www.thelancet.com Vol 380 July 7, 2012

Articles

# Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study

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## Summary

Background Long-term disorders are the main challenge facing health-care systems worldwide, but health systems are largely configured for individual diseases rather than multimorbidity. We examined the distribution of multimorbidity, and of comorbidity of physical and mental health disorders, in relation to age and socioeconomic deprivation.

Methods In a cross-sectional study we extracted data on 40 morbidities from a database of 1751841 people registered with 314 medical practices in Scotland as of March, 2007. We analysed the data according to the number of morbidities, disorder type (physical or mental), sex, age, and socioeconomic status. We defined multimorbidity as the presence of two or more disorders.

Findings 42.2% (95% CI 42.1-42.3) of all patients had one or more morbidities, and 23.2% (23.08-23.21) were multimorbid. Although the prevalence of multimorbidity increased substantially with age and was present in most people aged 65 years and older, the absolute number of people with multimorbidity was higher in those younger than 65 years (210500 vs 194996). Onset of multimorbidity occurred 10-15 years earlier in people living in the most deprived areas compared with the most affluent, with socioeconomic deprivation particularly associated with multimorbidity that included mental health disorders (prevalence of both physical and mental health disorder 11.0%, 95% CI 10.9-11.2% in most deprived area vs 5.9%, 5.8%-6.0% in least deprived). The presence of a mental health disorder increased as the number of physical morbidities increased (adjusted odds ratio 6.74, 95% CI 6.59-6.90 for five or more disorders vs 1.95, 1.93-1.98 for one disorder), and was much greater in more deprived than in less deprived people (2.28, 2.21-2.32 vs 1.08, 1.05-1.11).

Interpretation Our findings challenge the single-disease framework by which most health care, medical research, and medical education is configured. A complementary strategy is needed, supporting generalist clinicians to provide personalised, comprehensive continuity of care, especially in socioeconomically deprived areas.

Funding Scottish Government Chief Scientist Office.

# Introduction

Management of the rising prevalence of long-term disorders is the main challenge facing governments and health-care systems worldwide.1 Although individual diseases dominate health-care delivery, medical research, and medical education, people with multimorbiditythose with two or more chronic morbidities-need a broader approach. Use of many services to manage individual diseases can become duplicative and inefficient, and is burdensome and unsafe for patients because of poor coordination and integration.<sup>2-4</sup> Multimorbidity becomes progressively more common with age5-7 and is associated with high mortality,8 reduced functional status,<sup>9,10</sup> and increased use of both inpatient and ambulatory health care.<sup>2,7</sup> Estimates of the prevalence of multimorbidity vary widely; most studies have counted small numbers of morbidities, frequently based on self-reports, and focused on either older people or hospital populations.<sup>11</sup>

Although the association between socioeconomic status and prevalence of individual chronic diseases is well established,<sup>12,13</sup> few studies have examined the association between multimorbidity and socioeconomic status.67,14 In the most deprived 10% of the Scottish population, men have life expectancies 13 years shorter, and women 9 years shorter, than do those in the most affluent 10%. The most deprived people spend twice as many years in poor health before they die than do the most affluent (10.3 years vs 5.5 years for men; 14.4 years  $\nu$ s 6.0 years for women).<sup>15</sup>

Better understanding of the epidemiology of multimorbidity is necessary to develop interventions to prevent it, reduce its burden, and align health-care services more closely with patients' needs. We aimed to use a large, representative primary medical care electronic database to examine the distribution of multimorbidity in relation to age and socioeconomic deprivation, and the relation between comorbidity of physical and mental health disorders and deprivation.

# Methods

# Study design and participants

Our study is a cross-sectional analysis of a national dataset held by the Primary Care Clinical Informatics Unit at the University of Aberdeen, UK. The dataset consisted of complete copies of clinical data for all registered patients from 314 medical practices caring for about a third of the Scottish population. The UK National Health Service (NHS) requires registration with a medical practice to

#### Lancet 2012; 380: 37-43

Published Online May 10, 2012 DOI:10.1016/S0140-6736(12)60240-2

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access health-care services for people living at home or in nursing care homes. The NHS National Research Ethics Service had previously approved the anonymous use of these data for research purposes, therefore this study did not need individual ethics approval.

# Data collection

At the time of data extraction, participating practices systematically used electronic medical records for registration of patients, morbidity recording, and prescriptions. The data for this analysis are from all patients who were alive and permanently registered with a participating practice on March 31, 2007. The dataset included age, sex, and socioeconomic status, and is representative of all Scottish patients.<sup>16</sup> Deprivation of the area in which a

See Online for appendix

	n (%)	Mean number of morbidities	Percentage (95% Cl) with	Percentage (95% CI) with physical–
		(SD)*	multimorbidity†	mental health comorbidity†
All patients	1751841 (100%)	0.96 (1.56)	23·2% (23·1–23·2)	8.34% (8.3-8.4)
Sex				
Female	884 420 (50·5%)	1.09 (1.65)	26.2% (26.1–26.3)	10.2% (10.2–10.3)
Male	867 421 (49.5%)	0.84 (1.46)	20.1% (20.0–20.1)	6.4% (6.4–6.5)
Age, years				
0–24	479156 (27.4%)	0.16 (0.44)	1.9% (1.9–2.0)	0.5% (0.5–0.6)
25-44	508389 (29.0%)	0.50 (0.92)	11·3% (11·2–11·4)	5.7% (5.6–5.7)
45-64	473 127 (27.0%)	1.18 (1.50)	30.4% (30.2–30.5)	12.4% (12.3–12.5)
65-84	254 600 (14.5%)	2.60 (2.09)	64.9% (64.7-65.1)	17.5% (17.4–17.7)
≥85	36569 (2.1%)	3.62 (2.30)	81.5% (81.1-81.9)	30.8% (30.3–31.3)
Deprivation decile				
1 (affluent)	163283 (9·3%)	0.82 (1.42)	19·5% (19·3–19·6)	5.9% (5.8–6.0)
2	171 296 (9.8%)	0.83 (1.44)	19·9% (19·7–20·1)	6.2% (6.1-6.3)
3	165199 (9·4%)	0.92 (1.50)	22.2% (22.0–22.4)	7.0% (6.9–7.1)
4	207129 (11·8%)	0.95 (1.54)	23.0% (22.9–23.2)	7.5% (7.4–7.7)
5	198 419 (11·3%)	1.02 (1.60)	24·5% (24·3–24·7)	8.6% (8.5-8.7)
6	198 526 (11·3%)	0.97 (1.57)	23.4% (23.2-23.5)	8.4% (8.3-8.5)
7	186083 (10.6%)	1.00 (1.59)	24.4% (24.2–24.6)	9.1% (9.0–9.2)
8	147 836 (8.4%)	1.00 (1.59)	24.2% (24.0–24.4)	9·3% (9·2–9·5)
9	164386 (9·4%)	1.09 (1.70)	26.3% (26.1–26.5)	10.7% (10.6–10.9)
10 (deprived)	149 684 (8·5%)	1.01 (1.65)	24.1% (23.9–24.4)	11.0% (10.9–11.2)
Number of disorders				
0	1012980 (57.8%)			
1	333365 (19-0%)			
2	167518 (9.6%)			22·2% (22·0–22·4)
3	99 487 (5.7%)			36·1% (35·8–36·4)
4	60417 (3.4%)			44.8% (44.4-45.2)
5	35641 (2.0%)			52·1% (51·6–52·6)
6	20507 (1.2%)			59.0% (58.3–59.7)
7	11080 (0.6%)			65.7% (64.8–66.6)
≥8	10846 (0.6%)			73·9% (73·1–74·7)

\*Differences between means within each variable differed significantly p<0.0001 (t test for independent samples for sex; one-way ANOVA for age-group and deprivation) †Differences between categories within each variable differed significantly p<0.0001 ( $\chi^2$  test for 2×n tables).

Table 1: Demography, multimorbidity, and physical-mental health comorbidity

patient lived was used to define socioeconomic status, and was measured by Carstairs score (grouped into tenths of the distribution), which uses census and other routine data, and is widely used for research.<sup>v</sup>

No standard approach for the measurement of multimorbidity exists, and selection and definition of morbidities to include is inevitably partly subjective and dependent on the data available. We specifically sought to include morbidities recommended as core for any multimorbidity measure by a systematic review,<sup>11</sup> diseases in the quality and outcomes framework (QOF) of the UK general practice contract,18 and long-term disorders identified as important by NHS Scotland.<sup>19</sup> We selected 40 such morbidities, which were defined by Read codes (the clinical coding system used in UK general practice to record patient findings and procedures in health-care IT systems) and prescription data. When possible, we based our morbidity definitions on QOF business rules<sup>18</sup> and Read code groups for long-term disorders (as defined by NHS Scotland).19 When coding definitions were unavailable or did not apply to the available routine data, the clinicians in our team (BG, SM, MN, and GW) agreed new definitions by discussion. The appendix provides further detail of definitions and the 40 morbidities included. As in most other studies, we defined multimorbidity as the presence of two or more of these 40 morbidities in one patient.<sup>11</sup> To specifically examine comorbidity of physical and mental health disorders, we also defined each morbidity as either a physical or mental health disorder.

## Statistical analyses

We used frequencies, percentages, cross tabulations, and graphical display for descriptive analysis. We did a t test to analyse differences in mean number of morbidities between men and women and one-way ANOVA for differences across age groups and deprivation deciles. We applied the  $\chi^2$  test to measure differences in prevalence of multimorbidity and physical-mental health comorbidity between variables. We used binary logistic regression to examine associations between physical and mental health comorbidities, restricting the analysis to those aged 16 years and older because mental health morbidities in children are rare. Since the association with age is roughly quadratic in adults, we also fitted a term for age-squared. We reported unadjusted and adjusted odds ratios (ORs) and 95% CIs. We did all analyses with PASW Statistics (version 18).

# Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

# Results

We analysed data from 1751841 patients (about a third of the Scottish population) from 314 Scottish medical practices. Table 1 shows the demographic characteristics of the study population, the proportion of those with multimorbidity, and the proportion with physical and mental health comorbidity. Men and women were equally represented, as were all deprivation deciles.  $42 \cdot 2\%$  (95% CI  $42 \cdot 1-42 \cdot 3$ ) of the population had one or more chronic morbidities, 23.2% (23.1-23.2) had multimorbidity, and 8.3% (8.3-8.4) had physical and mental health comorbidity. Of people with at least one morbidity, 54.9% (54.8-55.0) had multimorbidity and 19.8% (19.8-19.9) had physical and mental health comorbidity. Most people with common chronic morbidities had at least two, and frequently more, other disorders (appendix).

The number of morbidities and the proportion of people with multimorbidity increased substantially with age (table 1). By age 50 years, half of the population had at least one morbidity, and by age 65 years most were multimorbid (figure 1). However, in absolute terms, more people with multimorbidity were younger than 65 years than 65 years and older (210 500 *vs* 194 966), although older people had more morbidities on average (table 1).

The crude prevalence of multimorbidity increased modestly with the deprivation of the area in which patients lived (19.5%, 95% CI 19.3-19.6, in the most affluent areas vs 24.1%, 23.9-24.4, in the most deprived; difference 4.6%, 95% CI 4.3-4.9; table 1). However, this finding should be interpreted with caution because the population in more deprived areas was, on average, younger (median age 37 years [IQR 21-53] in the most deprived areas vs 42 years [IQR 22-58] in the most affluent areas). People living in more deprived areas were more likely to be multimorbid than were those living in the most affluent areas at all ages, apart from those aged 85 years and older (figure 2). Young and middle-aged adults living in the most deprived areas had rates of multimorbidity equivalent to those aged 10-15 years older in the most affluent areas (figure 2 and appendix).

8.3% (95% CI 8.3–8.4) of all patients, and 36.0% (35.9–36.2) of people with multimorbidity, had both a physical and a mental health disorder. The prevalence of physical and mental health comorbidity was higher in women than in men, and was substantially higher in older people than in younger people (table 1). Although older people were much more likely to have physical–mental health comorbidity, the absolute numbers were greater in younger people (90139 people <65 years *vs* 55912 people ≥65 years). The crude socioeconomic gradient in physical–mental health comorbidity was greater than that for any multimorbidity, with a near doubling in prevalence in the most deprived versus the most affluent areas (table 1; difference 5.1%, 95% CI 4.9–5.3). In the logistic regression analysis with the presence of any mental health

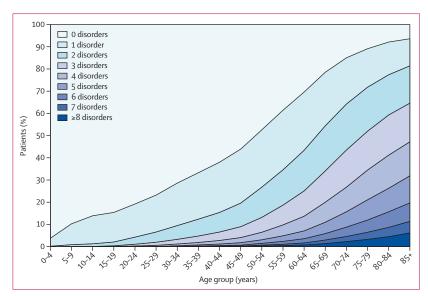


Figure 1: Number of chronic disorders by age-group

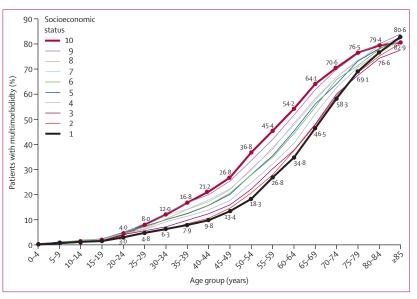


Figure 2: Prevalence of multimorbidity by age and socioeconomic status On socioeconomic status scale, 1=most affluent and 10=most deprived.

disorder as the outcome (table 2), we noted a non-linear association with age, so we included an age-squared term in the model. The predicted probability of having a mental health disorder increased with age up until about age 60 years, and then decreased (data not shown). Men were less likely to have a mental health disorder than were women, and those in the most deprived decile were more than twice as likely to have a mental health disorder than were those in the most affluent decile (adjusted OR 2.28, 95% CI 2.21-2.32). The presence of a mental health disorder was strongly associated with the number of physical disorders that an individual had—eg, people with five or more disorders had an OR of 6.74 (95% CI

6.59–6.90) compared with those with none (table 2). Figure 3 shows the consistent and large socioeconomic gradient in the presence of any mental health disorder by number of physical disorders.

Despite the most affluent people being on average 2–5 years older at onset of morbidity (dependent on the

	Any mental health disorder (unadjusted OR, 95% CI)	Any mental health disorder (adjusted OR, 95% CI)*		
Male (vs female)	0.66 (0.66–0.67)	0.71 (0.70–0.71)		
Age†	1.64 (1.62–1.66)	1.64 (1.62–1.66)		
Age squared†	0.972 (0.971-0.974)	0.954 (0.953-0.955)		
Deprivation decile				
1 (affluent)	1	1		
2	1.07 (1.05–1.10)	1.08 (1.05–1.11)		
3	1.21 (1.18–1.24)	1.17 (1.15–1.20)		
4	1.32 (1.29–1.35)	1.26 (1.23–1.29)		
5	1.52 (1.49–1.57)	1.44 (1.41–1.47)		
6	1.53 (1.50–1.56)	1.48 (1.45–1.52)		
7	1.66 (1.63–1.70)	1.60 (1.56–1.63)		
8	1.78 (1.74–1.82)	1.75 (1.71–1.79)		
9	2.00 (1.96–2.05)	1.91 (1.87–1.96)		
10 (deprived)	2.19 (2.15–2.24)	2.28 (2.21–2.32)		
Number of physical disorders				
0	1	1		
1	2.09 (2.06–2.11)	1.95 (1.93–1.98)		
2	3·16 (3·12–3·21)	2·95 (2·90–3·00)		
3	4.07 (4.00–4.14)	3.91 (3.83-3.98)		
4	4.88 (4.78–4.98)	4.85 (4.74–4.96)		
≥5	6.43 (6.31-6.56)	6.74 (6.59–6.90)		

"All adjusted for other listed variables in model. †ORs are per 10-year increase in age

Table 2: Odds ratios (OR) for any mental health disorder by age, sex, socioeconomic status, and number of physical disorders

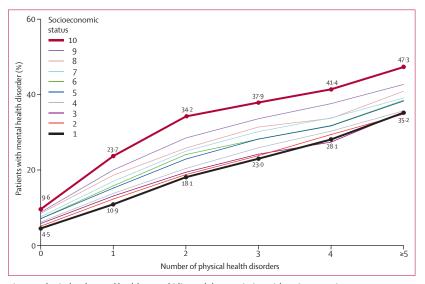


Figure 3: Physical and mental health comorbidity and the association with socioeconomic status On socioeconomic status scale, 1=most affluent and 10=most deprived.

disorder), comorbidities of people diagnosed with coronary heart disease, diabetes, chronic obstructive pulmonary disease, or cancer were more common in people living in deprived areas, with the exception of dementia and atrial fibrillation, in which a small reverse gradient was seen (figure 4). People living in deprived areas were much more likely to have chronic obstructive pulmonary disease, depression, and painful disorders as comorbidities than other disorders (figure 4).

# Discussion

By contrast with the assumptions implicit in healthcare organisation, our analysis of a large, nationally representative primary care dataset shows that multimorbidity is common, and that most of those with a long-term disorder are multimorbid. The strong association of multimorbidity with age is well recognised, but three other aspects of our findings are new or less well described. First, although the prevalence of multimorbidity is much higher in older people than in young or middle-aged people, more than half of people with multimorbidity and nearly two-thirds with physical-mental health comorbidity were younger than 65 years.<sup>20</sup> Second, although age had the strongest association with multimorbidity, we noted a substantial excess of multimorbidity in young and middleaged adults living in the most deprived areas who had the same prevalence of multimorbidity as people aged about 10-15 years older living in the most affluent areas.14 Whether this excess of multimorbidity in socioeconomically deprived people is a result of a concentration of common causes such as smoking, which would be amenable to preventive interventions affecting several diseases, or an accumulation of disparate causes, which would be harder to prevent, is unclear. Third, our study agrees with previous work showing that mental health disorders, particularly depression, are more prevalent in people with increasing numbers of physical disorders,<sup>21,22</sup> but it also shows that this association has a consistent social gradient. This data strongly suggests that clinicians working in highly deprived areas treating patients with common physical disorders have a greater number of both physical and mental health disorders to manage simultaneously than do their colleagues working in the most affluent areas, with substantially more depression in particular. Additionally, women had higher rates of multimorbidity than did men, and consistently higher rates of mental health disorders. Detailed examination of this finding was beyond the scope of our broad descriptive analysis, but would be useful in future research.

The study used a large primary-care database that is representative of the wider population. Because we used routine data, our study shares the limitations of other multimorbidity studies, particularly reliance on the quality of data recording. Some morbidities are probably under-recorded, implying that the findings underestimate the true prevalence of multimorbidity. Furthermore, no standard method for measuring multimorbidity exists. We used standardised definitions of individual morbidities when possible and, unlike most previous studies, we have explicitly reported the assumptions and limitations of our approach to make the design open to critique (appendix). We included 40 morbidities, which is substantially more than most similar studies, and incorporated those recommended as core disorders for any multimorbidity measure by the most recent systematic review at the time of our study.<sup>11</sup> We included morbidities that are not always thought of as clear-cut diseases because these morbidities play an important part in patients' ill health.

Our analysis weights all disorders equally, with a simple count to define multimorbidity, although the effect of multimorbidity on individuals will vary with the combination and severity of disorders. Older people typically have more morbidities and lower functional status, whereas multimorbidity in younger people is more often associated with combinations of physical and mental health disorders. Challenges presented by both age groups will probably call for different organisation of care to meet patients' needs.

People with multimorbidity have poorer functional status, quality of life, and health outcomes, and are higher users of ambulatory and inpatient care than are those without multimorbidity.<sup>2,8-10</sup> Although the quality of health care that they receive might be better than that for individuals with only one disorder, at least partly because of greater contact with health services,<sup>23</sup> people with multimorbidity have more difficulties with fragmentation of care and medical error because much specialist care is focused on treatment of one disease.<sup>4</sup> Improvement in the continuity and coordination of care for people with multimorbidity is a key challenge for health-care systems worldwide, and each patient needs a dedicated clinician to take responsibility for care coordination.<sup>24</sup>

The right clinician to take overall responsibility for people with multimorbidity will depend on individual circumstances.<sup>24</sup> For patients in whom one disease is dominant or comorbidities are closely related, a specialist will often be the best choice. For most multimorbid patients, however, a generalist service is needed. Geriatricians have a key role in provision of care for the frailest elderly patients with predominantly physical disorders, but in most countries most elderly people will be treated in primary care. Our data show that people younger than 65 years have as much multimorbidity as do older people, and that physical-mental health comorbidity is very common. For this younger age group, no equivalent to the geriatrician exists, and specialists are often reluctant to provide care or coordination outside their area of expertise. Person-centred approaches, together with longlasting doctor-patient relationships, should help clinicians and patients when making decisions that have to balance biotechnical rationales with patients' circumstances, priorities, and preferences.25 A strong, generalist primary care system based around an

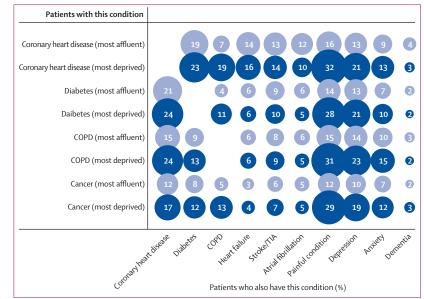


Figure 4: Selected comorbidities in people with four common, important disorders in the most affluent and most deprived deciles

COPD=chronic obstructive pulmonary disease. TIA=transient ischaemic attack.

appropriately skilled multiprofessional team is the most obvious way to deliver this holistic, longitudinal care for most people with multiple disorders, and should seek to maximise quality of life and minimise future disability and morbidity.<sup>325</sup>

Countries with strong primary health-care systems have better health outcomes and lower health-care costs than do those without,3,25 but primary care is weak and underdeveloped worldwide, and even countries with strong primary care systems face substantial challenges from ageing populations and increasing multimorbidity. Training for primary medical care is typically shorter than that for specialists, and-if present at all-training in geriatrics is only one of several components, with little structured training for most clinical disciplines focused on the organisation and delivery of systematic chronic disease management and care coordination. Undergraduate and postgraduate training and continuous professional development need reshaping to develop knowledge and skills in the management and coordination of longitudinal care.24,25

Clinical evidence and guidelines are largely created for individual diseases, and most randomised trials exclude multimorbid and elderly people.<sup>26</sup> Therefore, more externally valid trials examining effectiveness in more representative populations are needed to complement existing efficacy trials in highly selected populations.<sup>27</sup> Additionally, clinical guidelines rarely account for multimorbidity or help clinicians to prioritise recommendations from several guidelines.<sup>27,28</sup> A result is that patients with multimorbidity might be prescribed several drugs, each of which is recommended by a disease-specific guideline, but the overall drug

# Panel: Research in context

### Systematic review

We assessed the 39 measures of multimorbidity identified in Diederichs and colleagues'11 2010 systematic review, and searched Medline for relevant reports published in English after August, 2009, with the keywords "multimorbidity" and "multi-morbidity", selecting reports that described the measurement or prevalence of multimorbidity. Diederichs and colleagues'11 review reported major variation in how multimorbidity was defined (ie, the nature and number of morbidities included, and how they were weighted), the way in which data were collected (eg, by survey self-report, by research interview, or from clinical databases), and the populations studied (ranging from random community samples to specialist referral populations in hospitals). The estimated prevalence of multimorbidity in the studies reviewed varied substantially, and our study therefore sought to use a representative primary care population in a health system with universal registration with one primary care provider, include large numbers of morbidities in the count, and include all of the recommended core disorders for any multimorbidity measure. We specifically explored how multimorbidity varied with socioeconomic deprivation, which has previously been little studied, and examined physical-mental health comorbidity in particular, because this combination is the most discordant in terms of health-service organisation.

#### Interpretation

Multimorbidity is the norm for people with chronic disease, and although its prevalence increases with age, more than half of all people with multimorbidity are younger than 65 years. The most socioeconomically deprived young and middle-aged people have substantially more multimorbidity than do their most affluent peers. Prevalence of mental health disorders in an individual increases with the number of physical disorders that they have, and this association is stronger in younger people and has a consistent socioeconomic gradient. The appropriate management of long-term disorders is a key challenge for health systems internationally. Existing health systems are dominated by single-disease approaches that are increasingly inappropriate, and need to be complemented by strengthening generalism in both specialist and primary care. Physical and mental health care is particularly divided, despite the prevalence of physical-mental comorbidity. Research is needed into how multimorbidity develops (including the extent to which many disorders are driven by one cause, or whether they occur independently), its associations with a range of outcomes (including guality of life, functional status, health-service use, quality of care, and mortality), how preventable these outcomes are and how to intervene to minimise them, and how best to organise health care to address the needs of people with multimorbidity.

> burden is difficult for patients to manage and potentially harmful.<sup>28</sup> Evidence of how best to deliver care to people with several disorders in middle age is scarce, although this drawback is beginning to be addressed, particularly for people with both depression and a physical disorder—one of the most common comorbidities which is associated with poor physical and mental health outcomes.<sup>21,29</sup>

The representative nature of our data means that they are indicative of the higher rates of socioeconomic deprivation and lower life expectancy in Scotland than in most developed countries. However, our findings are consistent with multimorbidity studies from other countries that have used primary care or population data, included reasonable numbers of morbidities, and examined socioeconomic inequalities.<sup>5-7</sup> We believe that they will therefore broadly apply in other countries, although the relations in our study might be weaker or stronger, and the age of onset of multimorbidity will probably vary with population life expectancy. In relation to the challenges to health-care delivery, this study shows the concentration of multimorbidity in deprived areas, but has not examined the concentration of multimorbidity and other issues within families, the concentration of such families within practices, or the concentration of practices within areas.<sup>14,30</sup> Strengthening of primary care in such deprived areas is a particular priority.

As health systems evolve to address the emerging challenges of long-term care, widening inequality, and financial constraints, multimorbidity is becoming the norm rather than the exception. Existing approaches focusing on patients with only one disease dominate most medical education, clinical research, and hospital care, but increasingly need to be complemented by support for the work of generalists, mainly but not exclusively in primary care, providing continuity, coordination, and above all a personal approach for people with multimorbidity. This approach is most needed in socioeconomically deprived areas, where multimorbidity happens earlier, is more common, and more frequently includes physical–mental health comorbidity.

#### Contributors

BG, SWM, SW, and GW conceived the study and obtained the funding. All authors contributed to the analysis, which was mainly done by KB and BG. KB and MN wrote the first draft, and all authors contributed to the writing of the final report.

## **Conflicts of interest**

We declare that we have no conflicts of interest.

## Acknowledgments

We thank the Chief Scientist Office of the Scottish Government Health Directorates (Applied Research Programme Grant ARPG/07/1), which funded the work; the Scottish School of Primary Care, which part supported SWM's post and the development of the Applied Research Programme; and the Primary Care Clinical Informatics Unit at the University of Aberdeen, which provided the data contained herein. The views in this publication are not necessarily the views of the University of Aberdeen, its agents, or employees. We thank Katie Wilde and Fiona Chaloner of the University of Aberdeen, who did the initial data extraction and management.

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