FRESHER

FORESIGHT AND MODELLING FOR EUROPEAN HEALTH POLICY AND REGULATION

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Report on meta-analyses

Report Information

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1 INTRODUCTION

Comorbidity or multimorbidity is the concurrence of multiple diseases in the same person. Although the terms comorbidity and multimorbidity are used interchangeably, increasingly a distinction is being made comorbidity is used to designate the presence of other diseases in relation to an index disease and multimorbidity, meaning any co-occurrence of medical conditions within a person. The present report uses the term as designated by multimorbidity, the coexistence of two or more chronic conditions in the same individual.

Multimorbidity is increasingly common, probably due to ageing populations, lowered threshold of diagnosis, inclusion of traditional risk factors such as obesity into its definition, longevity achieved through advances in medical care or possibly a true increase in the prevalence of some chronic diseases. Ageing populations are characterized by the co-occurrence of multiple chronic conditions. Chronic conditions generally cluster and individuals with one chronic condition are likely to have other conditions as well. As such, many older adults now manage two or more chronic conditions at the same time; and evidence suggests that the presence of multimorbidity is expected to continue to rise. The continuing shifts in population demographic as the baby-boomers reach age 65, which will yield an elderly population characterized by declining death rates, increasing life expectancy, and increasing health care costs.

The research on multimorbidity remains in its infancy. Traditionally, studies on chronic diseases have focused mainly on a single disease or different disease conditions in isolation but not multimorbidity *per se*. The dearth of studies relevant to this issue, even in industrialised countries, is surprising given that prevalence of multimorbidity is very high in these countries. Indeed, multimorbidity in industrialised countries is described as the rule rather than the exception, at least in primary care. Healthcare delivery is typically guided by clinical practice guidelines that are oriented towards single-diseases. From a public health perspective, surveillance systems for chronic diseases tend to focus on single conditions. This poses a challenge for primary care professionals who try to implement evidence from these guidelines in caring for patients with multimorbidity. Individuals with multimorbidity are therefore at increased risk of receiving less than best practice care, more frequent and longer hospitalizations, higher health care costs and increased use of polypharmacy with the

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potential for adverse drug effects.

Multimorbidity is a challenge to patients, clinicians, healthcare systems, and researchers. It is associated with poor health outcomes, including higher mortality and lower quality of life, resulting in more complex healthcare needs and higher healthcare costs. Multimorbidity is also known to reduce quality of life significantly. This is "not only in terms of how people felt about their lives generally, but also in terms of the extent of their psychological distress. Due to the single disease focus in research and health care, we know relatively little about the determinants of multimorbidity. The factors e associated with various combinations of morbidity experienced by older adults is unclear, and such knowledge could potentially improve care and delay mortality for many managing multiple chronic conditions. It is possible that a common set of shared risk factors (e.g., smoking, obesity, physical activity) affect multiple outcomes, including multimorbidity but the evidence base is still scare.

In this chapter, we undertake a systematic review on multimorbidity; the methodology is described in section 2 and results in section 3. Due to lack of a research literature in this area, the paper is as systematic as possible.

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2 METHODOLOGY

A comprehensive review of the literature made it clear that there were almost no meta-analyses on multimorbidity. Thus, we decided to undertake further research on the association between socioeconomic factors, the most distal and comprehensive determinant, and multimorbidity/comorbidity. In order to undertake this exercise in a systematic manner we followed the following six steps.

Step 1. We searched Web of Science, EMBASE, Econlit until May 2016. We limited electronic searches to human populations and articles in English. The exact terms are described below.

"Educational level" OR "Socioeconomic status" OR "Socioeconomic position" OR "Social inequality" OR "Social disparity" OR "social determinant" OR "social status" OR "Income" OR "Occupation"

AND

"Multimorbidity" OR "Comorbidity"

Step 2. All identified papers were extracted to an excel database, and duplicates removed.

Step 3. The abstracts of all the papers identified in Step 2 were extracted. Then the abstracts were examined for whether the exposure (independent variable or risk factor) variable in the paper was a measure of SES.

Step 4. Of the papers that cleared step 3 we examined whether the study was on human populations, and whether it did not focus exclusively on countries outside Europe or special groups (ethnic minorities, pregnant women, etc.)

Step 5. For papers that cleared step 4 we examined whether the outcome was multimorbidity or comorbidity;

Step 6. For papers that cleared step 5 the full version of the paper was examined further and both SES (to ensure that SES was indeed the, or one of the, exposures examined (in studies that used psychosocial as a term) and outcome measures re-examined.

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Inclusion and exclusion criteria: We only included papers with a clear focus on social inequalities. SES was considered to be measured by education, occupation, income, or area level measures of SES. We also excluded reviews on specific populations such as prisoners, pregnant women, children with disabilities, or when focus was exclusively on low income countries. In all the extracted data, an attempt was made to pay attention to age, sex, and European differences.

Data extraction: Eligible studies were extracted by one person (AF) in close consultation with a second person (ASM).

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3 RESULTS

The search yielded a total of 1336 papers, after deletion of 28 duplicates. A total of 180 papers dealt with socioeconomic factors (step 3 above), of which 167 were on the correct population (step 4 above) but only 16 had to do with multimorbidity or comorbidity (step 5 above). These 13 papers are listed below and constitute the basis of our qualitative analysis.

- Droomers M, Westert GP. Do lower socioeconomic groups use more health services, because they suffer from more illnesses? Eur J Public Health. 2004;14(3):311-313.[1]
- Haider SI, Johnell K, Thorslund M, Fastbom J. Analysis of the association between polypharmacy and socioeconomic position among elderly aged > or =77 years in Sweden. Clin Ther. 2008;30(2):419-427.[2]
- Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. J Am Geriatr Soc. 2009;57(1):62-69.[3]
- Nagel G, Peter R, Braig S, Hermann S, Rohrmann S, Linseisen J. The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort. BMC Public Health. 2008;8:384.[4]
- Andrade LH, Bensenor IM, Viana MC, Andreoni S, Wang YP. Clustering of psychiatric and somatic illnesses in the general population: multimorbidity and socioeconomic correlates. Braz J Med Biol Res. 2010;43(5):483-491.[5]
- Tucker-Seeley RD, Li Y, Sorensen G, Subramanian SV. Lifecourse socioeconomic circumstances and multimorbidity among older adults. BMC Public Health. 2011;11:313.[6]
- Agborsangaya CB, Lau D, Lahtinen M, Cooke T, Johnson JA. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. BMC Public Health. 2012;12:201.[7]
- Ataguba JE. Inequalities in multimorbidity in South Africa. Int J Equity Health. 2013;12:64.[8]
- Boutayeb A, Boutayeb S, Boutayeb W. Multi-morbidity of non communicable diseases and equity in WHO Eastern Mediterranean countries. Int J Equity Health. 2013;12:60.[9]

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- McLean G, Gunn J, Wyke S, et al. The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. Br J Gen Pract. 2014;64(624):e440-447.[10]
- Skoog J, Midlov P, Beckman A, Sundquist J, Halling A. Drugs prescribed by general practitioners according to age, gender and socioeconomic status after adjustment for multimorbidity level. BMC Fam Pract. 2014;15:183.[11]
- Jackson CA, Dobson A, Tooth L, Mishra GD. Body mass index and socioeconomic position are associated with 9-year trajectories of multimorbidity: A population-based study. Prev Med. 2015;81:92-98.[12]
- Afshar S, Roderick PJ, Kowal P, Dimitrov BD, Hill AG. Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys. BMC Public Health. 2015;15:776.[13]

The results are divided into sections on prevalence, GDP and multimorbidity, socioeconomic factors and multimorbidity, health service and polypharmacy, and finally on the research on common risk factors.

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3.1 Prevalence Studies

The prevalence of multimorbidity is generally associated with increasing age. However, estimates of the prevalence of multimorbidity vary from 17% to over 90%. The wide variation is due to dissimilar study populations or data sources, usually entailing differences in demographic characteristics and disease types or classification. Most studies have been limited to patients in the primary care setting, having a specific index disease (referred to as comorbidity), or to just the elderly. Few studies have evaluated the prevalence of multimorbidity across age groups of the general population, including younger adults. There is some evidence to suggest that multimorbidity is not just a condition of the elderly.

A 2012 Canadian study examined multimorbidity prevalence in a sample of 5010 adults, aged 18 or over, drawn from the general population.[7] The presence of the following conditions was assessed: diabetes, chronic obstructive pulmonary disorder, asthma, hypertension, high cholesterol, sleep apnoea, congestive heart failure, obesity, depression or anxiety, chronic pain, arthritis, heart disease, stroke (or related conditions), cancer, gastro-intestinal tract (GIT disease), and kidney diseases. Multimorbidity was defined as the presence of two or more chronic conditions. The age and sex standardized prevalence of multimorbidity was 19.0% (95% CI 18.0-20.0). The age-standardized prevalence of multimorbidity was higher in females (19.2%, 95% CI 17.8-20.6) than in males (15.6%, 95% CI 14.2-16.9). The prevalence increased steadily with age, being 2.4% in those younger than 25 years, 9.3% in those aged 25-44 years, a quarter of the population aged 45-64 years and one in every three of those aged 65 years or older. Interestingly, 70.2% (657) of those with multimorbidity were less than 65 years of age. Among respondents with any two concurrent chronic conditions, the combination of arthritis and chronic pain was the most common (14.1%)

Regardless of how it is measured, multimorbidity is more common in older people, and in more deprived populations. Despite the growing recognition of the prevalence of multimorbidity amongst older adults, global prevalence studies have largely remained single-disease focused. Few studies have reported national level estimates stratified by age. Given the increasing prevalence of multimorbidity, understanding the prevalence and patterns of multimorbidity is important to help guide clinical care. One of the largest datasets to have assessed the prevalence of multimorbidity across age groups is one reported by Mclean et al in 2014.[10] The dataset was obtained from the Primary Care Clinical

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Informatics Unit at the University of Aberdeen, UK, and included data for 1 751 841 patients of all ages. The analysis was based on 40 chronic conditions: 32 physical and eight mental conditions.

Table 1. Prevalence of chronic morbidity, adapted from Mclean et al., 2014[10]

Age group years	Adult population % (95% CI)	No conditions % (95% CI)	One condition % (95% CI)	Two or more conditions % (95% CI)
25–34	18.0 (17.9, 18.1)	74.0 (73.8, 74.0)	17.9 (17.7, 18.0)	8.1 (8.0, 8.2)
35–44	21.9 (21.8, 22.0)	64.3 (64.2, 64.4)	21.8 (21.7, 21.9)	13.9 (13.8, 14.0)
45–54	19.9 (19.8, 20.0)	52.0 (51.0, 52.1)	25.0 (24.9, 25.1)	23.0 (22.8, 23.2)
55–64	17.2 (17.1, 17.3)	34.6 (34.5, 34.7)	26.5 (26.3, 26.7)	38.9 (38.7, 39.1)
65–74	12.2 (12.1, 12.3)	18.5 (18.3, 18.7)	22.6 (22.4, 22.8)	59.0 (58.7, 59.2)
≥75	10.7 (10.6, 10.8)	8.7 (8.5, 8.9)	15.2 (15.0, 15.3)	76.1 (75.9, 76.3)

Analysis based on 40 chronic conditions: 32 physical and eight mental.

Using these data, Table 1 shows differences in prevalence of morbidity in adults across the different age groups. Prevalence of multimorbidity was higher in each successive age group, rising from 8.1% of 25-34-year-olds to 76.1% of those aged ≥75 years. By the age of ≥55 years, there were more people with multimorbidity than there were with a single condition or no chronic condition.

Depression was the most prevalent condition for multimorbid patients in all age groups <55 years, whereas hypertension was the most prevalent condition for those aged ≥55 years. Ten conditions made up the top five most common conditions in multimorbid patients in each age group: seven physical conditions (four 'concordant' conditions with related aetiology and/or management: diabetes, CHD, hypertension, and CKD; and three 'discordant': pain, asthma, and dyspepsia), and three mental health conditions (depression, anxiety, and drugs misuse, which includes use of prescription drugs that GPs have coded as being problematic in some way). The prevalence of concordant physical conditions in multimorbid patients increased with age, whereas in younger age groups multimorbidity was characterised by discordant physical conditions and mental health conditions.

To characterise the prevalence and type of multimorbidity, patients were grouped as follows:

- two or more physical conditions but no mental health conditions (physical-only)

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- two or more mental health conditions but no physical conditions (mental-only)
- two or more conditions including at least one physical and one mental (mixed physical and mental).

Table 2 the prevalence of different types of multimorbidity (physical or mental or both) across age groups. In this study, physical-only multimorbidity accounted for 56% of all multimorbidity overall, and was the most common type of multimorbidity from ≥55 years. In contrast, the number of people with mental-only multimorbidity accounted for <4% of multimorbidity overall, and this was most common below the age of 45 years. Mixed physical and mental multimorbidity accounted for almost 40% of all multimorbidity. It was the most common type of multimorbidity in all age groups <55 years, and continued to rise in prevalence after this age.

Table 2. Prevalence of chronic morbidity, adapted from Mclean et al., 2014[10]

Age group Years	Physical only multimorbidity % (95% CI)	Mental only multimorbidity % (95% CI)	Mixed multimorbidity % (95% CI)
25–34 (n = 18 687)	27.3 (26.7, 28.0)	21.5 (20.9, 22.1)	51.1 (50.4, 51.9)
35–44 (n = 38 884)	34.0 (33.5, 34.5)	12.8 (12.4, 13.2)	53.1 (52.6, 53.6)
45–54 (n = 58 421)	45.6 (45.1, 46.0)	5.4 (5.1, 5.5)	49.0 (48.6, 49.4)
55–64 (n = 85 319)	58.3 (58.0, 58.6)	1.9 (1.8, 2.0)	39.8 (39.4, 40.1)
65–74 (n = 91 550)	68.3 (68.0, 68.6)	0.7 (0.6, 0.8)	31.0 (30.7, 31.3)
≥75 (n = 103 446)	63.7 (63.4, 67.0)	0.6 (0.5, 0.7)	35.7 (35.4, 36.0)
Total	56.3 (56.1, 56.4)	3.8 (3.7, 3.9)	39.9 (39.7, 40.0)

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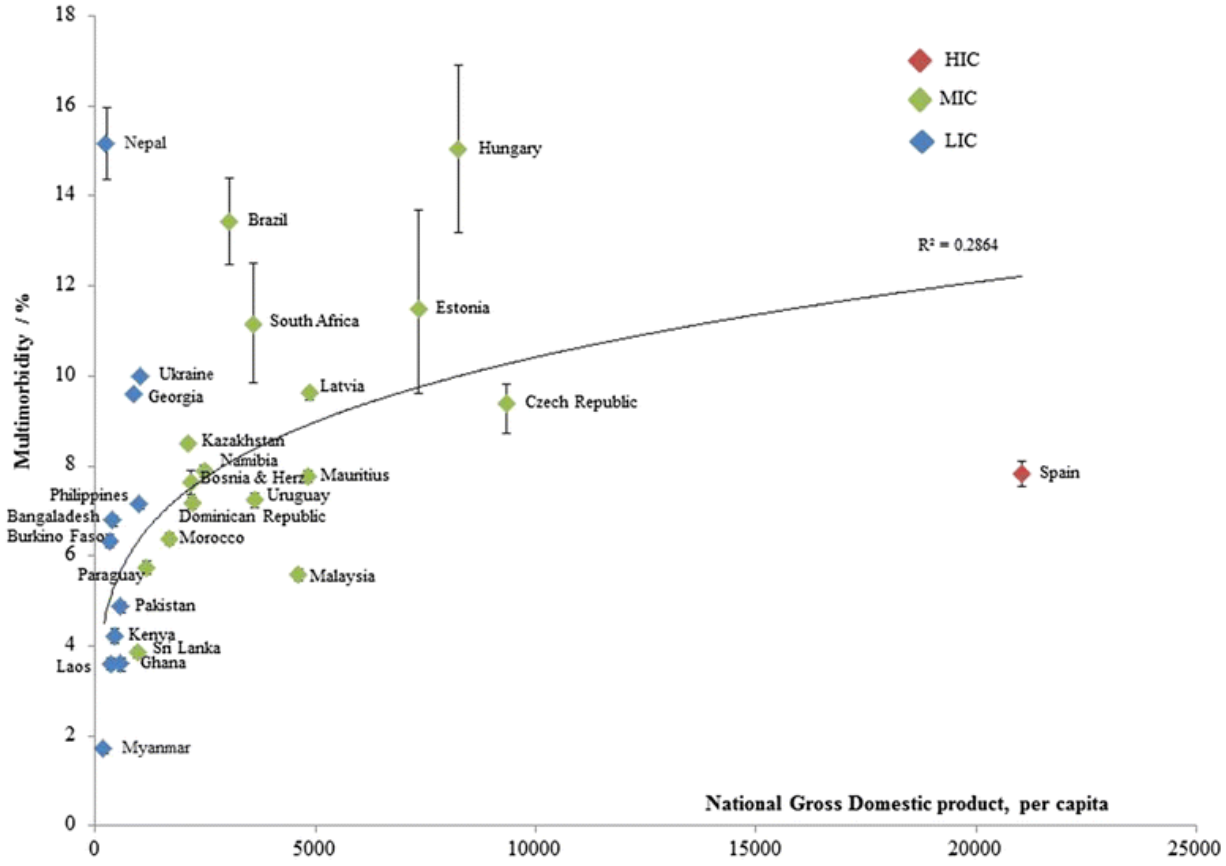
3.2 GDP & multimorbidity

Much of the scare evidence on multimorbidity comes from High Income Countries (HIC) where it is reportedly more prevalent for individuals of higher ages, female sex, low income, and low education. However, the situation in Low & Middle Income Countries (LMIC) is unclear. In a recent paper, Afshar and colleagues used the publically available data from the WHO World Health Survey (WHS), to examine multimorbidity prevalence in HICs and LMICs.[13] In total, six countries were randomly selected from Africa; five countries from South-East Asia; four from South Asia; eight from Eastern Europe & Central Asia; four from Central & South America; and, one from Western Europe. Sampling weights were applied, as well as post-stratification weights to account for non-response.

Figure 1. World Standardised Multimorbidity Prevalence by GDP across World Health Survey Countries (*n* = 28) in 2003 (with confidence intervals), from Afshar et al.2015.[13]



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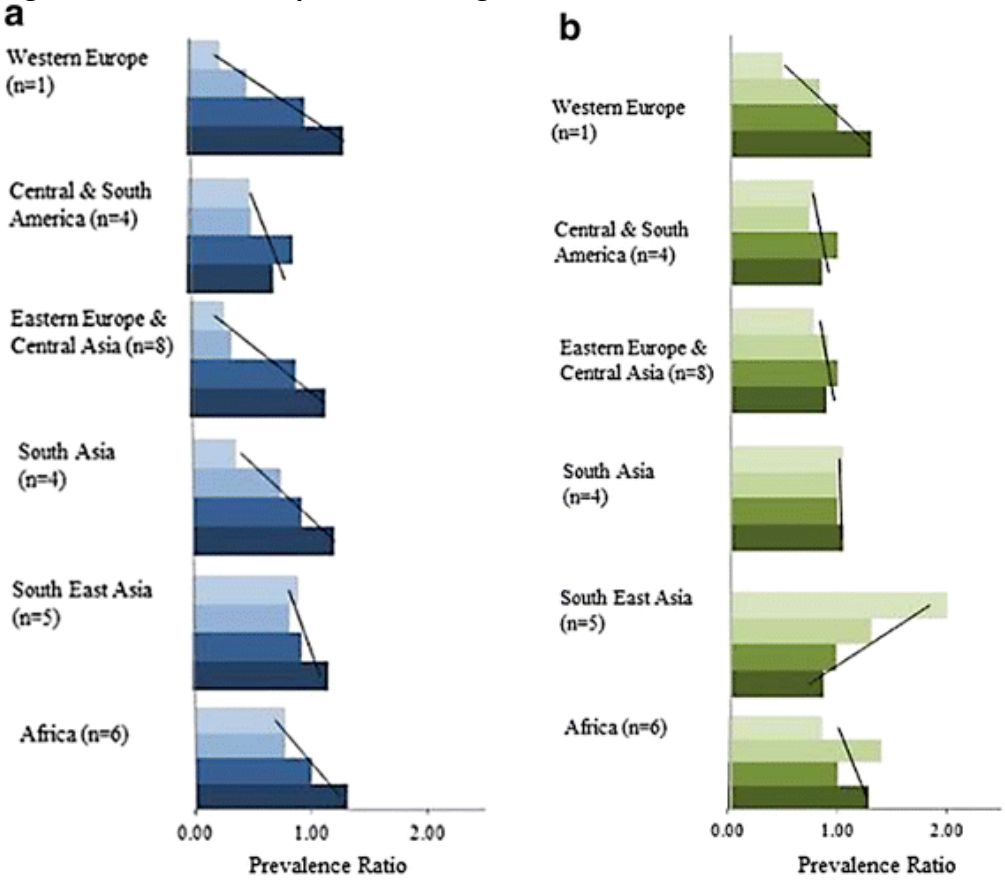
Multimorbidity was defined here as the presence of two or more of six conditions: arthritis, angina or angina pectoris (heart disease), asthma, depression, schizophrenia or psychosis, and diabetes. Their results show arthritis to be the most common condition across the WHS countries, with mean prevalence of 12.0% (95 % CI, 11.8 - 12.2). The mean prevalence for depression, angina, asthma, diabetes and schizophrenia, respectively, were 6.7 %, 7.5 %, 5.0 %, 4.0 % and 0.9 %.

The mean world standardized prevalence of multimorbidity for LMICs was 7.8 % (95 % CI, 6.5 - 9.1) and the range was 1.7 % (95 % CI, 1.4-2.0) to 15.2 % (14.3 – 16.0). The mean multimorbidity prevalence significantly increased with age in all countries ($p < 0.05$); 3.8 % (95 % CI, 3.0 – 4.6) for age 18–49, 12.8 % (95 % CI, 10.5 – 15.2) for 50–64; and 21.3 % (95 % CI, 17.1 – 25.5) for 65 + . Figure 1 shows national levels of multimorbidity by country GDP per capita. There was a positive association between multimorbidity prevalence and GDP per capita (from GDP per capita of $200 – $10,000). Above $10,000 the line flattens: Spain had a relatively low multimorbidity prevalence given their high GDP per capita.

Figure 2a. The socioeconomic gradient of multimorbidity by regions, for those <55 years.
Figure 2b. The socioeconomic gradient of multimorbidity by regions, for those ≥55 years.
Lightest shade represents higher education, dark shade low education.



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Figures 2a and 2b show the prevalence ratios of multimorbidity across socioeconomic groups, stratified into younger and older adults. Amongst the younger adults, across all regions, there was a distinct negative socioeconomic gradient, with the highest burden on the least educated. In Western Europe there appeared to be a wider variation between SES categories, compared to SE Asia and Africa. Amongst older adults, there was less variation between SES categories, compared to the younger adults. However, there was still a distinct negative gradient in Western Europe, with the highest burden on the least educated. South-East Asia on the other hand has a positive gradient, with the highest burden on the most educated.

Age was significantly associated with multimorbidity in all countries. Sex was significantly associated with multimorbidity in all but seven countries. Multimorbidity was associated with education in the univariate analyses, but was not significant when adjusted for both age and sex, except for certain education categories in Bangladesh, Brazil, Hungary, Mauritius, Namibia and Spain; which were all consistent with an inverse relationship.

Similar to the country level, age and sex were both significantly associated with multimorbidity in all regions. When adjusted for age and sex, the lowest education category was significantly associated with a higher risk of multimorbidity in Africa and Western Europe; and higher education categories were significantly associated with a decreased risk of multimorbidity in South Asia and Western Europe. Adjusted for age, sex, country and region, the 'all regions' model suggests an overall negative education gradient.

The authors of this study, the first of its kind to describe global patterns of multimorbidity and to compare prevalence across different countries, conclude that despite the variation in multimorbidity prevalence the mean world standard prevalence was fairly high at 7.8 % and significantly associated with age. Multimorbidity prevalence was positively associated with country GDP per capita. There was an inverse country association of multimorbidity with education, which indicates an inequity of disease burden. For adults aged <55 years, the gradient was always negative, with one exception of older adults in South-East Asia.

The negative gradient of multimorbidity with education may reflect the proliferation of several key risk factors for these chronic conditions. Better coordination and support through informed policy and planning of health care systems is needed to support the transition required for health systems to address future care needs.

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Boutayeb et al., 2013 examined multi-morbidity and equity in the WHO Eastern Mediterranean Region by undertaking an annotated bibliography.[9] In the WHO Eastern Mediterranean Region, non-communicable diseases account for 53% of annual mortality with 2.3 million deaths per year. Nearly 1.2 million deaths were caused by cardiovascular diseases, representing 55% of deaths caused by NCDs and 28.5% of all deaths in the region. The regional distribution range is, however, very wide (from 13% in Somalia to 49% in Oman). Cancer caused 14% of NCD-related deaths and 7.5% of all deaths in the region but, again, figures vary from a minimum of 3% in Afghanistan and Somalia to a maximum of 20% in Qatar. However, the percentage of deaths caused by respiratory diseases is homogenous in the whole region, ranging from 2% to 5% of total deaths

The words/strings used for search and inclusion criteria were multimorbidity, comorbidity, equity, non-communicable diseases, chronic diseases, WHO Eastern Mediterranean and Arab countries. They identified 26 papers, twelve dealt with comorbidity of depression and mental disorders with other chronic diseases. Another set of 11 publications was devoted to multimorbidity of diabetes, cardiovascular diseases, hypertension, metabolic syndrome and obesity. Their analysis suggests that female gender, low income, low level of education, old age and unemployed/retired are the factors most consistently associated with multimorbidity.

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3.3 Socioeconomic factors and multimorbidity

To date, research on multimorbidity has mainly focused on older people and most studies remain cross-sectional. A life-course approach to understanding the aetiology of chronic diseases has been well documented for single physical conditions, and more recently for single mental conditions such as depression. However, we found no systematic papers that have investigated multimorbidity in this context. In two sections below, we describe the importance of childhood socioeconomic circumstances and how age modifies the social gradient in multimorbidity.

3.3.1 Childhood socioeconomic factors

A 2011 paper by Tucker-Seeley and colleagues examined the role of childhood socioeconomic factors.[6] There is considerable research on the association between childhood SES and adult health. Low childhood socioeconomic status (e.g. parental occupation, parental educational attainment) has been linked to heart disease, stroke, diabetes, and some cancers among adults. Financial hardships in childhood can greatly influence subsequent access to financial/economic resources, which in turn affects the trajectory of health outcomes throughout the lifecourse. As such, cumulative disadvantage or low lifecourse SES has been shown to be associated with morbidity and mortality. However, the relationship among childhood financial hardship, earnings across adulthood, and multimorbidity remains to be investigated and were the focus of this study.

Data came from the American Health and Retirement Study (HRS). Multimorbidity was operationalized as the count of six chronic conditions, namely cancer, heart disease, lung disease, stroke, diabetes, and hypertension. Nineteen percent of the sample reported childhood financial hardship. The mean number of chronic conditions was 1.24, with 30% reporting no chronic conditions. The mean number of chronic conditions for those reporting childhood financial hardship was 1.35 and the mean number of chronic conditions for those reporting no childhood financial hardship was 1.20. Interestingly, they showed that as the average annual income during young and middle adulthood increases by $10,000 the number of chronic conditions decreases by 5%. Additionally, when both childhood financial hardship and lifetime earnings were included in the model, the association between lifetime

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earnings, multimorbidity remained unchanged, and the association between childhood financial hardship and multimorbidity was only slightly reduced.

3.3.2 Age as a modifier

Nagel and colleagues published a paper in 2008 with the aims of this study being to investigate the association between educational attainment and multimorbidity and to examine the mediating role of health behaviour in the EPIC subcohort of Heidelberg.[4] Multimorbidity (yes/no) was defined as two or more concurrent chronic conditions. In addition, multiple metabolic diseases is defined as the concomitant occurrence of metabolic diseases (0, 1, 2, ≥ 3) including diabetes, hypertension, dyslipidaemia and hyperuricemia; the dichotomous variable 'metabolic diseases' (yes/no) reflects the existence of any metabolic disease.

Among 13,781 participants aged 50 to 75 years, the prevalence of multimorbidity was 67.3% in men and 67.4% in women. In men and women, dyslipidaemia, hypertension, and gastro-intestinal diseases were the most common chronic conditions. In the age adjusted models, the associations between educational level and multimorbidity were slightly stronger in men (middle vs. high level OR = 1.32; 95% CI 1.12–1.55 and low vs. high level OR = 1.43; 95% CI 1.28–1.61) than in women (middle vs. high level OR = 1.13; 95% CI 0.97– 1.33 and low vs. high level OR = 1.33; 95% CI 1.18–1.57). In women, the educational level had stronger impact on the occurrence of metabolic diseases (low vs. high level OR = 1.64; 95% CI 1.42–1.90) than in men (low vs. high level OR = 1.38; 95% CI 1.22–1.57). Differences in the strength of the association may be predominantly attributed to diabetes, which was more strongly associated with education in women than in men.

Overall, multimorbidity was more prevalent among men and women aged 50–75 years with low educational level than in subjects with higher educational level. Higher BMI, but not smoking status, was identified as an intermediate factor in the relationships between education and multimorbidity and metabolic disease. However, the adjustment for these risk factors did not completely explain the effect of education on health outcomes. Thus, the authors suggest that differences in socio-economic position are associated with inequalities in health that may be mediated by differences in health-related behaviour.

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They found low educational level to be statistically significantly associated with a higher prevalence of multimorbidity compared to high educational level (**Table 3**). Stronger associations between education and multimorbidity were found among the participants aged 50 to 60 years than among elders, which can be explained by premature mortality in low SEP groups.

Mclean et al., 2014[10] also examine multimorbidity by age and deprivation in one of the largest studies to date on this issue using a wide range of conditions. The aim of their study was to characterise the prevalence and type of multimorbid conditions by socioeconomic status across different age groups, using cross-sectional data from a large, nationally representative primary care dataset, to help inform future prospective studies. As described previously, the data came from the Primary Care Clinical Informatics Unit at the University of Aberdeen, UK, and included copies of clinical data for 1 751 841 patients of all ages.

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Table 3. Multivariate adjusted odds ratios (OR, 95% CI) of multimorbidity and metabolic diseases by educational level in the EPIC-Heidelberg cohort, from Nagel et al. 2008.[4]

	Men					Women				
Educational Level	**High**	**Middle**		**Low**		**High**	**Middle**		**Low**	
	OR	**OR**	**95%-CI**	**OR**	**95%-CI**	**OR**	**OR**	**95%-CI**	**OR**	**95%-CI**
Multimorbidity: yes										
Age <= 60 years at recruitment	1	1.24	1.03–1.50	1.36	1.17–1.59	1	1.05	0.87–1.26	1.20	1.00–1.43
Age > 60 years at recruitment	1	0.95	0.65–1.39	0.90	0.68–1.19	1	1.08	0.70–1.67	0.93	0.64–1.35
Metabolic diseases: yes										
Age <= 60 years at recruitment	1	1.38	1.12–1.71	1.18	1.00–1.38	1	1.24	1.03–1.49	1.32	1.11–1.58
Age > 60 years at recruitment	1	1.16	0.74–1.83	0.97	0.71–1.32	1	1.16	0.74–1.82	1.24	0.84–1.83

Analysis adjusted for BMI (continuous; kg/m2), fruit intake (continuous; g/day), vegetable intake (continuous, g/day), alcohol consumption (continuous; g/day), age (continuous; years, total physical activity (inactive, moderately inactive, moderately active, active)

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Table 4. Differences between types of multimorbidity by age group and deprivation, from Mclean et al., 2014.

	Physical-only multimorbidity %, (95% CI)		Mental-only multimorbidity %, (95% CI)		Mixed multimorbidity %, (95% CI)	
Age group, years	Most deprived	Least deprived	Most deprived	Least deprived	Most deprived	Least deprived
25–34	1.9 (1.7, 2.1)	1.9 (1.7, 2.1)	2.6 (2.4, 2.8)	0.9 (0.7, 1.1)	5.4 (5.1, 5.6)	2.7 (2.4, 2.9)
35–44	4.3 (4.1, 4.5)	4.1 (3.8, 4.3)	3.3 (3.0, 3.5)	0.9 (0.7, 1.1)	11.5 (11.1, 11.9)	3.9 (3.7, 4.1)
45–54	10.3 (10.0, 10.7)	8.9 (8.5, 9.2)	2.2 (2.0, 2.4)	0.7 (6.2, 8.3)	18.8 (18.2, 19.3)	6.1 (5.8, 6.4)
55–64	22.9 (22.1, 23.8)	20.4 (19.9, 20.9)	1.0 (0.8, 1.2)	0.6 (4.5, 6.5)	25.7 (24.9, 26.4)	9.7 (9.2, 10.0)
65–74	39.1 (38.2, 39.9)	37.9 (37.1, 38.7)	0.4 (0.2, 0.4)	0.5 (0.3, 0.5)	27.6 (26.8, 28.4)	13.6 (13.0, 14.1)
≥75	46.1 (45.0, 47.1)	48.1 (47.2, 48.9)	0.4 (0.2, 0.5)	0.4 (0.3, 0.5)	31.8 (30.8, 32.8)	27.0 (26.2, 27.8)

Analysis based on 40 chronic conditions: 32 physical and eight mental.

Multimorbidity was defined as the presence of two or more of 40 conditions in one patient (32 physical and eight mental). **Table 4** shows the prevalence of different types of multimorbidity (physical or mental or both) across age groups for the least and most deprived deciles. Physical-only multimorbidity had a similar prevalence in the most and least deprived deciles. In contrast, the number of people with mental-only multimorbidity was markedly higher in the most deprived than in the least deprived especially in the younger age groups. The prevalence was similar in both deprivation groups ≥65 years. Mixed physical and mental multimorbidity was two- to threefold more common in the most deprived compared with the least deprived in all age groups <75 years.

Deprivation was associated with a higher prevalence of seven out of the 10 conditions (depression, drugs misuse, anxiety, dyspepsia, pain, CHD, and diabetes). Deprivation correlated with drug misuse and pain across all age groups; in depression and anxiety in all age groups up to those aged ≥75 years; in dyspepsia in all age groups <65 years; in CHD for

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those aged ≥45 years; and in diabetes for those ≥55 years. In earlier adulthood, multiple mental health conditions and mixed physical and mental conditions were more prevalent. Mixed physical and mental multimorbidity was much more common in the deprived compared with the affluent at all ages <75 years. The higher prevalence of mixed mental and physical conditions that exists in the more deprived, particularly at an earlier age, may reflect previous evidence, which shows that mental health conditions are more prevalent in people with increasing physical disorders.

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3.4 Health services & Polypharmacy

The burden to the health services and polypharmacy are growing concerns in relation to multimorbidity. In this section, we review the research literature on these issues.

Health services

Drommers et al., 2004[1] examined the effect of socioeconomic differences in health care utilization in the Netherlands. The analysis of multiple health care utilization was based on 47,129 persons. These authors first showed that the lowest educated group was 2 1/2 times more likely to report two or more chronic conditions than the highest educated group. This educational pattern of comorbidity explained almost 40% of the variation in the use of multiple health care services by educational level. Almost one quarter of the higher odds of using multiple health services of the lower educated groups was due to educational differences in comorbidity (table 2). Nevertheless, after adjustment for comorbidity, lower educated people still had significantly higher odds of using multiple health services. Thus, the authors concluded that health status itself could not account for all of the socioeconomic differences in the use of health care. The remaining socioeconomic differences in multiple health care utilization may be dictated by differences in social life circumstances, extra costs incurred for health care services, or other constraints or inconveniences reducing access to health services.

Polypharmacy

Polypharmacy has been defined in different ways. The most common definition is the concurrent use of multiple drugs. Others have defined it as the use of more drugs than clinically indicated or too many inappropriate drugs, such as the use of >2 medications to treat the same condition or the use of >2 drugs of the same chemical class. Increases in the ageing population and longevity mean higher demands on health care, including the use of medications. The elderly have been found to use more drugs than other age groups. Multiple medication regimens may lead to difficulties in administering different drugs, noncompliance, and therapeutic duplication in the elderly. Furthermore, polypharmacy is associated with increased hospitalization and mortality in the elderly. The prevalence of polypharmacy in elderly people is reported to be approximately 5% to 78%. Polypharmacy

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has been associated with multiple diseases, advanced age, being female, low level of self-rated health, living in an institution, and number of visits to a primary care provider per year.

Haider et al., 2008 examined the extent to which elderly persons are exposed to polypharmacy and the association between polypharmacy and SES, as measured by education, occupation, and income, in a representative sample of the Swedish population aged >77 years. [2] Polypharmacy was defined as concurrent use of >5 drugs. The mean age of the 621 participants in this study was 83.3 years, 59.3% were women, 68.2% had <8 years of education. Polypharmacy (use of >5 drugs) was observed in 42.2% of the sample.

Low education was associated with polypharmacy (OR, 1.46; 95% CI, 1.02-2.07), after adjustment for age and sex. However, after additional adjustment for comorbidity, marital status, and living situation, the association between education and polypharmacy was not statistically significant (OR, 1.39; 95% CI, 0.95-2.04). These findings suggest that the association between polypharmacy and low education is explained by the fact that most diseases are more prevalent in people with lower SES than in the general population.

In a further paper, Haider and colleagues whether educational attainment in elderly people is associated with polypharmacy, excessive polypharmacy, and potential inappropriate drug use (IDU), after controlling for age, sex, type of residential area, and comorbidity, in a nationwide sample of Swedish elderly persons.[3] The analyses are based on 626,258 adults; mean age of the patients was 80.9; most were women (60%) and lived in urban areas (65%). The majority were low educated (55%).

During the 3-month study period, polypharmacy was documented in 57% of patients; 18% had excessive polypharmacy. Subjects used a mean standard deviation of 5.8 (4.0) drugs. The majority of patients were taking a cardiovascular drug (70%), most commonly an antithrombotic agent (B01A, 44%), followed by beta-blocking agents (C07A, 35%), hypnotics and sedatives (N05C, 22%), high ceiling diuretics (C03C, 22%), and analgesics and antipyretics (N02B, 21%). The results of this register study reveal a modest yet significant difference in quantity and quality of drug use in different educational groups of elderly people. The findings of the current study suggest that elderly women with low education are more prone to a higher level of IDU than elderly men with low education. Adjustment for comorbidity did not substantially reduce the effect of education on polypharmacy and

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potential IDU. This indicates that inequalities in drug use exist even in a healthcare system that claims to ensure equity.

Skoog et al., 2014 investigated the use of prescription drugs among individuals in the population treated by general practitioners (GP), and the rate of prescription drug use among patients treated by GPs depending on age, gender and socioeconomic status after adjusting for multimorbidity level. The main findings were that age increased the odds ratio of having prescription drugs, despite adjustment for multimorbidity level. Men had lower odds ratios of having prescription drugs compared to females. The differences in the socioeconomic groups were also substantial, where people with the highest income level had the lowest prescription drug use and people with the second to lowest income level had the highest prescription drug use. People with the lowest educational level had the highest prescription drug use. Despite adjustment for multimorbidity level, there are substantial differences between the lowest and highest levels of income in drug use in primary health care.

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3.5 Common risk factors

The understanding of how multimorbidity relates to health service use, management of disease and health outcomes has been a target of research over the past decade. Very little is known about risk factors for multimorbidity with previous studies having used cross-sectional designs that may be limited by reverse causation due to the development of morbidity consequently affecting lifestyle or socioeconomic circumstances. Few studies have prospectively investigated whether lifestyle or socioeconomic status prior to the development of chronic diseases is associated with future multimorbidity trajectory as identified by repeat measure of chronic disease over time. Improved understanding of factors associated with accumulation of morbidities could identify high-risk individuals and inform preventative and management measures.

Lifestyle factors

Jackson et al., 2015 examined multimorbidity trajectories in a cohort of mid-aged women using an objective statistical method, and investigate how baseline lifestyle and socioeconomic factors relate to these trajectories.[12] Participants were from the Australian Longitudinal Study on Women's Health (ALSWH), a national population-based study of women born in 1921–26, 1946–51 and 1973–78. Five multimorbidity trajectories were identified: no morbidity, low morbidity, moderate morbidity, increasing from no morbidity, increasing from low morbidity. The most common conditions within each trajectory were arthritis, hypertension, depression, anxiety, and diabetes (mostly type 2 diabetes), which accurately reflects disease prevalence among mid-life women.

Their results show that being overweight or obese, having a lower education level and difficulty managing on income emerged as key risk factors for belonging to a trajectory where conditions accumulated over time. Smoking, alcohol intake and physical activity level also appeared to be important risk factors for the development of some trajectories. These findings highlight the role of BMI in the development of multimorbidity among mid-aged women, identifying it is a key modifiable risk factor for the accumulation of chronic conditions. The associations with education and income remained after accounting for measured lifestyle behaviours.

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Clustering of mental and somatic illness

The co-occurrence of medical and psychiatric morbidity is common. When disorders occur in combination more often than expected, one of two processes might be operative involving shared risk factors, or, one disorder may possibly act as a risk factor for another disease. An explanation for the co-occurrence of psychiatric and chronic medical conditions is that disorders tend to concentrate in individuals according to a morbidity-dependent mechanism, whereby psychiatric and physical morbidities are possibly associated in a self-perpetuating and mutually reinforcing causality. In a Brazilian study, Andrade et al. 2015 found that morbidity is concentrated in low socioeconomic groups and in psychologically distressed individuals, both for psychiatric and medical conditions.[5]

The main determinants of physical multimorbidity were age (increasing number of disorders with increasing age), being separated/divorced or widowed, having a low educational level, and the presence of psychological distress. For psychiatric disorders, multimorbidity was higher in the middle years, with lower rates in old age. An important general finding of this study is that medical illness and mental disorders frequently co-occur even in a population sample of a developing country.

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4 CONCLUSIONS

Although chronic disease factors are considered to be drivers of multimorbidity, the observed increase in multimorbidity is also related to both the demographic and the epidemiologic transition. As the global population continues to grow in size, and becomes increasingly aged, there is an expectant increase in multimorbidity prevalence. Tackling multimorbidity as part of NCD burden remains one of the key challenges faced by the global community. In particular, health systems need to examine its socio-economic determinants in order to provide the most equitable health care to their populations and to drive NCD prevention.

Results from our analysis highlight. Although relatively small proportions of the population of younger adults (<45 years) had multimorbidity, the mix of mental health, pain, and substance misuse in early adult life may increase premature mortality and/or the potential for this group of young adults (if they survive) to develop 'high burden' multimorbidity in later life. The higher prevalence in more deprived areas of mixed physical and mental multimorbidity highlights the need for holistic and integrated primary care services led by generalists, which if not met — because of the persistence of the inverse care law — is likely to widen inequalities in health.

Existing approaches to medical education, research, and healthcare delivery focus on single diseases, but a growing body of research has called for a redesign in health systems to meet the challenges of increasing multimorbidity. Results from this study add weight to this call but also suggest the need for interventions, particularly in the most deprived areas, aimed at the younger adults and the large numbers of patients with coexisting physical and mental multimorbidity. Mixed physical and mental multimorbidity is common across the life-span and is exacerbated by deprivation from early adulthood onwards. Individuals in more deprived areas face the challenge of multimorbidity in greater numbers characterised by mixed mental and physical conditions from an earlier age and lasting longer over the life-course. The findings of this study highlight the need for longitudinal studies that can take a life-course approach to aetiological understandings of the determinants of different patterns of multimorbidity and how they interact over the life-span

Additional research focused on the specific socioeconomic factors associated with multimorbidity across the lifecourse can also be used to inform the development of

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appropriate interventions that target socioeconomic groups at greatest risk for multimorbidity before they enter the health care system. In particular, interventions that target specific socioeconomic pathways might prove useful in helping reduce the burden of multimorbidity; more specifically, interventions that focus on material resources such as reducing hardships during childhood and increasing earnings throughout young and middle adulthood may have a substantial impact on prevention efforts with those at risk for various combinations of chronic disease multimorbidity

There is a large difference in prescription drug use with regard to age, gender and socioeconomic status in primary health care after adjustment for multimorbidity. This implies that the prescription drug use is not equal in society, and that factors other than medical ones affect the prescribing of drugs. This should be emphasised to both decision-makers and medical staff. Our study suggests that among early mid-aged women in a high-income country, targeting BMI and reducing the proportion that are overweight or obese may be central to preventing women from embarking on a downward spiral of multimorbidity. In addition targeting preventive measures towards those with a lower SEP may be appropriate. However, further research is needed to identify which factors, aside from lifestyle behaviours, are responsible for the increased risk of a poor multimorbidity trajectory in these less advantaged groups.

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