

A Systematic Review and Meta-Epidemiology Study on Multimorbidity

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ABSTRACT

Background: With enhanced life expectancy and ageing global populations, the prevalence of multimorbidity continues to increase. However, there is a dearth of evidence linked to multimorbidity diagnoses, treatments, and health outcomes, which remains a concern for future proofing optimal healthcare services. Generating evidence is critical to managing multimorbidity, promoting public health, and minimizing health inequalities via effective healthcare policies that improve quality of life for vulnerable populations. In this study, we assessed meta-epidemiology of multimorbidity to report the gaps in scientific knowledge and clinical practice.

Methods: A systematic methodology was designed and published in PROSPERO (CRD42022347308) to report meta-epidemiology analyses using databases, including PubMed, Web of Science, ScienceDirect, EMBASE, The Cochrane Gynaecology and Fertility Group Specialised Register of Controlled Trials, and MEDLINE for studies published between the 1st of January 1980–31st December 2022. A random-effects model was used to estimate the pooled proportion of multimorbidity in adults. Forest plots, pooled odds ratios, and statistical heterogeneity metrics were used to assess the association between multimorbidity and investigated factors. Funnel plots and Egger's test were used to detect and correct for publication bias.

Findings: We identified women to be 0.32 times more likely to have multimorbidity in comparison to males. In regard to ethnicity, white people were 0.47 times less likely to develop comorbidities than black people. People who identified as a drinker or unmarried were more likely to develop comorbidities than those who are non-drinkers or married, respectively. Regardless of smoking status, people were equally likely to have comorbidity. In terms of environmental influences, people in rural areas were 0.2 times less likely to have comorbidity in comparison to those living in urban areas. Interestingly, people with a higher education level were 0.57 times more likely to develop comorbidities than those with only a high school education.

Conclusion: It is evident that multimorbidity has a significant burden globally and impacts the provision of care necessitated across populations given its association with several social determinants of health. Robust research and healthcare policies are required to better manage multimorbidity in patients. An example of such intervention includes employing prevention programs to reduce risk and incidence of multimorbidity within at-risk populations.

Keywords: Multimorbidity; Public Health; Epidemiology; Health Inequalities; Systematic Review; Meta-Epidemiology

Research in Context

Evidence Before this Study

Despite a growing need for multimorbidity research, studies remain limited. The dearth of evidence linked to multimorbidity diagnoses, treatment, and health outcomes is a concern given that such evidence is key to future proofing enhanced treatments and optimal healthcare services.

Added Value of this Study

To our knowledge this is the first meta-epidemiology study conducted using peer review studies. We provide an evidence base to conduct a meta-epidemiology study in the real-world to compare findings as well as address knowledge and practice gaps to provide better care for populations with multimorbidity.

Implications of the Available Evidence

Our findings provide sufficient information to develop evidence-based policies and better processes for polypharmacy and suggest using cultural adaptations to optimize therapeutic benefit.

Introduction

Multimorbidity is defined as the presence of two or more chronic conditions in a given individual. The rise in ageing populations globally due to improvements in life expectancy elevates risk of chronic health conditions such as diabetes, cancer, human immunodeficiency virus/acquired immunodeficiency syndrome, mental health, and pain conditions [1,2]. Multimorbidity is common amongst vulnerable populations such as those impacted by socioeconomic inequities that accelerate the process for deprivations. In fact, Link and Phelan have found socioeconomic status and support to be “fundamental causes” of disease outcomes due to these factors enabling access to resources regardless of individual-based interventions [3]. On the other hand, younger populations such as adolescents and children with congenital or acquired impairments may suffer from multimorbidity as a result of becoming physically or mentally ill. Patients with multimorbidity are at a higher risk of safety issues due to the use of polypharmacy and complex regimen management prescribed by multidisciplinary healthcare professionals. Given the complexities of combination treatments and competing priorities regarding clinical regimens, communication failure between healthcare professional and patients remains a challenge. Multimorbidity is also highly

associated with worsening clinical outcomes, poorer quality of life, and increasing healthcare expenditures [3-6]. Multimorbidity trends present a challenge for key stakeholders ranging from medical professions across disciplines to community care, which require extensive specialization for hospitals.

On a macroscale, multimorbidity has been associated with varying demographic factors such as gender and region. For instance, women have been linked with higher multimorbidity in certain countries—a consideration for further research and health policy [6,7]. Similarly, emerging research includes systematic reviews and meta-analyses exploring multimorbidity in community settings; however, their study designs included fewer chronic conditions and were restricted to a specific geographic region [8-11]. Researchers who incorporated longitudinal data from 1992 to 2017 concluded that the global pooled prevalence of multimorbidity in community settings was 33.1% [8]; however, no insights on changes in multimorbidity patterns changed as a function of time or number of conditions provided. These multimorbidity patterns were observed by Chowdhury and colleagues while investigating the prevalence of multimorbidity across WHO geographic regions among adults between 2000 and 2021 [12]. They found that multimorbidity patterns by geographic regions, time, age, and gender suggested noticeable demographic and regional differences in the burden of multimorbidity and that the global burden continues at the same pace. Moreover, the authors highlighted the need for effective, integrated interventions to reduce burden of morbidity for older adults in regions with high prevalence such as South America, Europe, and North America. They also found a low prevalence in Africa suggesting the need for improved screening and diagnosis for chronic illness as underdiagnosis may be underlying these observed discrepancies. Similarly, mixed findings regarding prevalence of multimorbidity and the most common comorbid diseases have been found in literature. Tacken, et al. [13] considered 3 categories of chronic diseases: Diabetes, pulmonary diseases, and cardiovascular diseases, and they predicted that multimorbidity among patients over 65 years of age would be over 30%. Moreover, Souza and colleagues [14] analyzed the prevalence trends of multimorbidity among 15 European community-dwelling adults to find large variability in prevalence of multimorbidity in adults aged 50 and older between European countries. In terms of most prevalent co-occurring chronic diseases, systematic reviews on multimorbidity identified depression, hypertension, and diabetes as most prevalent [15,16]. On the

other hand, Garin et al. identified cardiovascular and metabolic diseases as the most common diseases, followed by mental health disorders and musculoskeletal conditions [17]. Overall, the three major broad multimorbidity patterns identified by Wallace and co-authors in individuals aged 65 and older are cardiovascular/metabolic disorders, anxiety/depression disorders, and pain/neuropsychiatric disorders [17,18]. Given the mixed literature in regard to multimorbidity trends, our primary aim for this study was to conduct a comprehensive meta-epidemiology to update the status and identify trends of multimorbidity globally to address gaps in scientific knowledge and clinical practice, thereby effectively contributing enhanced care for multimorbidity populations. We considered gender, age, ethnicities, and races and reported the prevalence of cardiometabolic diseases, musculoskeletal, respiratory, neurodegenerative disorders, and pharmacological treatments used, which were our secondary aims for this study.

Materials and Methods

A systematic methodology was developed and peer reviewed, and the protocol was published in PROSPERO (CRD42022347308). Data from studies that met the eligibility criteria were extracted.

Aim

We aimed to report the differences in multimorbidity by gender, age, race, wealth, marital status, smoking, alcohol consumption, geographic location, and education level.

Eligibility Criteria

Our search strategy included the use of multiple databases, including PubMed, Web of Science, ScienceDirect, EMBASE, The Cochrane Gynaecology and Fertility Group Specialised Register of Controlled Trials, and MEDLINE. The search terms used included multimorbidity, cardiometabolic disease, diabetes type I, diabetes type II, stroke, cardiovascular diseases, cardiomyopathy, heart arrhythmias, myocardial infarction, aortic disease, coronary artery disease, pericardial diseases, insulin, hormone replacement treatments, and menopause. All studies that have been peer reviewed and published in English and that include women born between the 30th of April 1980 and 30th of April 2022 were included. All studies included quantitative measures and designs such as randomized clinical trials, mixed-methods, and epidemiology studies. Studies were excluded from the meta-analysis based on their inability to meet this predetermined criterion to ensure consistency and maintain studies with similar methodological rigor within analyses.

Data Extraction and Management

All participants included within the study experienced multimorbidity. A study specific extraction sheet was designed and employed to include interventions used, tools used, and numerical results. The extraction template also included objectives, outcomes, and demo-

graphics. Studies that included either a sub-analysis linked to a sub-study or an additional analysis were extracted separately if the study duration periods varied. The results of different stages were included as a new row to the data analysis. The extracted, final pooled data was reviewed by two investigators to ensure any disputes were discussed and agreed. The final analysis was reviewed by an independent reviewer prior to submission.

Outcomes

The outcomes included the prevalence of multimorbidity based on biological gender, geographical location, and socio-demographical indicators such as ethnicity, smoking, alcohol consumption, and economical status.

Statistical Analysis Plan

Throughout this study, meta-analysis of single proportion was utilized to synthesize the overall prevalence of selected outcomes of interest. Additionally, a pairwise meta-analysis was used to combine the results of multiple studies containing common denominators and/or outcomes. We used rate and composition ratios to conduct a descriptive analysis of primary demographics and other sociological denominators. Differences were regarded as statistically significant if the p-value was less than 0.05. When the p-value was less than 0.01, the difference was considered to have a higher level of significance. Conducting pairwise meta-analysis enabled us to summarize the overall effect size based on the differences between two interventions. Given that most outcomes of interest in the analysis were dichotomous, meta-analysis with binary data was conducted. Consequently, the pooled odds ratio (OR) with a 95% confidence interval (CI) was employed to assess the effects of the two interventions. Statistical heterogeneity was evaluated by the commonly used measure I² with a p-value; if I² was greater than 50% and the associated p-value was less than 0.01, the dataset being analyzed was determined to be heterogeneous. Conversely, an I² below 50% with a large p-value was determined to have weak heterogeneity.

The random effects model was used in meta-analysis when there is heterogeneity among studies being analyzed and the fixed effects model was employed if no heterogeneity existed. A statistical approach to dealing with heterogeneity is to stratify the dataset into subgroups based on relevant characteristics. When there are more than 10 studies, a subgroup analysis was employed to help identify differences between subgroups and relationships that may be obscured by the heterogeneity in the overall dataset. A chi-squared test was used to determine if there was a significant difference between subgroups. If the test was significant, there may have been publication bias, which means that studies with negative or non-significant results may be less likely to be published than those with positive results. The analysis was performed using R, involving the estimation of treatment effects, subgroup analyses, and result presentation. Egger's

test was utilized to detect publication bias in meta-analysis. This was based on the regression of its accuracy on the size of the standardization effect and evaluated whether there was significant asymmetry in the funnel plot included in the studies.

Results

In total, 165 reported studies are associated with the presence of physical health conditions and physical multimorbidity. These multi-national studies offer potentially valuable insights into several

hypotheses that may influence multimorbidity prevalence. After evaluating 165 systematically, we identified 84 studies to be eligible for inclusion in the meta-analysis (Table 1). The associations between marital status, gender, age group, race, wealth, region, smoking, drinking, living environment, and multimorbidity were analyzed. An increase in multimorbidity functioning was associated with being male, being younger, having a high level of education, wealth, marriage, alcohol, being Caucasian, and living in rural areas. The most prevalent multimorbidity pattern was among people older than 50 years of age with lower education levels (OR = 1.57, 95% CI = 0.80–3.08) [11-175].

Table 1: Characteristics of the studies included in systematic review.

Study ID	Authors	Year	Study Type	Country	Sample Size	Mean Age	Age Range	Meta-analysis Inclusion Y/N
1	Violan, et al. [11]	2014	Cross-sectional	Spain	1,356,761	47.4	19-100	Y
2	Afshar, et al. [19]	2015	Cross-sectional	Myanmar	125,404	72		N
3	Anushree, et al. [20]	2022		India	42,756		60-100	N
4	Arias-de la Torre, et al. [21]	2021	Observational cohort study	UK	34,776		20-50	Y
5	Ataguba [22]	2013		South Africa		26.8		N
6	Banjare, et al. [23]	2014		India	310		60-100	Y
7	Bennett, et al. [24]	2021		UK	15,431	75.6		N
8	Van den Akker, et al. [25]	1998	Longitudinal	Netherlands	60,857		25-100	Y
9	Wolff, et al. [26]	2002	Cross sectional	USA	1,217,103	75.4	65-100	Y
10	Bernardes, et al. [27]	2021	Cohort study.	Brazil	1768	67.5	60-100	Y
11	Bisquera, et al. [28]	2021	Retrospective cohort	UK	826,936	42.4	18-80	Y
12	Bustos-Vázquez, et al. [29]	2017	Cross-sectional study	Mexico	8874		60-100	N
13	Butterworth, et al. [30]	2020	Cluster randomized controlled feasibility trial					N
14	Caraballo, et al. [31]	2022	Cross-sectional	USA	596,355	48.4	18-80	Y
15	Carrilero, et al. [32]	2020	Cross-sectional	Spain	1,189,325		0-14	N
16	Charlton, et al. [33]	2013	Cohort study	England.	282,887		55-100	Y
17	Chauhan, et al. [34]	2022	Cross-sectional	India	31,373		60-100	N
18	Chung, et al. [35]	2021		China	3074	48.5	18-100	Y
19	Cooper, et al. [36]	2015	Cross-sectional analysis	Scotland	1,424,378	43.1 (Participants with intellectual disabilities) 48.0 (Participants with no intellectual disabilities)	18-100	Y
20	Corrao, et al. [37]	2020	A nationwide study	Italy				N
21	Costa, et al. [38]	2020	Cross-sectional	Brazil	23,329	37.9	0-100	Y
22	Costa, et al. [39]	2018	Cross-sectional	Brazil	1451		60-100	Y
23	Diderichsen, et al. [40]	2021						N

24	González-Chica, et al. [41]	2017	Cross-sectional study	Australian	2912	48.9		N
25	Guimarães, et al. [42]	2020	Cross-sectional	Brazil			60–100	N
26	Halonen, et al. [43]	2019	Cross-sectional	Finland	2862	91	90–107	Y
27	Hamiduzzaman, et al. [44]	2022	Qualitative study	Bangladesh	22	72		N
28	Alshamsan, et al. [45]	2017	Cross-sectional study	UK	6690			N
29	Kuan, et al. [46]	2023	Observational cohort study		99,648		25–85	N
30	Siddiqi, et al. [47]	2017	Cross sectional	UK	2234	26.8		N
31	Afuwape, et al. [48]	2006	Retrospective cohort	UK	213	37		N
32	Barron, et al. [49]	2020	Cross sectional	UK	#####	40.9		N
33	Ronaldson, et al. [50]	2021	Longitudinal study	England	56,770	63		Y
34	Earle, et al. [51]	2001	Retrospective case note review	UK	45	66		N
35	Pinto, et al. [52]	2010	Cross-sectional study	England	1090	46.8	16–74	N
36	Wijlaars, et al. [53]	2018	Cross-sectional study	England	763,199		10–24	N
37	Head, et al. [54]	2021	Descriptive epidemiology	England	1,000,000	46		N
38	Head, et al. [55]	2021	Descriptive study	England	991,243		18–81	Y
39	Hussain, et al. [56]	2015	Cross-sectional study	Indonesia	9438		40–100	Y
40	Agborsangaya, et al. [57]	2012	Cross-sectional survey	Canada	5010	46.7	18–80	Y
41	Jackson, et al. [58]	2015	Longitudinal Study	Australian	4896	49.5		N
42	Jantsch, et al. [59]	2018	Cross-sectional	Brazil	3092	41.3	24–69	Y
43	Jerliu, et al. [60]	2013	Cross-sectional	Kosovo	1890	73.4	65–100	Y
44	Johnston, et al. [61]	2020	Prospective cohort study	Scotland	12,150	48		Y
45	Katikireddi, et al. [62]	2017	Cohort study	Scotland	12,743			N
46	Keller, et al. [63]	2018	Cohort study	the Netherlands, Sweden, Denmark, and German	19,013			N
47	Khanolkar, et al. [64]	2021	Cohort study		3723			N
48	Knies, et al. [65]	2022	Longitudinal, nationally representative study	UK	28,523		16–100	Y
49	Kunna, et al. [66]	2017		China and Ghana	15,864		18–100	Y
50	Kuo, et al. [67]	2013	Longitudinal study	Taiwan	959,990			N
51	Mondor, et al. [68]	2017	Retrospective cohort	Canada	1,518,939	75.5		N
52	Lawson, et al. [69]	2013	Cross-sectional	Scotland	7054			N
53	Lu, et al. [70]	2021	Cross-sectional	China	7480	70.79	60–100	Y
54	McQueenie, et al. [71]	2019	National retrospective	Scotland	824,374			N

55	Mercer, et al. [72]	2018	Secondary cross-sectional	UK	659	51.2	18-100	Y
56	Mondor, et al. [73]	2018	Cross-sectional	Canada	113,627		18-100	Y
57	Nielsen, et al. [74]	2017	Cross-sectional	Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Switzerland, Belgium, Czech Republic, Luxembourg, Slovenia, Estonia and Israel	63,842		50-100	Y
58	Niksic, et al. [75]	2021	Cohort study	Spain	1259	68.4	18-100	Y
59	Nunes, et al. [76]	2020	Cross-sectional	Brazil	9412		50-100	Y
60	Or, et al. [77]	2021	The analysis is based on patient-level linked routine data sources on health care	Australia, Canada, England, France, Germany, New Zealand, Spain, Switzerland, and the United States	56,364		65-90	N
61	Orueta, et al. [78]	2013	Cross-sectional	Basque Country	452,698			N
62	Sun, et al. [79]	2022	Anecdotal analysis	UK				N
63	Reilly, et al. [80]	2015	Retrospective cohort	UK	346,551			N
64	Reis-Santos, et al. [81]	2013	Cross-sectional	Brazil	39,881		20-60	Y
65	Kislaya, et al. [82]	2019	Cross-sectional, observational, epidemiological	Portugal	4911			N
66	Ryan, et al. [83]	2018	Cross-sectional	Canada	13,581,191	39.6	0-105	Y
67	Singer, et al. [84]	2019	Longitudinal Study	England	7,130	66 (10.9)	50-100	N
68	Singh-Manoux, et al. [85]	2018	Cohort study	UK	8270	50.2		N
69	Smith, et al. [86]	2014	Cross sectional	UK	1,751,841	54.5		Y
70	Smith, et al. [87]	2021	Multilevel cohort study	England	45,414			N
71	van Zon, et al. [88]	2020	Longitudinal cohort	US	10,719	53.8	50-64	Y
73	Vasiliadis, et al. [89]	2021	Longitudinal cohort	Canada	1570			N
75	Lu, et al. [90]	2023	Cohort study	Australia	11,914	47.7	45-50	Y
76	Zhao, et al. [91]	2020	Population-based, panel data analysis	China	11,817	62	50-100	Y
77	Zhou, et al. [92]	2021	A two-stage cluster sampling method	China	64,395	60	5-98	Y
78	Aarts, et al. [93]	2012	Cohort study	Netherlands	1184	55.4	24-81	Y
79	Aarts, et al. [94]	2011	Cross-sectional	Netherlands	15,188	70	55-90	N
81	Aarts, et al. [95]	2011	Prospective study	Netherlands	1763	55.4	24-81	Y
82	Abizanda, et al. [96]	2014	Cohort study	Spain	842	78.6	70-100	N

85	Agborsangaya, et al. [97]	2013	Cross-sectional	Canada	4946	46.6	18-85	Y
86	Agborsangaya, et al. [98]	2013		Canada	4752	47.7	18-100	Y
88	Alimohammadian, et al. [99]	2017	Cohort Study	Iran	49,946		40-75	Y
89	Angst, et al. [100]	2002	Prospective cohort	Switzerland	591			N
90	Rizzi, et al. [101]	2020	Cross-sectional	Europe	244,258	66.25		N
91	Appa, et al. [102]	2014	Multiethnic cross-sectional cohort	USA	1997	60.2		Y
92	Adams, et al. [103]	2017		USA	400,000			N
93	Amaral, et al. [104]	2018	Cross-sectional	Brazil	264		60-100	Y
94	An, et al. [105]	2016	Cross-sectional	South Korea	10,118	54.8		N
95	Brett, et al. [106]	2013	Retrospective cohort study	Australia	4285	38.2	18-90	Y
96	Arokiasamy, et al. [107]	2015		China, Ghana, India, Mexico, Russia, South	42,236		18-100	Y
97	Sinnige, et al. [108]	2013		Netherlands	120,480	66.9	55-80	Y
98	Zemedikun, et al. [109]	2018	Cluster analysis	UK	502,643	58	40-69	Y
99	Mounce, et al. [110]	2018	Cohort	UK	4564		50-100	Y
100	Taylor, et al. [111]	2010	logistic regression	Australia	3206		20-80	Y
101	Vancampfort, et al. [112]	2017	Cross-sectional	Multiple continents	34,129	62.4		N
103	Vancampfort, et al. [113]	2017	Cross-sectional study	Multiple continents	14,585	72.6	65-100	Y
104	Aubert, et al. [114]	2020	Cross-sectional	Switzerland	1002	63.5	50-80	Y
105	Autenrieth, et al. [115]	2013	Cross-sectional	Germany	1007	75.7	65-94	Y
106	Bähler, et al. [116]	2015	Observational study	Switzerland	229,493	74.9	65-100	Y
108	Bernard, et al. [117]	2016	Prospective cohort	Australia	306	81.8	65-105	Y
109	Biswas, et al. [118]	2019	Cross-sectional	Bangladesh	8763		35-100	N
110	Blakemore et al. [119]	2016	Prospective cohort design	UK	4377	75		N
111	Bowling, et al. [120]	2019	Cross-sectional	USA	4217	56.7	50-64	Y
112	Stewart, et al. [121]	2013	Secondary analysis of data from a sub study of the BEACH (Bettering the Evaluation And Care of Health)	Australia	9156			N
113	Broeiro-Gonçalves, et al. [122]	2019	Cross-sectional	Portugal	800,376	59.8		N
114	Uhlig, et al. [123]	2014		France, Germany, Canada, Australia, Netherlands, New Zealand, UK, USA	8973			N
115	Buurman, et al. [124]	2016	Prospective cohort	The Netherlands	639	78.2		N
116	Calderón-Larrañaga, et al. [125]	2017		Sweden	3363	74.6		N

117	Canevelli, et al. [126]	2020		Italy	185	75.1		N
118	Chamberlain, et al. [127]	2015		USA	198,941			N
119	Chen, et al. [128]	2018		China	30,774			N
120	Ng, et al. [129]	2022	Retrospective cross-sectional study	China	382			N
121	Chudasama, et al. [130]	2019	Longitudinal study	UK	491,939	58	18-100	Y
122	Cimarras-Otal, et al. [131]	2014	Cross-sectional	Spain	22,190			N
124	Chin, et al. [132]	2016	Cross-sectional	China	9259	48	18-100	Y
125	Agrawal, et al. [133]	2016	Cross-sectional	India, China, Russia, Mexico, South Africa, Ghana	40,166	57.8		N
126	Gunn, et al. [134]	2012	Cross-sectional	Australia	6864	50.89	18-76	Y
127	Koh, et al. [135]	2019	Cross-sectional	USA	159	76		Y
128	Hanlon, et al. [136]	2018	Prospective, population-based cohort study	UK	493,737		37-73	N
130	Jovic, et al. [137]	2016	Secondary data analysis	Serbia	13,103	49.4	20-100	Y
131	Juul-Larsen, et al. [138]	2020	Longitudinal prospective cohort	Denmark	369			N
132	Fortin, et al. [139]	2005	Secondary analysis	Canada	16,782			N
133	Ie, et al. [140]	2017	A cross-sectional	USA	1084			N
134	Ishizaki, et al. [141]	2019		Japan	2525	76.9	60-100	Y
135	Schwartz, et al. [142]	2017	A stratified, two-stage, randomized, cross-sectional health survey	Mexico	1002	47.72	18-100	Y
136	Demirchyan, et al. [143]	2013		Armenia	721	58.8		N
137	Fabbri, et al. [144]	2015	Cross-sectionally	Italy	695	72.3	60-95	Y
138	Blay, et al. [145]	2015	Longitudinal study	USA	4034	73.44	64-100	Y
139	Kang, et al. [146]	2017	Cross sectional	South Korea	590	32.2	20-80	Y
140	Harrison, et al. [147]	2014	Cross sectional	Australia	8707		20-89	Y
141	Khan, et al. [148]	2019	Cross sectional	Bangladesh	12,338	58.6 (SD $\pm$ 9.2) years	35-100	Y
142	Khanam, et al. [149]	2011	Cross sectional	Bangladesh	452		60-100	Y
144	King, et al. [150]	2018	Cross-sectional	USA	57,303		20-100	Y
145	Gandhi, et al. [151]	2020	Cross-sectional	USA	9499		20-80	Y
146	Gaulin, et al. [152]	2019	Retrospective cohort	Canada	5,316,832	51.2 $\pm$ 17.93		N
148	Rizzuto, et al. [153]	2017	Population-based cohort study	Sweden	1099		78-100	Y
149	Dhalwani, et al. [154]	2017	Longitudinal Study	UK	5476	61	50-100	Y
150	Excoffier, et al. [155]	2018	Longitudinal Study	UK		56.5 (20.5)		N
152	Galenkamp, et al. [156]	2016	Longitudinal Study	The Netherlands	2046	69.2		N
153	Gawron, et al. [157]	2020	Retrospective cohort study	USA	741,612			N

154	Habib, et al. [158]	2014	Cross-sectional	Lebanon	2501	46.6		N
156	Hayek, et al. [159]	2017		Australia	8707			N
157	Miller, et al. [160]	2019	Cross-sectional	USA	3212	76	68-100	Y
158	Hernández, et al. [161]	2019		Ireland	6101			N
159	Ho, et al. [162]	2014	Cross-sectional and longitudinal	Singapore	1844	66.15		N
160	Kingston, et al. [163]	2018	Dynamic microsimulation model		9,723,900			N
161	Garin, et al. [17]	2016	Cross-sectional	China, Ghana, India, Mexico, Russia, and South Africa	32,715	62.1	50-100	Y
162	Kriegsman, et al. [164]	2004	Longitudinal design	Netherlands	2489	69.2	55-85	Y
163	Kristensen, et al. [165]	2019	Cross-sectional	Germany	7604	64.37	40-80	Y
164	Kristensen, et al. [166]	2019	Longitudinal	Germany	19,605	63.47	40-80	Y
165	Lai, et al. [167]	2019	Sex-specific age-period-cohort analysis with repeated cross-sectional surveys	Hong Kong (SAR of China)	69,636			N
158	Lai, et al. [168]	2019	Prospective	Hong Kong (SAR of China)	300		18-77	Y
159	Laires,, et al. [169]	2019	Cross-sectional	Portugal	15,196		25-79	Y
160	Lang, et al. [170]	2015	Cross-sectional,	USA	3058	53.4	40-64	Y
161	Le Cossec, et al. [171]	2016	Cross-sectional	France	15,325	70		N
162	Vogeli, et al. [172]	2007	Cohort study	USA	741,847			N
163	Li, et al. [173]	2021		Taiwan	20,898		65-100	Y
164	Lujic, et al. [174]	2022	cohort study	Australia	90,352	70.2	45-80	Y
165	Lupiáñez-Villanueva, et al. [175]	2018	Cross-sectional	14 European countries	14,000			N

Meta-Analysis

Prevalence of Multimorbidity Cohort: We explored the prevalence of the multimorbidity cohort to assess the proportion of people with multimorbidity. Meta-analysis of single proportions was applied to 84 studies with a sample of 24,160,411 individuals, resulting in a prevalence of 33% [95% CI = (0.28, 0.38)]. Figure 1 shows the forest plot for 84 studies. A high degree of heterogeneity with 100% of I² (p-value < 0.05) was seen indicating statistically significant heterogeneity. To explore the sources of heterogeneity, a subgroup analysis was conducted based on the geographical locations of the studies and demonstrated in a forest plot (Figure 2). Of the 84 studies, 59 studies were from high-income countries (HICs), whereas 24 were from middle-income countries (MICs). No significant subgroup difference (p-value = 0.95 and I² of 100%) was identified between high-income

countries and middle-income countries when considering approximately all age groups, as shown in Figure 2. A moderate level of heterogeneity was seen across countries when exploring the association between age and multimorbidity. Figure 3 shows a statistically significant difference (p-value < 0.05) identified between HICs and MICs when considering only adults aged 50 and older, where the pooled prevalence was 36% [95% CI = (0.26, 0.49)] and 53% [95% CI = (0.44, 0.64)], respectively. Additionally, heterogeneity remained unchanged in HICs (I² = 100%, p-value < 0.05) and MICs (I² = 100%, p-value < 0.05), indicating that the identified heterogeneity was not influenced by geographical location (Figure 3). The value of χ^2 was 4.24, indicating the differences between subgroups to be significant. Therefore, people over 50 in middle-income countries were found to be more likely to have multimorbidity than their counterparts in high-income countries.

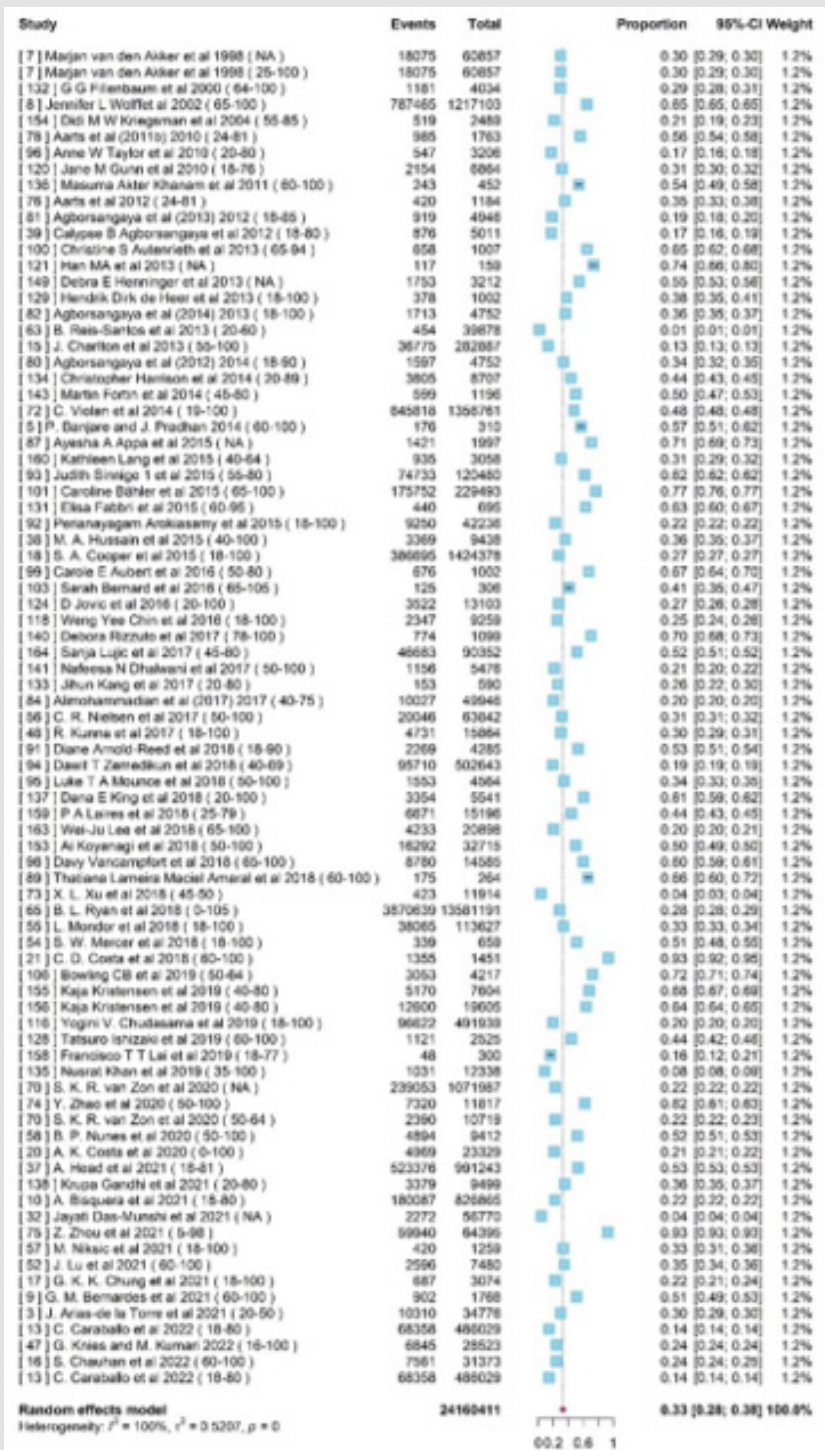


Figure 1: Forest plot for the prevalence of multimorbidity cohort across 84 studies.

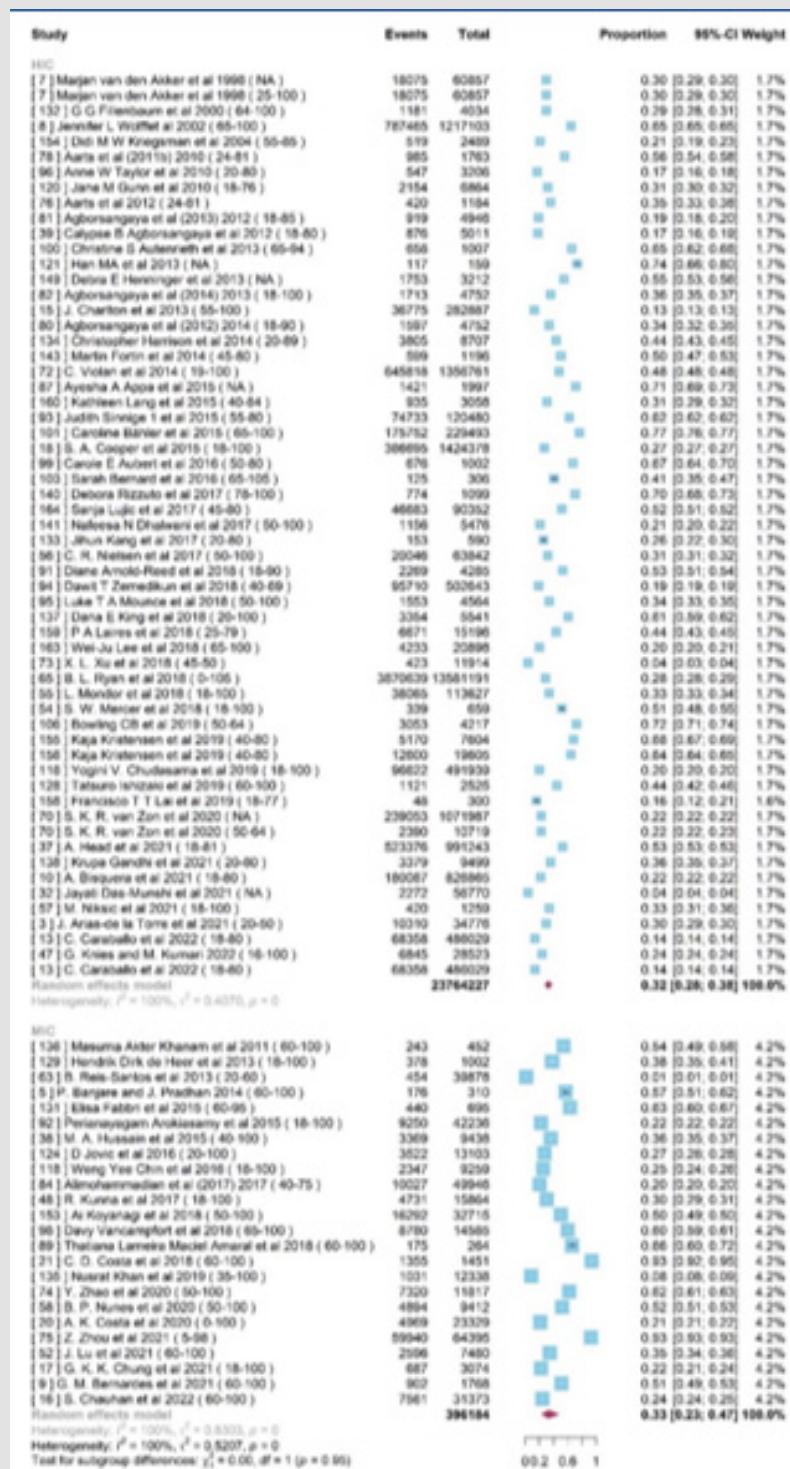


Figure 2: Forest plot for the prevalence of multimorbidity in MICs and HICs.

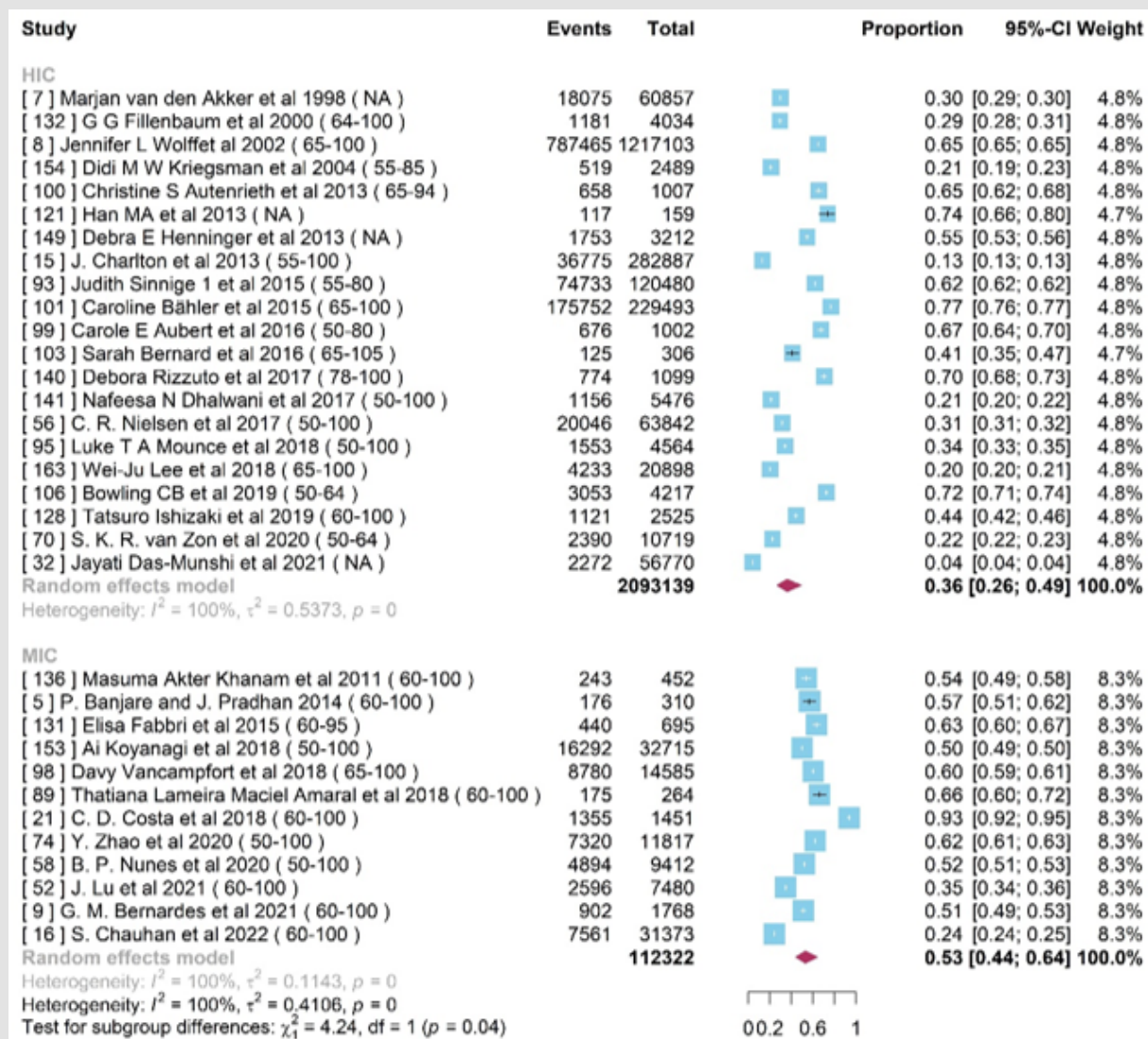


Figure 3: Forest plot for the prevalence of multimorbidity in MIC and HIC age 50 above.

Gender Differences: A total of 34 studies with a sample size of 17,267,458 people reported differences in multimorbidity levels between females and males. The pooled odds ratio (OR) of multimorbidity between females and males was 1.32 [95% CI = (1.21, 1.43)],

indicating that females were 0.32-times more likely to have multimorbidity in comparison to males. A high heterogeneity of 99% of 12 (p-value < 0.01) is identified in Figure 4.

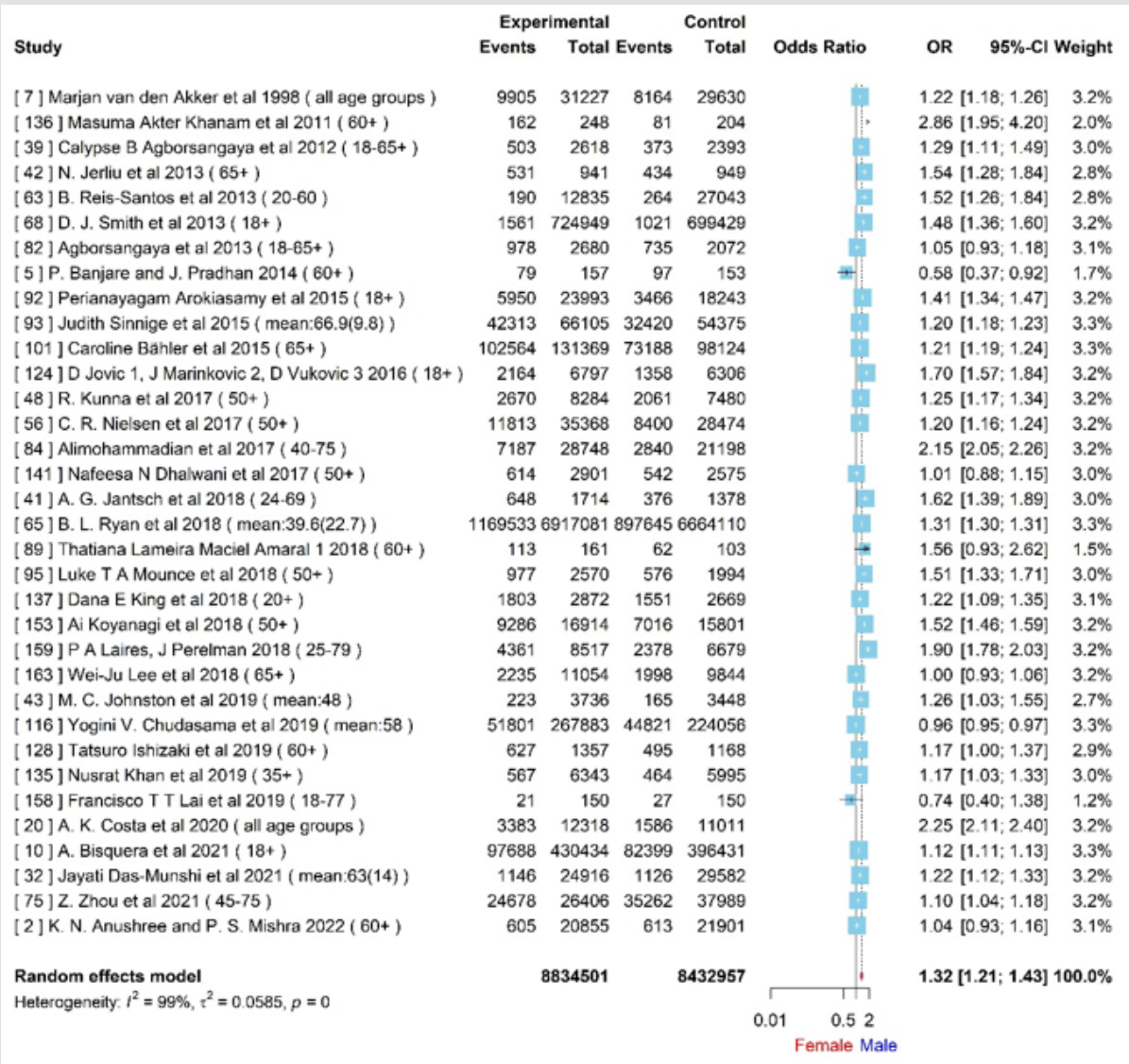


Figure 4: Forest plot for the association between multimorbidity and gender.

Rural-Urban Differences: Of the sample, five studies included rural and urban populations. This is significant evidence of statistical heterogeneity (of $I^2 = 99\%$, p -value < 0.01). Figure 5 shows a pooled OR of 0.8, but [95% CI = (0.60, 1.06)] included 1, which indicates no

statistical significance. Based on systematic analyses, our findings indicated that people living in rural areas are 0.2 times less likely to have comorbidity compared to those living in urban areas.

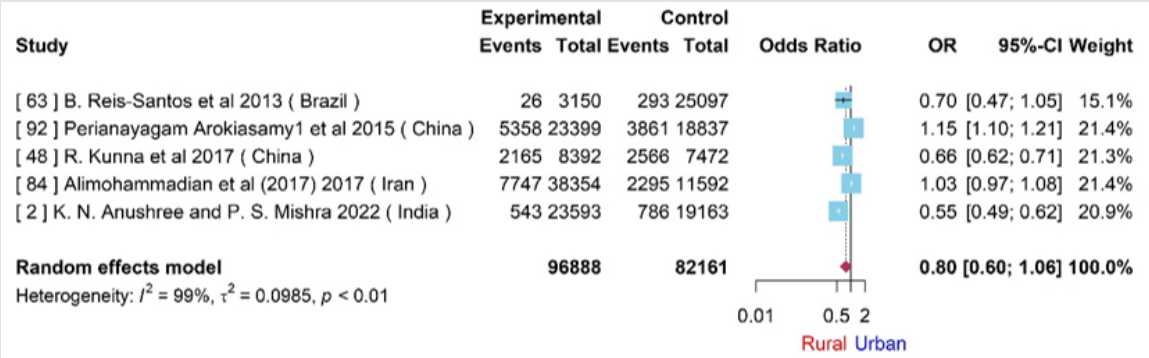


Figure 5: Forest plot for difference of multimorbidity with rural and urban areas.

Difference between Smokers and Non-Smokers: Figure 6 depicts how researchers of eight studies conducted a large-scale survey covering 10 countries (n = 619,862) to study the comorbidity responses to smoking versus not smoking. Moreover, significant evidence of statistical heterogeneity was found (of $I^2 = 99\%$, p-value <

0.01). A pooled OR of 1.00 [95% CI = (0.84, 1.19)] was not statistically significant. Based on systematic analyses, our findings indicated that people are equally likely to have comorbidity whether they smoke or not.

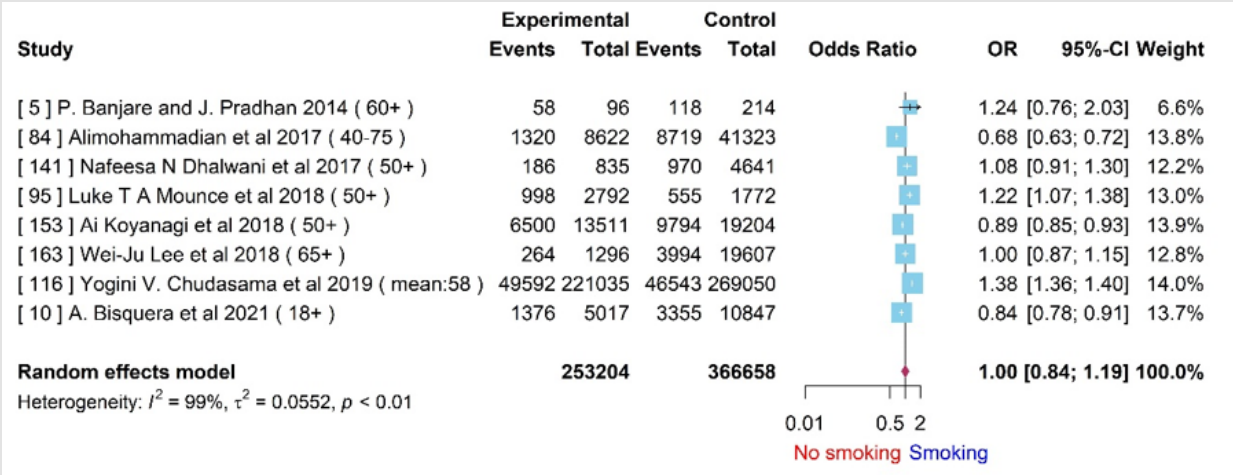
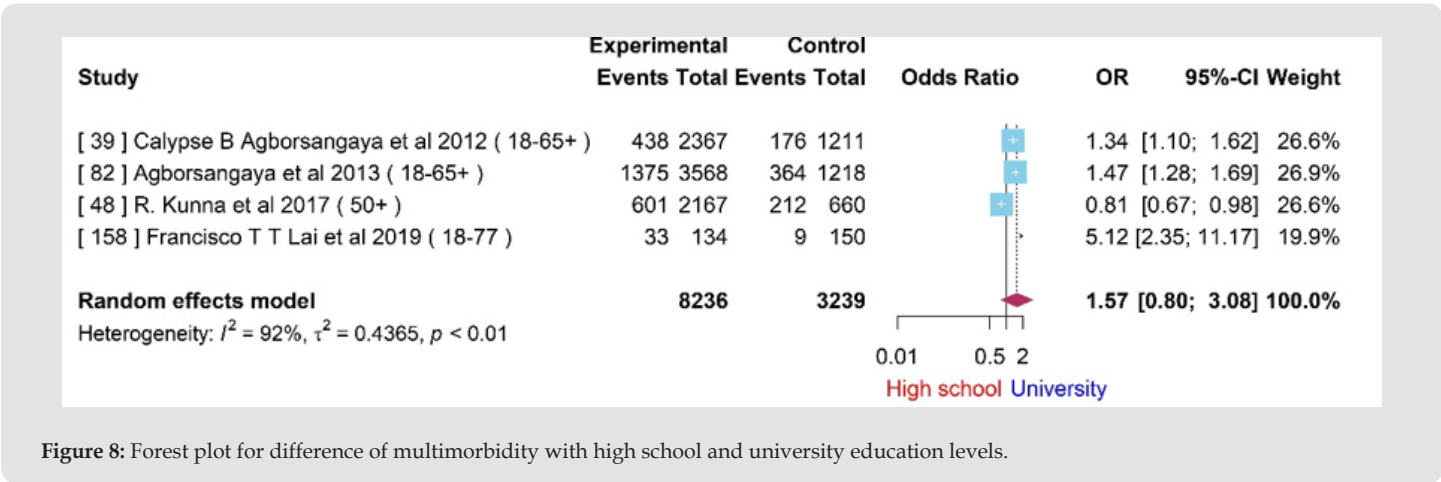
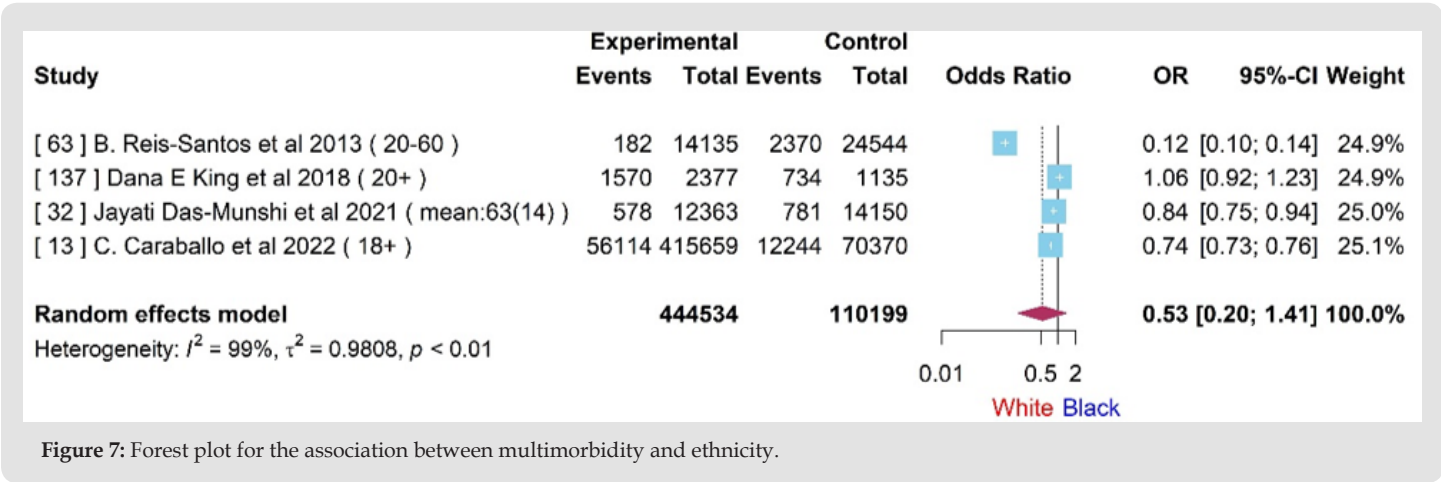


Figure 6: Forest plot for the association between multimorbidity and smoke.

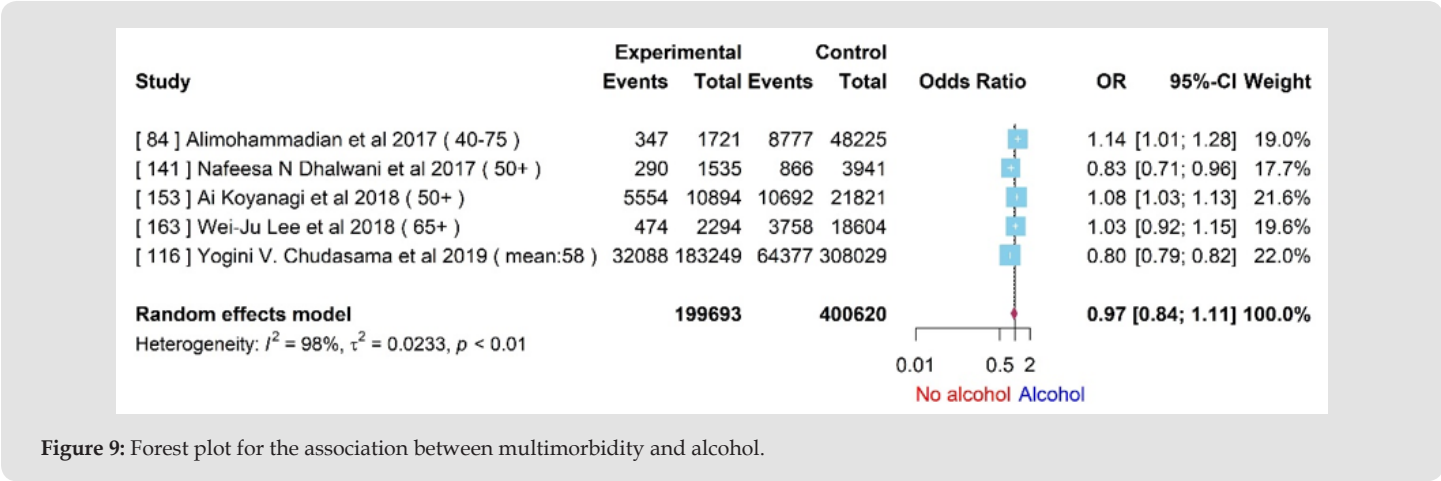
Differences between Black and White Patients: The factor of ethnicity has been extensively discussed in numerous studies; for example, Caraballo, et al. [31] and King, et al. [150] discovered that multimorbidity was common and had been increasing in the United States due to temporal trends in ethnic disparities. By examining the roles of white and black ethnicities in multimorbidity and improving a forest plot targeted systematic review, a meta-analysis was conducted with a total sample size of 554,733 people across 4 studies (Figure 7). The pooled odds ratio (OR) was 0.53 [95% CI = (0.20, 1.41)], which was not statistically significant. Based on systematic analyses, our findings indicated that white people are 0.47 times less likely to develop

comorbidities than black people. The associated $I^2 = 99\%$ (p-value < 0.01) showed that the sample had a high degree of heterogeneity.

Differences in Educational Status: A total of four studies with a sample size of 11,475 people reported differences in comorbidity levels between high school and university settings. The pooled odds ratio (OR) was 1.57 [95% CI = (0.80, 3.08)], which was not statistically significant. Based on systematic analyses, our findings indicated that people with a college education are 0.57 times more likely to develop comorbidities than those with only a high school education. Figure 8 indicates significant evidence of statistical heterogeneity ($I^2 = 92\%$, p-value < 0.01).



Difference among Patients that Consume Alcohol: We conducted a meta-analysis of five studies with a sample size of 600,313 patients. A high heterogeneity was detected with $I^2 = 98\%$ and p -value < 0.01 (Figure 9). The random effects model reported an odds ratio (OR) of 0.97 [95% CI = (0.84, 1.11)], which was not statistically significant. Based on systematic analyses, our findings indicated that people who do not drink are less likely to develop comorbidities than those who drink.



Socioeconomical Status: To assess if wealth is a helpful indicator of comorbidity, it is crucial to study a sample size of 215,766 people across five studies; the results are shown in Figure 10. As indicated in the forest plot, the pooled odds ratio (OR) of multimorbidity between poor people and rich people was found to be 1.34 [95% CI = (0.86,

2.07)], which was not statistically significant. Based on systematic analyses, our findings indicated that poor people are 0.34 times more likely to have multimorbidity compared to rich people. The value of 100% of I2 (p-value < 0.01) indicated significant statistical heterogeneity.

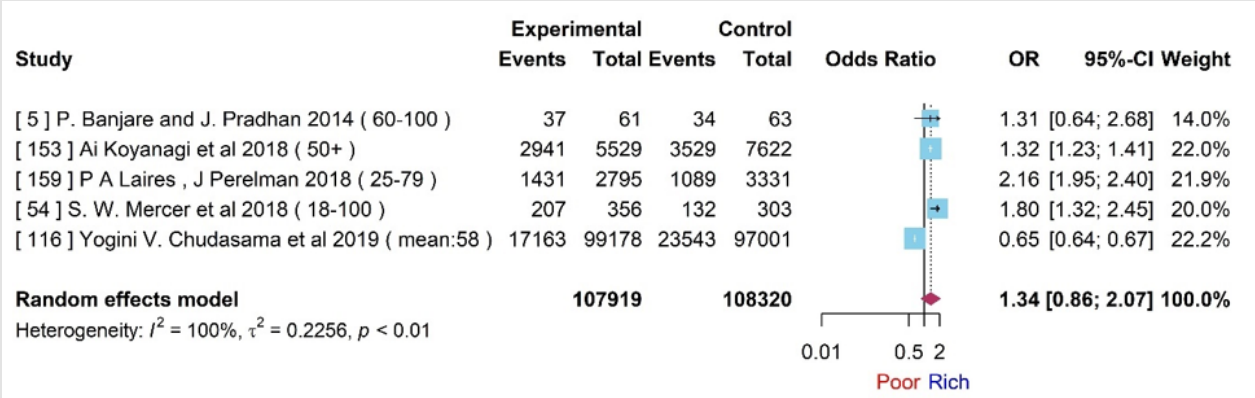


Figure 10: Forest plot for the rich-poor difference in multimorbidity cohort.

Difference between Married and Non-Married Individuals: To explore the association between multimorbidity cohorts in married and non-married people, a meta-analysis was applied to four studies with a total sample size of 63,043 people. Our findings revealed that people have a substantial reduction in their risk of having comorbidities when they are married. Figure 11 shows that the pooled

odds ratio (OR) of multimorbidity between married and non-married people was 0.94 [95% CI = (0.52, 1.68)], which was not statistically significant. Figure 11 indicates significant evidence of statistical heterogeneity (I2 =98%, p-value < 0.01). We observed that, on average, unmarried people are more likely to develop multimorbidity than people who are married.

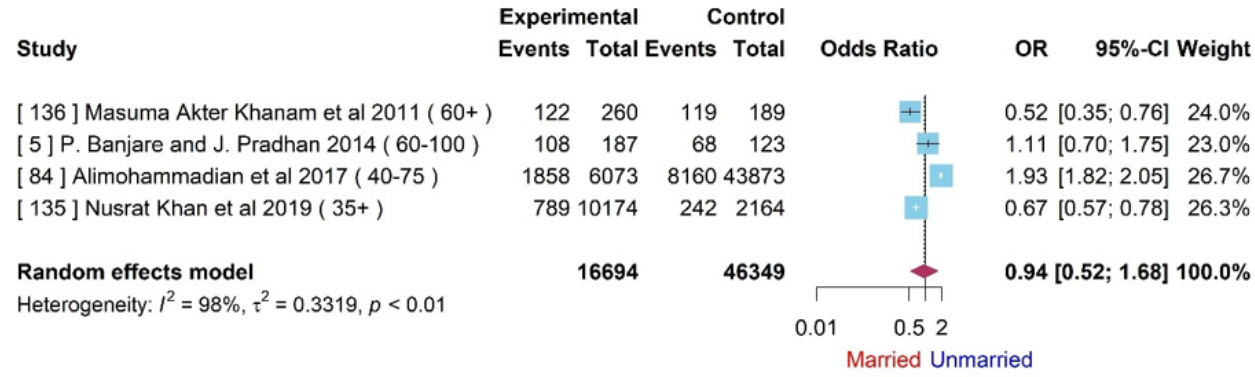


Figure 11: Forest plot for the association between multimorbidity and marriage.

Publication Bias: Considering that studies reporting statistically significant outcomes are more likely to be published, this bias can distort the representation of the true effect size, leading to an overestimation of the effectiveness of certain treatments or interventions. To address the impact of publication bias, we utilized funnel plots and Egger’s test to identify such bias. Given the limitations of a small sample size, which can result in a more dispersed distribution in the funnel plot and diminish the statistical power of Egger’s test, we pres-

ent the publication bias analysis specifically for our gender-specific meta-analysis (Figure 4), in which the number of studies was 34. It is noteworthy that within this gender-specific analysis, we found a greater proportion of female representation compared to males in the multimorbidity-affected group. The heterogeneity among the studies was strikingly high (I2 = 99%, t2 = 0.0585, p < 0.01), indicating substantial variability in the study results.

The funnel plot displayed in Figure 12 suggests moderate publication bias, as evidenced by the asymmetric distribution of the studies, which is a common visual indicator of such bias. Nonetheless, the p-value obtained from the Egger’s test, depicted in Table 2, for our meta-analysis examining the relationship between multimorbidity and gender was 0.8196. This value, which was higher than the conventional threshold for statistical significance, indicated that there was no detectable effect size associated with publication bias in this analysis. Consequently, we concluded that there was no significant publication bias present. It is important to recognize that these methods may be susceptible to other biases, including differences in study design variations in study quality, which can confound the interpretation of the results.

Table 2: Egger’s test for the gender effect on multimorbidity.

Linear regression test of funnel plot asymmetry			
Test result: t = -0.23, df = 32, p-value = 0.8196			
Sample estimates:			
bias se.bias intercept se.intercept			
-0.4692	2.0407	0.2474	0.0164
Details:			
- multiplicative residual heterogeneity variance (tau2 = 115.4231)			
- predictor: standard error			
- weight: inverse variance			
- reference: Egger et al. (1997), BMJ			

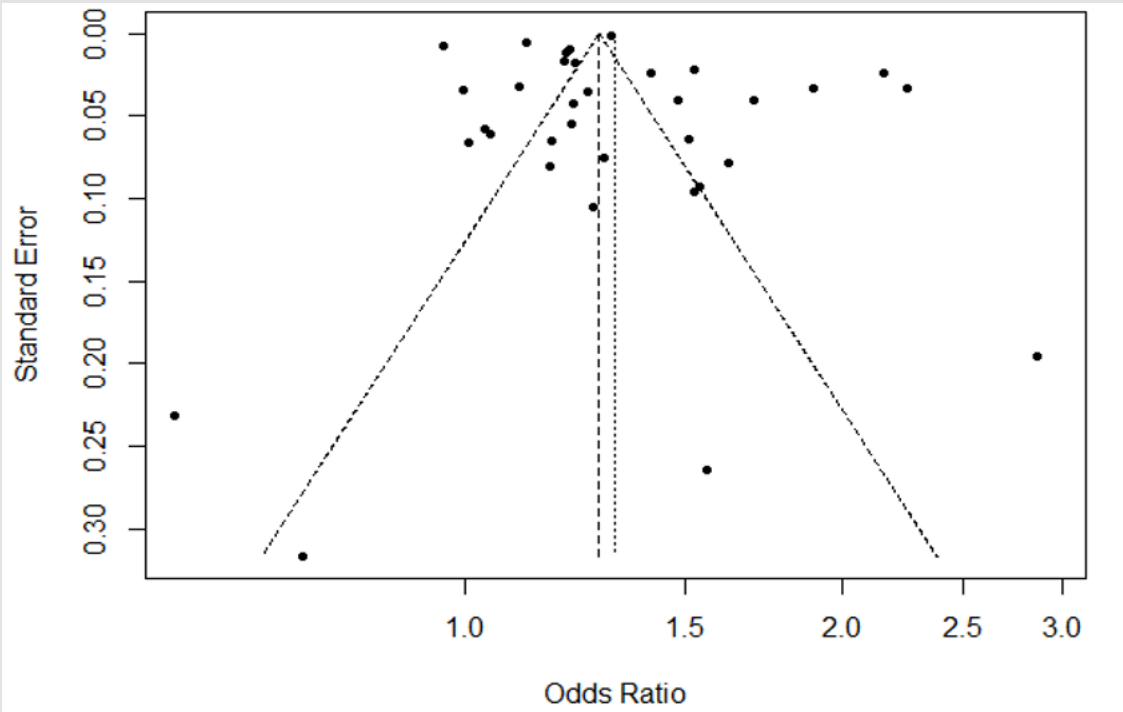


Figure 12: Funnel plot of studies included in the meta-analysis of multimorbidity with gender effect.

Discussion

This study represents the first meta-epidemiology study that includes review papers published more than 42 years ago on the increasingly critical condition of multimorbidity. Multimorbidity is considered, by WHO, to greatly burden the health of people globally, with the sole exception of Africa, wherein the challenge of underdiagnosis plagues our understanding of true burden in patient populations. We included 165 papers for systematic review and 84 papers within the meta-analysis of a total of 278 identified publications. Researchers [12-18] have identified a vast spectrum of medical conditions as the

most prevalent co-occurring chronic diseases in people with multimorbidity. This spectrum includes depression, hypertension, diabetes, mental health disorders, cardiovascular and metabolic diseases, musculoskeletal conditions, and neuropsychiatric disorders. Despite these conditions being considered the major broad multimorbidity patterns, limited insights on how multimorbidity patterns evolve over time or based on the number of conditions have been reported. In this study, we assessed the association between multimorbidity and demographic factors, including gender, age, ethnicity, and geographical location.

We also evaluated lifestyle factors such as smoking and alcohol consumption as well as economic indicators, including wealth, marriage status, and education level to report comprehensive findings. In doing so, we were able to holistically evaluate the relationships between social determinants of health and multimorbidity and report effect sizes found via meta-analysis. In exploring gender and multimorbidity, our results aligned with the findings by Zielinski & colleagues, and multimorbidity is highly prevalent among women of all ages, which is contrary to the common perception that it is confined to geriatric populations [176]. It is possible these findings are attributable to more realistic reporting as women tend to share more information with healthcare facilities compared to males. On the other hand, exposure to common risk factors, such as higher rates of smoking, physical inactivity, and obesity, as well as psychosocial stressors and socioeconomic disadvantages, could also be a driving factor for the elevated prevalence of multimorbidity. These factors are well-documented in the literature as having a significant impact on women's health, thereby contributing to the higher incidence of multiple chronic conditions. Given the significant rise in life expectancy and declining fertility rates, the increase in older populations globally is expected with 1 in 6 people predicted to be over 65 years old by 2050 [177]. Countries such as India and China are experiencing major transitions leading to a significant increase in the proportion of older populations, rise in associated medical and biopsychosocial needs, and, thus, elevated prevalence of multimorbidity.

Similar to gender and age, ethnicity is one of the factors that has been extensively investigated in association with multimorbidity over the last 40 years. We found that white people are 0.47 times less likely to develop comorbidities compared to black people. Interestingly, Kuan and co-authors [46] examined multimorbidity patterns stratified by ethnicity and other factors such as race, sex, and age for 308 health conditions ($n = 872,451$; eligible patients). They reported that white individuals (78.7% of 2,666,234) are more likely to be diagnosed with two or more conditions than black individuals (60.1% of 98,815) or south Asian individuals (60.2% of 155,435). Additionally, they identified that spinal fractures are most strongly non-randomly associated with malignancy in black individuals, but with osteoporosis in white individuals. It was reported that multimorbidity has been increasing in the United States due to temporal trends in ethnic disparities [31,150]. Taking our findings in conjunction with the findings of Kuan et al. regarding differential diagnosis of spinal fractures, this highlights the dire need for improved understanding and management of multimorbidity across ethnic groups. To manage multimorbidity patients, it is also vital to ensure local healthcare systems understand the differences between the rural and urban comorbidities. This is crucial as multimorbidity is also a strong predictor of mortality, disability, and poor quality of life [178]. We found that rural populations are 0.8 times less likely to face multimorbidity compared to those in urban areas. From an economic perspective, having knowledge of the difference in prevalence and type of comorbidities found

by region may inform improved resource and expenditure allocation in healthcare systems. From a clinical perspective, these findings and further research can be a step towards personalized healthcare by improving patient-physician interaction, as physicians will be more aware of regional differences in comorbidity to prescribe polypharmacy use or self-management. Lifestyle factors such as smoking and alcohol consumption that are known to have a negative causal impact on health were also evaluated in relation to multimorbidity. There is significant evidence that smoking negatively impacts individual health and worsens comorbidities such as hypertension, cardiac conditions, and diabetes [179].

Though our results indicated that women may have comorbidities regardless of their smoking status, a study conducted by Han and colleagues indicated smoking cessation in a Canadian cohort reporting the need for behavioral change following cancer, diabetes, cardiac disease, and stroke [180]. Similarly, there is sufficient evidence of excessive alcoholic consumption and an increased risk of health issues such as unintentional injuries, depression, brain disorders, violence, liver diseases, cancer, and reduced health-related quality of life, elevating the likelihood of multimorbidity and mortality. Our results indicated that people who do not drink are less likely to develop comorbidities than those who do. A national survey in the United States [181] on Drug Use and Health from 2005 to 2014 involving excessive alcohol consumption and lifetime medical conditions (13 medical conditions and medical multimorbidity of at least 2 diseases) among adults over 50 years old who are either binge drinkers or non-binge drinkers reflected that multimorbidity is lower among binge drinkers compared to non-binge drinkers; this causes significant health risks, especially with the concurrent use of other substances. Moreover, providing that socio-economic indicators such as education levels, wealth, and marriage impact access to resources and health outcomes, it is imperative that they are assessed in relation to multimorbidity.

Pathirana and colleagues [182] reported, from a review of 24 cross-sectional studies, that low versus high education level and deprivation are consistently associated with increased risk of multimorbidity, whereas the evidence on association with family income is inconclusive (or mixed). A German cross-sectional study involving 19,294 adults with a total of 17 self-reported health conditions along with sociodemographic characteristics [183] indicated that adults aged 40–49 years with lower levels of education are more likely to suffer multimorbidity with a prevalence of 47.4% matching those of highly educated individuals. Our findings indicated that people with higher education level are 0.57 times more likely to develop comorbidities than those with a low level of education. Regarding the correlation between wealth and multimorbidity, our results indicated no significant difference between high-income countries ($n = 59$) and middle-income countries ($n = 24$) when all age groups were considered; however, people over 50 years in middle-income countries are more likely to have multimorbidity compared to high-income countries. In light of such findings, it is key that emphasis in the develop-

ment of national public health approaches and prevention programs on multimorbidity is placed on supporting adults over the age of 50, especially those in middle income countries and individuals with lower levels of education. It is key to note the limitations that underdiagnosis or underreporting in certain countries may have on the findings of economic indicators and reported multimorbidities.

On the other hand, we found that prevalence of marriage was inversely associated with multimorbidity, and people showed a substantial reduction in risk of having comorbidities when they got married. These findings align with existing evidence that married individuals have better health-related quality of life and wellbeing compared to those who are unmarried. A study by Wang and team [184] was conducted using a nationally representative data on 23,641 adults aged 50–60 years old who participated in four longitudinal studies in the US, UK, Europe, and China. The researchers reported that individuals who have been married for 21–30 years have a lower multimorbidity rate than those who are married for less than 10 years. These associations remained robust after adjusting for socioeconomic and lifestyle factors. Though the association of marriage and multimorbidity has not been investigated across all age groups, these results are mainly due to influence of marital partners on reinforcing healthy behaviors and discouraging habits such as smoking and drinking. These findings highlight the protective role that marital relationships may play against multimorbidity by preserving overall health and wellbeing. While we identified several differences and associations in the prevalence of multimorbidity among demographic groups, it is important to note that not all of these findings reached statistical significance. This limitation underscores the need for cautious interpretation of the results, as the observed trends may not necessarily reflect true associations. Future research with larger sample sizes and more rigorous study designs is warranted to confirm these findings and elucidate the underlying mechanisms driving these associations.

Limitations and Future Recommendations

Considering that studies reporting statistically significant outcomes are more likely to be published, this bias can distort the representation of the true effect size, leading to an overestimation of the effectiveness of certain treatments or interventions. To address the impact of publication bias, we utilized both funnel plots and Egger's test to identify any such bias. Given the limitations of a small sample size, which can result in a more dispersed distribution in the funnel plot and diminish the statistical power of Egger's test, we present the publication bias analysis specifically for our gender-specific meta-analysis (Figure 4), in which the number of studies was 34. It is noteworthy that within this gender-specific analysis, we found a greater proportion of female representation compared to males in the multimorbidity-affected group. The heterogeneity among the studies was strikingly high ($I^2 = 99\%$, $t_2 = 0.0585$, $p < 0.01$), indicating substantial variability in the study results. The funnel plot displayed in Figure 12 suggests moderate publication bias, as evidenced by the

asymmetric distribution of the studies, which is a common visual indicator of such bias. Nonetheless, the p-value obtained from the Egger's test, depicted in Table 2, for our meta-analysis examining the relationship between multimorbidity and gender, was 0.8196. This value, which is higher than the conventional threshold for statistical significance, indicated that there was no detectable effect size associated with publication bias in this analysis. Consequently, we concluded that there was no significant publication bias present. It is important to recognize that these methods may be susceptible to other biases, including differences in study design and variations in study quality, which can confound the interpretation of the results.

Conclusions

Our findings regarding multimorbidity and its association with demographic, lifestyle, and economic factors can support development of evidence-based policies and inform cultural or regional adaptations of clinical management such as polypharmacy to optimize therapeutic benefits for patients with multimorbidity. Some key considerations for clinical management from our findings include identifying women, black people, and unmarried individuals who are drinkers at high risk of multimorbidity. Additionally, the finding that marital status may have protective effects against multimorbidity through the encouragement of healthier behaviors alludes to the role that socially focused interventions may have in negatively reinforcing lifestyle factors that increase risk of multimorbidity in populations. High prevalence of multimorbidity places significant burden on healthcare systems as well as the global population. Thus, it is imperative that robust research and healthcare policy be implemented for optimal multimorbidity management. It is also essential to acknowledge that some of the observed associations in our study did not reach statistical significance, and the potential for publication bias must be considered when interpreting these findings. Last, earlier stage interventions such as prevention programs to reduce risk of multimorbidity in at-risk populations may support a decreased incidence of cases. Future research with larger sample sizes and comprehensive methodologies is necessary to validate our findings and inform evidence-based policies and interventions.

Use of AI Tools Declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Authors' Contribution

GD developed the FEINMAN project as part of the ELEMI program. The statistical analysis was developed by GD and JQS. The analysis was performed by GD, GL, XY and JQS. GD and YB wrote the initial

draft of the manuscript. PP reviewed the subsequent draft: GD, YB, PJ, GL, XY, HC, SK, AS, PP, and JQS reviewed and approved the final manuscript version.

Conflicts of Interest

All authors report no conflict of interest. The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health and Social Care or the Academic institutions.

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