Hussin et al., 2019 ^a	One condition at baseline	342 per 1,000 person-years	Unadjusted
Kivimäki et al., 2017 ^a	Overall	1.26 per 1,000 person-years (cardiometabolic multimorbidity)	Unadjusted
Lau et al., 2019 ^a	At 18 months follow-up	237 per 1,000 person-years	Unadjusted
Lau et al., 2019 ^a	At 36 months follow-up	215 per 1,000 person-years	Unadjusted
Licher et al., 2019 ^a	Overall	20.7 per 1,000 person-years	Unadjusted
Melis et al., 2014 ^a	Zero conditions at baseline	126 per 1,000 person-years	Unadjusted
Melis et al., 2014 ^a	One condition at baseline	329 per 1,000 person-years	Unadjusted
St Sauver et al., 2015 ^a	Women	38.8 per 1,000 person-years	Adjusted by age and sex to the total US 2010 Decennial Census
St Sauver et al., 2015 ^a	Men	35.5 per 1,000 person-years	Adjusted by age and sex to the total US 2010 Decennial Census
Studies reporting cumulative incidence (n = 18)			
Demirchyan et al., 2013 ^a	Overall	61.0% over 22 years	Unadjusted
Guaraldi et al., 2015	Overall	9.7% over 3 years	Unadjusted
Hohmann et al., 2019 ^a	Multiple	Varied between 0.3% and 5.4% by sex, birth cohort, length of follow-up period, and age group (4 to 20 years) (respiratory multimorbidity)	Unadjusted
Marengoni et al., 2018 ^a	Control with zero chronic conditions at baseline	16.5% over 2 years	Unadjusted
Marengoni et al., 2018 ^a	Control with one chronic condition at baseline	44% over 2 years	Unadjusted
Marengoni et al., 2018 ^a	Intervention with zero chronic conditions at baseline	10.8% over 2 years	Unadjusted

(continued)

Table 3. (continued)

Study, year of publication	Group	Incidence	Adjustment
Studies reporting cumulative incidence (n = 18)			
Marengoni et al., 2018 ^a	Intervention with one chronic condition at baseline	33.2% over 2 years	Unadjusted
Mounce et al., 2018 ^a	Zero conditions at baseline	25.5% over 10.1 years	Unadjusted
Mounce et al., 2018 ^a	One condition at baseline	65.3% over 10.1 years	Unadjusted
Niedzwiedz et al., 2019	Overall	30.3% over 6 years	Unadjusted
Ryan et al., 2018 ^a	Overall	30.4% over 2 years	Unadjusted
Salloum et al., 2019 ^a	Cohort diagnosed with medulloblastoma in 1970s	12.2% over 15 years	Unadjusted
Salloum et al., 2019 ^a	Cohort diagnosed with medulloblastoma in 1980s	19.6% over 15 years	Unadjusted
Salloum et al., 2019 ^a	Cohort diagnosed with medulloblastoma in 1990s	23.9% over 15 years	Unadjusted
Singh-Manoux et al., 2018 ^a	Overall	6.18% over 23.7 years (cardiometabolic multimorbidity)	Unadjusted
Tomasdottir et al., 2016 ^a	Overall	30.8% over 11 years	Unadjusted
Ungprasert et al., 2017 ^a	Referent (non-sarcoidosis participants)	31.7% over 15.6 years (median)	Unadjusted
Ungprasert et al., 2017 ^a	Participants with sarcoidosis	45.5% over 12.9 years (median)	Unadjusted
van den Akker et al., 1998 ^a	Overall	1.3% over 1 year	Unadjusted
Wikström et al., 2015	Women with zero conditions at baseline	1% over 10 years	Unadjusted
Wikström et al., 2015	Men with zero conditions at baseline	2% over 10 years	Unadjusted
Wikström et al., 2015	Women with DM at baseline	22.6% over 10 years	Unadjusted
Wikström et al., 2015	Men with DM at baseline	30.8% over 10 years	Unadjusted
Wikström et al., 2015	Women with CVD at baseline	24% over 10 years	Unadjusted
Wikström et al., 2015	Men with CVD at baseline	23.3% over 10 years	Unadjusted
Wilson-Genderson et al., 2017 ^a	Overall	41.6% over 12 years (by T4)	Unadjusted
Xu et al., 2018 ^a	Overall	16.8% over 20 years	Unadjusted
Xu et al., 2019 ^a	Overall	60.4% over 20 years	Unadjusted
Xu et al., 2020 ^a	Multiple	Varied between 35.9% and 66.7% by age group at natural menopause (≤ 40 to ≥ 54 years)	Unadjusted
Xu, Mishra & Jones, 2019 ^a	Control (women without DEP)	52.6% over 18 years	Unadjusted
Xu, Mishra & Jones, 2019 ^a	Women with DEP	76.8% over 18 years	Unadjusted

ANM, age at natural menopause; BMI, body mass index; CVD, cardiovascular disease; DEP, depression; DM, diabetes mellitus; HIV, human immunodeficiency virus; T2D, type II diabetes.
^aAdditional incidence rate(s) and/or cumulative incidence available in study text.

Table 4. Patterns in accumulation of component chronic conditions in multimorbidity and methods used to ascertain patterns (n = 5).

Study, year of publication	Patterns in accumulation
Ashworth et al., 2019	<p>Overall: Diabetes and depression were the most common starting conditions. Chronic pain was more common as a second or third acquired condition.</p> <p>Age: Under 65 years, the most common starting condition was depression. In 65+ years, the most common starting conditions were diabetes and CHD.</p> <p>Deprivation: In most deprived, the most common starting conditions were diabetes and depression. In least deprived, the most common starting conditions were diabetes and CHD.</p> <p>Ethnicity: Among Black participants, diabetes was the most common starting condition; serious mental illness and depression were also common starting conditions. Among White participants, depression was the most common starting condition.</p>
Freisling et al., 2020	<p>Cancer: Transitions to multimorbidity through acquiring CVD or T2D at 6.5 events/1,000 person-years.</p> <p>CVD: Transition to multimorbidity through acquiring cancer at 16.6 events/1,000 person-years and through acquiring T2D at 14.7 events/1,000 person-years.</p> <p>T2D: Transition to multimorbidity through acquiring cancer at 14.3 events per 1,000 person-years and through acquiring CVD at 10.7 events/1,000 person-years.</p>
Haug et al., 2020	<p>Overall: 132 clusters of chronic conditions (ICD-10 diagnoses) identified with cluster 0 (no known prior diagnoses) a beginning healthy state for participants. Reduced disease trajectory was defined by accumulation of additional clusters over time, with time period where no new clusters accumulated were removed.</p> <p>Cerebrovascular disease: More than 50% followed reduced trajectories of length greater than two. Most frequent reduced trajectory of length 3 is (0, 114, 123); patients from healthy cluster 0 move to cluster 114 (hypertensive diseases 110–115 and heart diseases 130–152) to cluster 123 where cerebrovascular diseases become included (cluster 123). Malignant neoplasms: More than 50% only visit two different clusters, and 44% of those had reduced trajectory (0, 55), healthy cluster to a cancer cluster. Most frequent reduced trajectory of length 3, was 0, 55, 109, where patients acquire hypertensive diseases (110–115) after cancer.</p> <p>Mood disorders: 9.5% ended their trajectory in cluster 71 where, additional to mood disorders, they were diagnosed with mental and behavioral disorders due to psychoactive substance use (F10–F19).</p>
Jørgensen et al., 2020	<p>Overall: For both types of dementia, many trajectories contained F03 “Unspecified dementia” and subsequently F00 “Dementia in Alzheimer disease.” E10 “Type I diabetes mellitus” and E11 “Type II diabetes mellitus” are common paths toward a dementia diagnosis, as are cardiovascular diseases like I10 “Hypertension,” I20 “Angina pectoris,” and I50 “Heart failure.”</p> <p>Alzheimer’s Disease: 50 significant directional trajectories consisting of three consecutive diseases.</p> <p>Vascular Dementia: 215 significant directional trajectories consisting of three consecutive diseases.</p>
Strauss et al., 2014	<p>Overall: Five trajectories identified: 1) those with no recorded chronic problems; 2) those who developed first chronic morbidity over 3 years; 3) developing multimorbidity group characterized by progressing from zero or one chronic morbidity at the first period to two or three by the sixth period; 4) those with increasing number of chronic morbidities; and 5) multi-chronic group with many chronic morbidities. The most common trajectories started with hypertension in the first period and developed osteoarthritis, diabetes mellitus, and/or pure hypercholesterolemia over the six periods.</p>

CHD: coronary heart disease; CVD: Cardiovascular disease; ICD-10: International Classification of Diseases, version 10.

for movement from one starting condition to another, reported as the number of cases per 1,000 person-years. Separate pathway diagrams representing acquisition sequencing of three conditions were presented.

Haug et al.¹¹⁸ employed machine learning to develop trajectories for risk of cardiovascular mortality based on divisive cluster analysis, in which all persons started in the same cluster and were algorithmically divided into different clusters according to the chronic conditions acquired over time. The study presented cluster trajectories as a multilayer network diagram.

Jørgensen et al.¹¹¹ examined pre-dementia temporal accumulation of multimorbidity for persons with Alzheimer’s disease and vascular dementia. Disease pairs were

examined to determine which condition came first. The relative risk for acquiring the second condition for those with dementia compared to matched controls, was calculated. In addition to relative risks, the study presented temporal disease trajectory networks of diagnoses for persons with dementia, where each condition is a node joined by lines that indicate accumulation pathways.

Strauss et al.²⁵ conducted a latent class growth analysis to identify distinct multimorbidity trajectories. The analysis began with a one-cluster model (all persons having the same trajectory). The number of clusters was increased until most heterogeneity was explained. Quadratic growth curves were applied, and persons were assigned to a cluster in which their posterior probability of membership was

highest. The trajectories of numbers of accumulating conditions were presented graphically using latent class growth trajectories.

Discussion

This systematic review contributes to a growing body of literature concerning the epidemiology of multimorbidity by providing a comprehensive, qualitative analysis of multimorbidity incidence and patterns in the accumulation of chronic conditions. The purpose of most included studies was to determine the incidence of multimorbidity and/or accumulation of component chronic conditions leading to multimorbidity. However, nine studies had other primary objectives and were able to opportunistically examine incidence.^{111,112,116,119,122,123,134,136,141}

Of the 32 studies reporting incidence, five studies reported overall IRs ranging from 1.26 to 68.5 per 1,000 person-years, and 10 studies reported overall cumulative incidence ranging from 1.3% to 61.0%. The wide variation among incidence estimates in these 15 studies may be attributed to differences in: study populations being examined, with some sampling general populations and others sampling patient populations with specific baseline conditions; age and race or ethnicities of study participants; follow-up duration; as well as a lack of uniformity in the criteria that were used to define multimorbidity. The remaining 17 incidence studies reported incidence stratified by sociodemographic and medical factors. This helps elucidate factors impacting multimorbidity; however, it would facilitate comparisons across studies if authors report, where possible, overall rates adjusted for factors known to be associated with multimorbidity, including (at minimum) age, sex/gender, and number of baseline conditions.^{58,142} Only two studies in this review adjusted overall incidence for age and sex.^{129,130}

The findings from this review regarding the relationship between multimorbidity and the number of baseline chronic condition(s), age, and sex generally aligned with previous literature. In studies which presented incidence stratified by baseline disease counts, persons with one chronic condition at baseline had higher incidence of multimorbidity later in life, compared to those with zero at baseline. This may be due in part to underlying genetic mechanisms of chronic diseases¹⁴³; systemic health impacts of chronic conditions in diagnosed individuals¹⁴⁴; and/or persons with a baseline chronic condition being more likely to seek medical help,¹⁴⁵ and therefore more likely to be diagnosed with other illnesses unrelated to the initial illness. Both incidence rates and cumulative incidence were higher in older populations, consistent with the well-documented relationship between age and multimorbidity.^{146–148} Amongst studies reporting incidence by sex, IRs and cumulative incidence were higher for women than men. This relationship between sex and multimorbidity is consistent with literature indicating that women may be

more likely to be diagnosed with chronic conditions because they are more likely to seek medical help^{149–152} and have higher life expectancies than men.^{142,153,154}

Of all identified studies reporting patterns in the accumulation of multimorbidity's component chronic conditions, only five studies met our selection criteria. This review indicates distinct patterns in accumulation of chronic conditions, as reported by studies elucidating cardiovascular and metabolic conditions amongst the most common starting conditions, and cerebrovascular and mental illnesses as common second conditions resulting in multimorbidity. Together, cardiometabolic conditions including stroke, heart disease, and diabetes, contribute to leading causes of morbidity, mortality, lower quality of life, and health resource use globally.^{117,155–157} Understanding disease trajectories as discussed in this review may help clinicians identify persons at greater risk of developing such conditions and better understand their prognosis in order to effectively prevent and manage this set of diseases. Depression was noted as a common starting condition in persons below 65 years of age, which may be attributed in part to cultural trends in digital and communication media, sleep deprivation, and social deprivation in younger persons, contributing to rising rates of mood disorders and suicidal thoughts and behaviors since the mid-2000s, factors which may have a greater impact on younger persons compared to older generations.^{107,158} This result was found only in one study in accumulation, demonstrating the need for future research to confirm these findings in other populations. There is significant diversity in the definition of "patterns" in multimorbidity research, with some studies employing a temporal component^{25,107,111,117,118} and others using the term almost synonymously with patient clusters.⁶³ Methods used to discern accumulation were highly heterogeneous and showed novel applications of advanced statistical techniques. A common feature of the five articles was the use of diagrams to demonstrate temporal relationships. Ongoing innovation in this area bodes well for future research that examines the accumulation of component chronic conditions in multimorbidity and may inform preventative efforts.

We identified articles that used the term accumulation differently than we had initially set out in our objectives, which was to examine the order of chronic condition accumulation leading to an individual having multimorbidity. As such, we excluded studies that measured speed of accumulation of chronic conditions⁴⁶ and those that measured accumulation as most commonly occurring incident dyads and triads of chronic conditions without consideration for order or disease onset.¹³⁰ However, this diversity in the definition of accumulation can add to the richness of understanding multimorbidity incidence, and therefore an in-depth examination taking into account all aspects and forms of accumulation reported across the literature is warranted.

Our review found limitations in the included studies with respect to age, sex and gender, and race and ethnicity. The study of multimorbidity is heavily focused toward adult and elderly populations^{159–161}; however, incidence of multimorbidity amongst children and adolescents who have chronic conditions warrants more attention given their increased risk of developing additional diseases later in life.^{162,163} Additionally, most studies reported patterns by chronic conditions and only one reported patterns by demographic factors, such as age.

All studies in our review were not explicit in their definitions of sex and gender. Such studies are failing to define sex and gender as non-binary variables when studying the health of populations.^{164,165} Among studies that reported race and/or ethnicity, data were collected from different sources ranging from medical records to self-report. The COVID-19 pandemic underscored the importance of calculating race and ethnic-specific incidence of multimorbidity.^{166,167} Routine collection of these data is a necessary step to understanding the role of race and/or ethnicity in multimorbidity incidence.

The findings from our systematic review demonstrate heterogeneity across studies with respect to incidence of multimorbidity and with respect to the order in which component chronic conditions that lead to multimorbidity were accumulated. This is consistent with reviews reporting the prevalence of multimorbidity^{26,28} for similar reasons as have been found in these prevalence studies. The heterogeneity across articles may be due in part to diverse study objectives, study designs, and operational definitions for multimorbidity across the included studies. More specifically, the widely varying number and selection of chronic conditions contributing to the definition of multimorbidity poses significant challenges to the comparison of findings among studies. For example, there is well-established evidence that hypertension is a precursor to multimorbidity in adult populations^{168,169}; however, some studies did not include hypertension in their definition of multimorbidity. This finding may be the result of specific studies' consideration of hypertension as a risk factor and not as a disease.¹⁷⁰

While study specificity in design or operational definition of multimorbidity may allow for more targeted study of multimorbidity within a given population, it contributes to the complexity of comparing incidence and accumulation of multimorbidity across studies. Given the heterogeneity among incidence studies, authors should be transparent in reporting results. At minimum, authors should explicitly state their definition of multimorbidity, clearly indicating the number of co-occurring conditions required to define multimorbidity, and the number and selection of chronic conditions included in their list of component chronic conditions. Additionally, where the available data permit, studies are encouraged to limit defining conditions of multimorbidity to five relevant chronic conditions, including those with well-established links to

increased risk of multimorbidity development, including cardiovascular diseases,^{171,172} hypertension,^{168,170} and diabetes.^{173,174}

This systematic review studied the incidence of multimorbidity and patterns in accumulation of chronic conditions across the lifespan, including children. Our consideration of all age groups is a strength of this review in light of evidence demonstrating the onset of a number of morbidities at younger ages; possibilities for illnesses to transition to chronic status; and the value of early identification in timely intervention and mitigating disease progression.¹²⁷ In addition, incidence rates were stratified by reporting format (IR or cumulative incidence) for more accurate comparison among study findings. This review was conducted in accordance with PROSPERO guidelines by two reviewers, with title and abstract screening, full-text review, data extraction, and quality assessment of studies completed independently. Included studies were mostly of high quality in accordance with the NOS, AHRQ, and Cochrane RoB criteria.

An inherent limitation amongst all systematic reviews is the omission of potentially relevant articles. Due to our inclusion criteria requiring articles to be of either English or French language, 122 non-English/French studies were excluded early in the review process without consideration for inclusion, some of which may have been relevant to our study. In addition, studies of low quality in reporting were not excluded to ensure the full spectrum of literature in multimorbidity was included in this review. This may have impacted the accuracy of these studies' estimates. For example, studies which scored low on representativeness may produce estimates that do not represent the true estimates for their target population; however, it is not possible to discern whether such estimates are inflated or deflated. Similarly, studies which scored low on reporting outcome assessment may have estimates lower than actual because they did not adequately capture every occurrence of multimorbidity. Finally, while studies in this review reported on chronic conditions or non-communicable diseases, three studies also included a small count of acute conditions in their definitions and four did not specify a definition of multimorbidity (Supplementary Table S6). Despite the lack of explicit definition of multimorbidity in these studies, we were confident in including their work given reference to 2+ conditions in prose and/or tables.

Conclusion

Establishing the incidence of multimorbidity is a critical step in understanding the etiology and informing prevention of multimorbidity in general and specific patient populations across the lifespan. This systematic review of 36 studies presents that nearly 31 per 1,000 person-years (IQR 39.5 per 1,000 person-years) and 3% (IQR 28.7%) of the studied populations included in this review are affected by multimorbidity, and that component chronic conditions

contributing to the development of multimorbidity are highly heterogeneous. We recommend that researchers be transparent in reporting the components of their operational definitions of multimorbidity, and that patterns in multimorbidity be differentiated by age group and sex and/or gender to allow more specific analyses of the incidence of multimorbidity, and its implication for health care and health systems. Our findings support the importance of work underway to determine a standardized operational definition of multimorbidity.¹⁷⁵ These practices will allow for more accurate comparison and estimation of the incidence and progression of multimorbidity, and subsequently, more effective disease management and preventative interventions across all stages of life.

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Supplemental material

Supplemental material for this article is available online.

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