Title:

Polypharmacy difference between older people with and without diabetes: evidence from the English Longitudinal Study of Ageing.

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Abstract

Aim

To study the association between diabetes and the prevalence of and risk factors for polypharmacy among adults aged 50 and older in England.

Methods

A cross-sectional study (2012−2013) of the English Longitudinal Study of Ageing. Polypharmacy was defined as taking 5-9 long-term medications a day and heightened polypharmacy as 10 or more. Diabetes included diagnosed and undiagnosed cases (glycated haemoglobin ⩾ 6.5% (48 mmol/mol)).

Results

Of 7729 participants, 1100 people had diabetes and showed higher prevalence rates of polypharmacy (41.1% vs 14.8%) and heightened polypharmacy (5.8% vs 1.7%) than those without diabetes, even when antihyperglycemic medications were excluded. Risk factors for polypharmacy also differed according to diabetes status. Among people with diabetes, risk factors for polypharmacy and heightened polypharmacy were having more long-term conditions (relative risk ratio (RRR) =1.86; 3.51) and being obese (RRR=1.68; 3.68), while females were less likely to show polypharmacy (RRR=0.51) and heightened polypharmacy (RRR=0.51) than males. Older age (RRR=1.04) was only related to polypharmacy among people without diabetes.

Conclusions

Adults with diabetes had higher prevalence rates of polypharmacy and heightened polypharmacy than those without diabetes, regardless of including antihyperglycemic drugs. Early detection of polypharmacy among older people with diabetes needs to focus on co-morbidities and obesity.

Keywords

Ageing, diabetes, pharmacoepidemiology, polypharmacy, prevalence, risk factor

Highlights

Little is known about whether polypharmacy differs according to diabetes status.

Diabetics had a higher prevalence of polypharmacy even when excluding diabetes drugs.

Age was not associated with polypharmacy in older people with diabetes.

Older people with diabetes need greater attention to polypharmacy.

Focus on comorbidities and obesity help early detect polypharmacy in older diabetics.

Introduction

Diabetes is a common long-term condition among older adults. In England, 15% of people aged 65 and older reported having diabetes in 2017 [1]. Diabetes and its complications have been shown to be associated with polypharmacy, which is also common in cardiovascular diseases (CVD), dyslipidaemia, gastrointestinal and mental illnesses [2-6]. Diabetes progression and its treatment guidelines may link diabetes to the presence of polypharmacy. As diabetes progresses, microvascular and/or macrovascular complications appear. Inevitably, people with diabetes develop multimorbidity, defined as the coexistence of two or more chronic conditions, according to the World Health Organisation (WHO) [7]. This phenomenon therefore brings about polypharmacy in this population [8]. Moreover, both the American Diabetes Association and the National Institute for Health and Care Excellence (NICE) in the UK suggest intensification with additional medications when lifestyle management or monotherapy fails to reach individuals' treatment goals. These treatment guidelines increase the risk of developing polypharmacy among people with diabetes. More importantly, the direct effects of ageing on metabolic regulation aggravate the underlying pathophysiology of type 2 diabetes [9]. The occurrence of type 2 diabetes in older adults is a result of complex interactions between genetic, lifestyle, and ageing factors [10]. Ageing effects may also interact with diabetes to accelerate the progression of diabetes complications [9]. Older people with diabetes are therefore more likely to show polypharmacy.

Polypharmacy is defined as taking multiple concurrent drugs; however, no firm definition has been developed in clinical practice. A WHO report suggested defining polypharmacy as taking more than four or five medications for chronic conditions simultaneously [11]. A systematic review of polypharmacy identified three different definitions: (1) numerical-only definitions; (2) numerical definitions that take account of the duration of therapy or the healthcare setting; (3) descriptive definitions [12]. Using different definitions of

polypharmacy makes current studies difficult to compare, so the burden and consequences of polypharmacy among older people are difficult to study. Beyond the numerical definitions, NICE proposed a concept of appropriate or problematic polypharmacy, classified by whether the medicines used had been optimised and whether the medicines were prescribed according to the best evidence [13]. This classification has been adopted in much polypharmacy research investigating potentially inappropriate prescriptions. However, determining whether polypharmacy is appropriate is often limited by study designs and data availability, especially in population-based studies.

The prevalence of polypharmacy varies from 4% to 87.5% among older people when polypharmacy is defined as taking five or more drugs a day [2-6,14-18]. Several factors have been reported to be associated with polypharmacy. These can be divided into two categories: socio-demographic characteristics such as age, gender, wealth, education and ethnicity; and health factors including the number of co-morbidities, specific long-term conditions, obesity (BMI 30+), cognitive performance, malnutrition, and the use of supplements and oral antihyperglycemic drugs [2-6,14-17,19,20]. Factors that have been consistently reported being associated with a high risk of polypharmacy are older age and an increasing number of co-morbidities [2-5,14-17,19].

Some polypharmacy is a legitimate response to multimorbidity and patient management according to clinical treatment guidelines. However, the recommendation for deprescribing for people with limited life expectancy [21] has been increasingly endorsed. As a result of evidence of the positive and negative consequences of polypharmacy [22-24], there has been increasing debate about the rationality of polypharmacy, especially among older adults. Diabetes is one of the long-term conditions that have been identified as implicated in polypharmacy. However, to date, no studies have compared polypharmacy issues, either prevalence or risk factors, between people with and without diabetes. Therefore, this study

aimed to disentangle the effect of diabetes on polypharmacy by studying the prevalence of and risk factors for polypharmacy between older people with and without diabetes.

Methodology

Study population

Data came from Wave 6 (2012−2013) of the English Longitudinal Study of Ageing (ELSA), a nationally representative study of adults in England age 50 and older living in private households [25]. Data collection is carried out using computer-assisted interviews every two years, and home visits from a study nurse every four years in which blood samples and other health-related measurements are taken [26,27]. At Wave 6, a total of 9169 interviews with core members were conducted. Of these, 7730 participants were visited by a study nurse who recorded information on all medications for the first time. The analytical sample for this study consisted of 7729 individuals who took part in the nurse assessments and had information on diabetes diagnosis.

Main outcome variables

Polypharmacy was defined as taking between five and nine long-term medications a day; taking ten or more medications was defined as heightened polypharmacy. Long-term medications were either drugs for chronic conditions such as antihyperglycemic and antihypertensive agents, or drugs for chronic symptoms such as sedatives for insomnia and relievers for tremor. Polypharmacy excluding antihyperglycemic drugs and heightened polypharmacy excluding antihyperglycemic drugs were also calculated for people with diabetes. Over-the-counter (OTC) drugs used for chronic conditions were also included in this study. Each distinct pharmacological agent was treated as an individual drug, so distinguishable drug combinations were counted as two or three drugs.

Risk factors

Socio-demographic characteristics

A continuous variable for age was employed. Binary variables were employed for gender (male and female), ethnicity (white and non-white), education (no qualifications versus some qualifications), occupational social class (intermediate/professional-managerial versus manual), and cohabiting status (living or not with a partner). Wealth was used as the measure of economic resources, since it is more consistently associated with health outcomes at older ages than income [28]. Wealth was computed from detailed assessments of housing wealth, savings, investments and possessions net of debt. It was presented as quintiles from poorest to richest.

Health factors

Diabetes included diagnosed and undiagnosed cases. Diagnosed diabetes was defined as either self-reporting doctor-diagnosed diabetes or taking diabetic medications. Undiagnosed diabetes was defined as not self-reporting diabetes and not taking any diabetic medications, but having a glycated haemoglobin measurement ≥ 6.5% (48 mmol/mol). The number of long-term conditions was derived from self-reported diagnoses and specific treatments. Sixteen diagnoses were included to generate the number of conditions: hypertension, coronary heart disease (including angina and heart attack), stroke, other heart problems (including congestive heart failure, heart murmur, abnormal heart rhythm and other heart diseases), hyperlipidemia, lung disease and asthma, arthritis, bone disease (including osteoporosis, Paget's disease and heterotopic ossification), cancer and malignant blood disorder, Parkinson's disease, Alzheimer's disease and dementia, psychiatric conditions, any one of four eye diseases (including glaucoma, diabetic eye disease, macular degeneration and cataracts), hyperuricemia (including gout), epilepsy, and inflammatory bowel disease. Smoking status was coded as current smoker or not. Frequency of alcohol consumption was classified as 'daily (five to seven days per week)' and 'less than daily'. Obesity was derived

from body mass index (BMI) and waist circumference (WC), and categorized into 'normal BMI and WC', 'high BMI and WC' and 'either high BMI or WC'. High BMI was defined as BMI 30 and over. The cut-off values of waist circumference were 102 cm in males and 88 cm in females. Depressive symptoms and cognitive function were also included in the study. Depressive symptoms were assessed by the eight-item version of the Centre for Epidemiological Studies Depression Scale (CES-D) [29], and total scores were used (ranging from zero to eight). Cognitive function was assessed by immediate and delayed recall. Participants were administered a list of 10 words orally, and then asked to recall as many words as possible. Recall was repeated after a five-minute delay. Scores derived from memory scores ranged from zero to 20.

Statistical analysis

Multinomial logistic regression was used to determine the risk factors significantly associated with polypharmacy. Relative risk ratios (RRRs) were reported to denote relative risk of each category compared to the reference category, conditional on fixed covariates in the model. The variables were entered into the model simultaneously and included age, gender, ethnicity, total wealth, education, social class, cohabitation status, number of conditions (excluding diabetes), smoking status, alcohol consumption, obesity, depressive symptoms, and cognitive function. Statistical analyses were conducted using Stata (version 15.1; StataCorp LP, College Station, TX, USA).

Weighting

Analyses of polypharmacy prevalence were weighted by inverse probability weight to adjust for sampling probabilities and differential non-responses to the nurse visit in 2012. The weighting is designed to render the results representative of adults in England age 50 and older living in private households in 2012 (Wave 6).

Sensitivity analysis

Sensitivity analyses were performed to check the robustness of results when employing specific long-term conditions plus the number of conditions instead of the sum of all conditions (Table S2 and S3).

Results

Prevalence of polypharmacy

A total of 7729 participants (1100 with diabetes and 6629 without diabetes) were included in this study, and the characteristics of participants are summarised in Table 1. People with diabetes tended to have more long-term conditions, be older, be men, be non-white, be poorer, lack educational qualifications, be in a manual social class, live without a partner, drink less than daily, be obese, have worse cognitive performance, and have greater depressive symptoms.

Of all participants, 2093 (31.1%) did not take any drugs, 3752 (46.5%) took one to four long-term medications a day, 1656 (19.6%) took five to nine medications (polypharmacy), and 228 (2.8%) took ten or more medications (heightened polypharmacy). As Figure 1, significant differences in the prevalence rates emerged when the study samples were divided by diabetes status. Of people with diabetes, only 4.1% did not take long-term medications, while 35.4% of people without diabetes did not either. People with diabetes tended to take more medications, with a higher prevalence of polypharmacy (50.2% vs 14.8%) and heightened polypharmacy (10.2% vs 1.7%) than those without diabetes ($P < 0.001$). The gap in the prevalence between the two groups remained significant even when antihyperglycemic drugs were excluded. For people with diabetes, the prevalence of polypharmacy dropped from 50.2% to 41.1% and of heightened polypharmacy was from 10.2% to 5.8% (Figure 1).

Risk factors for polypharmacy and heightened polypharmacy

The associations between potential risk factors and polypharmacy and heightened polypharmacy in people without diabetes are summarised in Table 2. Factors significantly associated with a higher risk of polypharmacy were older age (RRR = 1.04), living with a partner (RRR = 1.40), a higher number of conditions (RRR = 2.43), being a current smoker (RRR = 1.76), obesity (high BMI and WC) (RRR = 1.70) and reporting a higher number of depressive symptoms (RRR = 1.07). Females (RRR = 0.74), those in the richest wealth group (RRR = 0.64) and those with better cognitive function (RRR = 0.95) were less likely to show polypharmacy. Better cognitive function (RRR = 0.90) was related to a lower risk of heightened polypharmacy, whereas a larger number of long-term conditions (RRR = 3.81) and reporting a higher number of depressive symptoms (RRR = 1.14) were associated with increased risk. Other factors assessed in the study were not significantly related to heightened polypharmacy.

Table 3 shows the risk factors for polypharmacy and heightened polypharmacy among people with diabetes. After accounting for all other factors, females were less likely to show polypharmacy (RRR = 0.51) and heightened polypharmacy (RRR = 0.51) than males. Having a larger number of long-term conditions (RRR =1.86, 3.51) and being obese with high BMI and WC (RRR = 1.68, 3.68) significantly increased the risk of polypharmacy and heightened polypharmacy, while reporting a higher number of depressive symptoms (RRR = 1.24) was related to heightened polypharmacy only.

Sensitivity analysis with specific conditions – CVD, hypertension, hyperlipidemia, and psychiatric conditions – contrasted with the remaining conditions was carried out. A larger number of CVD and remaining conditions, and the presence of hypertension, hyperlipidemia and psychiatric conditions were associated with an increased likelihood of developing polypharmacy and heightened polypharmacy. Similar estimates for other factors were observed in Table S2 and S3, demonstrating the robustness of our results. We also examined

the contribution of different factors to the final results. The number of long-term conditions was the main contributor to the lack of associations between socio-demographic characteristics and polypharmacy, as well as to the attenuation of associations between health factors and polypharmacy. Age effects disappeared when adjusting for long-term conditions and health factors simultaneously. Diabetes status interacted with age and the number of long-term conditions, justifying the stratification by diabetes in this study. We found that the interaction between diabetes and age groups (50-59, 60-69, 70-79, 80+) was significant for polypharmacy only. For people without diabetes, the risk of polypharmacy increased with age, while the risk in people with diabetes was similar across age groups. The number of antihyperglycemic medications in each age group was further examined, and people aged 80 and older were found to be taking fewer antihyperglycemic drugs, compared with younger age groups.

Discussion

There was a higher prevalence of polypharmacy and heightened polypharmacy among people with diabetes compared with those without diabetes, and risk factors for polypharmacy also differed to some extent. Of people with diabetes, 50.2% and 10.2% showed polypharmacy and heightened polypharmacy, while people without diabetes showed 14.8% and 1.7%, respectively. Even when antihyperglycemic drugs were excluded, people with diabetes still showed a substantially higher prevalence of polypharmacy (41.1%) and heightened polypharmacy (5.8%) than non-diabetic participants. These results indicate that the elevated rate of polypharmacy among people with diabetes is not merely due to prescriptions for antihyperglycemic medications, and imply people with diabetes aged 50 and older tend to have more co-morbidities that need pharmacological treatment.

A greater number of long-term conditions was a risk factor for polypharmacy for all participants, while other factors were differentially related to polypharmacy in people with and without diabetes. Male sex and obesity were related to polypharmacy and heightened polypharmacy among participants with diabetes, while these relationships were less consistent in those without diabetes. By contrast, a higher number of depressive symptoms and worse cognitive function were consistently associated with polypharmacy and heightened polypharmacy in participants without diabetes but not in those with diabetes. On the other hand, a variety of factors were related to polypharmacy (but not heightened polypharmacy) in people without diabetes, including socio-demographic factors (age, gender, the richest quintile of wealth and cohabitation) and health factors (smoking status and obesity).

The impact of long-term conditions on polypharmacy is well-known; however, this is the first study to demonstrate that the association with the number of long-term conditions was similar in people with and without diabetes. The addition of a single long-term condition doubled the risk of polypharmacy and increased the risk of heightened polypharmacy by more than three times. Furthermore, age was not a risk factor either for polypharmacy or heightened polypharmacy among people with diabetes, in contrast with much of the literature [2,3,5,14-16]. This suggests that for people with diabetes, health status − long-term conditions and health factors − play a more prominent role than socio-demographics such as age. Therefore, our findings provide evidence about the characteristics related to a higher risk of polypharmacy among older people with diabetes.

Prevalence of polypharmacy

As noted earlier, the prevalence of polypharmacy in the literature varies substantially with definitions and study characteristics. In this nationally representative sample, we found 19.6% of participants had polypharmacy, and the prevalence was similar to that in two previous UK-based studies [16,17]. However, heightened polypharmacy (2.8%) in this study was

slightly lower than in previous studies: 6.4% and 4.7%. One of these studies [16] did not limit the definition to long-term or regularly used medications, while the second [17] used nine or more medications as the definition of extreme polypharmacy. These differences may account for the varying levels of heightened polypharmacy.

Among participants with diabetes, 50.2% showed polypharmacy, which was similar to 57.1% reported in the Italian diabetic population aged 65 and older [4]. Our study is the first to show the gap in prevalence rates between people with and without diabetes, indicating the clinical importance of diabetes in terms of coexistence of co-morbidities and concurrent use of multiple medications.

Risk factors

Diabetes and its complications are well-established risk factors for polypharmacy [2-6]; however, this is the first study to compare risk factors for polypharmacy between older people with and without diabetes. Direct comparisons with previous studies are difficult to make. Slater et al [16] also analysed polypharmacy in ELSA, and identified different risk factors. This may be a result of the different definitions used for long-term conditions and polypharmacy. Slater et al employed a dichotomous self-reported chronic health condition variable, whereas we took account of the number of long-term conditions that were self-reported and verified by medication profiles. Also, we only included long-term medications in our definition of polypharmacy, while Slater and colleagues did not place any restriction on types of medications.

Despite variations in definitions, there is a consensus that a larger number of long-term conditions increase risks for the development of polypharmacy and heightened polypharmacy [4,5,14,17,19,20]. But other factors vary across diabetes-focused studies. For example, an Italian cross-sectional study of adults aged 65 and older [4] reported that females had a 56% increase in the risk of polypharmacy, whereas we found women had a lower rate of polypharmacy and

heightened polypharmacy than men. The same Italian study [4] also reported better cognitive performance as a risk factor for polypharmacy, but no relation was found in the diabetic group in our study. Although diabetes is believed to contribute to cognitive impairment [30,31], the association between cognitive function and polypharmacy remains questionable and could be bidirectional. On the other hand, our estimate of obesity is partially in line with the Italian study [4], where BMI 30 or more was a risk factor. We only found people with high BMI and high WC had a higher risk of polypharmacy and heightened polypharmacy, but those with only one did not.

Our findings partially support the concept that ageing is related to the development of polypharmacy [2,3,5,14-16], but this association seems stronger among individuals without diabetes. Some characteristics of diabetes, such as diabetic complications and treatment guidelines, may contribute to polypharmacy at an early age. Also, fewer antihyperglycemic drugs were observed in the oldest age group (80 and older). These may account for diminishing association with age in people with diabetes.

People without diabetes who had more depressive symptoms and who had worse cognitive function showed a higher risk of polypharmacy and heightened polypharmacy. Both depression and cognitive impairment are thought to be related to diabetes [30-33], so their associations with polypharmacy in people with diabetes may not appear in this cross-sectional study.

Strengths and limitations

This study has several strengths. First, self-reported diagnoses were verified by medication profiles that were collected by nurses. The verification and collection process help to reduce misreporting bias. Second, the inclusion of undiagnosed cases decreased misclassification bias. Third, we used a rigorous definition of polypharmacy that refers to drugs in long-term use rather than includes temporary use of painkillers. Fourth, OTC drugs for chronic

conditions were included, since some interactions between OTC and prescribed medications could be life-threatening, such as angiotensin-converting enzyme inhibitors in combination with potassium supplements. Lastly, this study contained comprehensive assessments of multiple factors related to socio-demographic characteristics and health status. ELSA provided the opportunity to investigate associations between these factors and polypharmacy, since previous hospital-based studies have typically not included much information on socio-demographics.

Some limitations of this study should also be acknowledged. Information on drug duration, dose, and frequency was not collected during the nurse visit, so no definite cut-off could be used to define long-term medications, nor appropriate or problematic polypharmacy could be assessed. Despite this limitation, the strong association between diabetes and polypharmacy disclosed in this study is likely justified by the burden of comorbidities in people with diabetes regardless of their polypharmacy status (Table S4). Also, some drug combinations shared the same code with a single drug that cannot be separated, so the prevalence of polypharmacy and heightened polypharmacy would be underestimated in this case. Finally, this is a cross-sectional study so causal conclusions cannot be drawn, and there may be underlying unmeasured factors responsible for the associations observed.

Clinical significance

The findings highlight the importance of greater awareness of polypharmacy among older adults living in England. The contrast between people with and without diabetes emphasises the importance of special care for older people with diabetes. Although polypharmacy is often not negative or inappropriate, early detection could contribute to prompt interventions, such as mediation review or deprescribing [34,35]. Medication review is regarded as a standard method of medication optimisation and is advocated by the NICE [36], NHS Scotland [37] and NHS England [38], even though its effectiveness seems unclear. A meta-analysis of randomised

clinical trials showed medication review that included comprehensive clinical evaluation for disease management reduced hospitalisations in older adults with polypharmacy [39]. However, other authorities suggest that while medication review may be useful in the identification and reduction in medication-related problems, its effect on clinical outcomes is still uncertain [40-43]. The monitoring of medication profiles would ensure treatment appropriateness, reduce polypharmacy-related complications and unnecessary medication use, and improve older adults' health.

Conclusions

Adults with diabetes had a significantly higher prevalence of polypharmacy and heightened polypharmacy than those without diabetes, regardless of including antihyperglycemic drugs. Risk factors for polypharmacy and heightened polypharmacy in the two groups also differed. People with diabetes who were men and obese were more likely to show polypharmacy and heightened polypharmacy. Greater attention to polypharmacy among older people with diabetes would benefit clinical practice, help detect inappropriate polypharmacy, and potentially help reduce polypharmacy-associated adverse effects.

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Conflict of Interest

The authors have no conflict of interest to declare.

Contributors

YTH who is guarantor carried out all statistical analyses, wrote the paper and takes responsibility for the work. All authors contributed to the interpretation of results and approved the final version of the paper.

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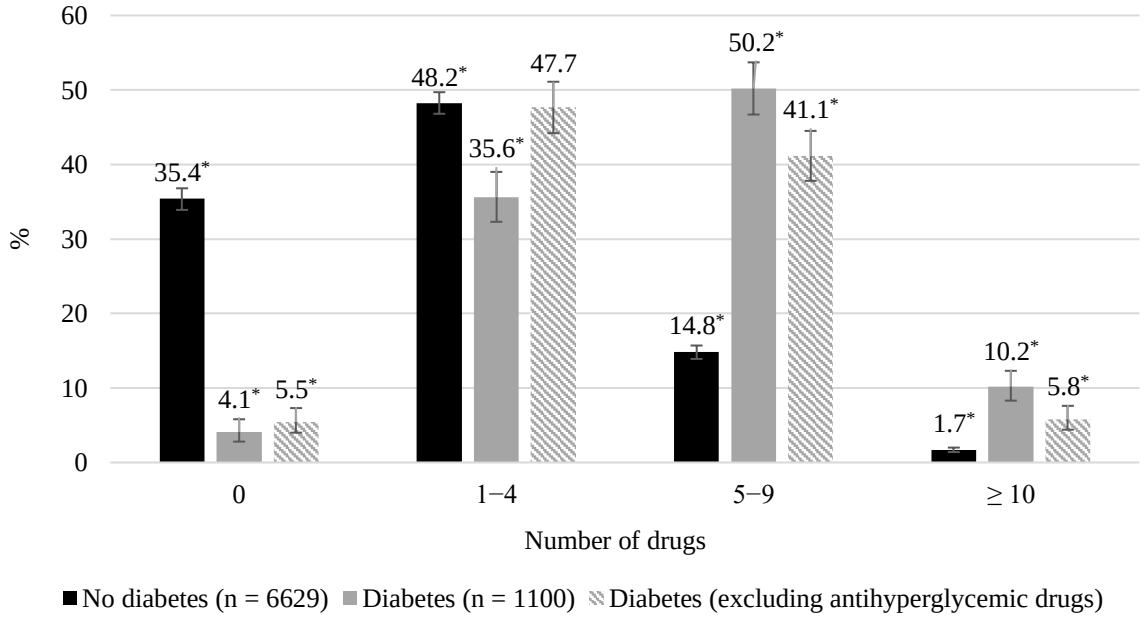
Table 1 Cohort characteristics in ELSA 2012, stratified by diabetes.

	No diabetes (n = 6629)	Diabetes (n = 1100)	*P*
Age (years) mean ± SD	67.2 ± 9.5	70.0 ± 9.1	**<0.001**
Gender % (n)			
Men	43.6 (2889)	50.7 (558)	**<0.001**
Women	56.4 (3740)	49.3 (542)	
Ethnicity % (n)			
White	97.5 (6464)	93.5 (1029)	**<0.001**
Non-white	2.5 (165)	6.5 (71)	
Total wealth % (n)			
1 (lowest)	19.0 (1187)	27.5 (277)	**<0.001**
2	19.3 (1203)	23.6 (237)	
3	20.0 (1247)	20.9 (210)	
4	20.8 (1294)	15.4 (155)	
5 (highest)	20.9 (1301)	12.6 (127)	
Education % (n)			
No qualifications	23.3 (1543)	32.2 (350)	**<0.001**
Some qualifications	76.7 (5064)	67.8 (738)	
Social class based on occupation % (n)			
Manual	37.0 (2426)	47.3 (511)	**<0.001**
Intermediate or professional-managerial	63.0 (4129)	52.7 (570)	
Live with a partner % (n)			
Yes	69.0 (4572)	61.6 (678)	**<0.001**
No	31.0 (2057)	38.4 (422)	
Number of conditions [#] mean ± SD	2.3 ± 1.8	3.7 ± 1.8	**<0.001**
Current smoker % (n)			
Yes	11.4 (753)	12.6 (139)	0.220
No	88.6 (5876)	87.4 (961)	
Alcohol consumption % (n)			
Less than daily	78.1 (4715)	86.4 (834)	**<0.001**
Daily (5−7 days per week)	21.9 (1319)	13.6 (131)	
Obesity % (n)			

High BMI and WC	26.4 (1664)	52.7 (524)	**<0.001**
Either high BMI or WC	23.5 (1480)	25.6 (254)	
Cognitive function mean ± SD	10.9 ± 3.6	9.7 ± 3.8	**<0.001**
Number of depressive symptoms mean ± SD	1.3 ± 1.8	1.8 ± 2.1	**<0.001**

[#] Not including diabetes

Figure 1 Prevalence of polypharmacy in ELSA 2012, stratified by diabetes.



[*] Significantly different between people with and without diabetes ($P < 0.001$). The number of 5−9 was defined as polypharmacy; ≥ 10 was defined as heightened polypharmacy.

Table 2 Risk factors for polypharmacy in people without diabetes (n = 5372).

	Polypharmacy (n = 806)			Heightened polypharmacy (n = 72)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.04	1.03, 1.05	**<0.001**	1.02	0.98, 1.05	0.358
Female sex	0.74	0.61, 0.90	**0.002**	0.66	0.38, 1.16	0.147
Ethnicity non-white	0.75	0.36, 1.60	0.46	2.41	0.59, 9.87	0.221
Total wealth						
2nd	0.89	0.67, 1.18	0.413	1.24	0.60, 2.56	0.554
3rd	0.78	0.58, 1.05	0.099	0.87	0.40, 1.91	0.727
4th	0.98	0.72, 1.33	0.874	1.12	0.46, 2.68	0.806
5th quintile (richest)	0.64	0.45, 0.90	**0.01**	0.84	0.32, 2.21	0.724
No educational qualification	1.09	0.87, 1.36	0.455	1.00	0.55, 1.81	0.996
Manual social class	0.99	0.81, 1.22	0.95	0.88	0.50, 1.56	0.665
Live with a partner	1.40	1.12, 1.75	**0.003**	1.02	0.58, 1.82	0.934
Number of conditions #	2.43	2.27, 2.60	**<0.001**	3.81	3.23, 4.49	**<0.001**
Current smoker	1.76	1.28, 2.42	**0.001**	1.89	0.82, 4.36	0.137
Alcohol consumption: daily (5−7 days per week)	1.14	0.91, 1.42	0.265	0.85	0.43, 1.69	0.642
Obesity						
High BMI and WC	1.70	1.37, 2.12	**<0.001**	1.14	0.61, 2.13	0.679
Either high BMI or WC	1.16	0.92, 1.46	0.201	1.08	0.58, 2.02	0.81
Cognitive function	0.95	0.93, 0.98	**0.003**	0.90	0.83, 0.97	**0.008**
Number of depressive symptoms	1.07	1.02, 1.13	**0.006**	1.14	1.01, 1.29	**0.028**

* Unweighted relative risk ratio

Not including diabetes

Table 3 Risk factors for polypharmacy in people with diabetes (n = 783).

	Polypharmacy (n = 397)			Heightened polypharmacy (n = 66)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.00	0.98, 1.03	0.707	0.98	0.94, 1.02	0.363
Female sex	0.51	0.35, 0.73	**<0.001**	0.51	0.25, 1.01	**0.052**†
Ethnicity non-white	1.02	0.47, 2.22	0.963	1.12	0.26, 4.94	0.877
Total wealth						
2nd	0.95	0.57, 1.57	0.831	1.49	0.59, 3.80	0.399
3rd	0.74	0.44, 1.24	0.256	1.95	0.75, 5.06	0.171
4th	1.21	0.68, 2.16	0.521	1.11	0.31, 4.00	0.868
5th quintile (richest)	0.56	0.30, 1.04	0.068	1.21	0.35, 4.21	0.769
No educational qualification	1.08	0.71, 1.64	0.723	1.04	0.48, 2.22	0.928
Manual social class	1.38	0.95, 2.02	0.091	1.57	0.77, 3.20	0.211
Live with a partner	0.96	0.65, 1.41	0.83	0.98	0.48, 2.01	0.966
Number of conditions #	1.86	1.63, 2.13	**<0.001**	3.51	2.77, 4.45	**<0.001**
Current smoker	1.30	0.74, 2.29	0.359	1.26	0.45, 3.54	0.662
Alcohol consumption: daily (5−7 days per week)	0.96	0.59, 1.54	0.852	0.53	0.18, 1.55	0.245
Obesity						
High BMI and WC	1.68	1.10, 2.57	**0.016**	3.68	1.31, 10.35	**0.013**
Either high BMI or WC	1.14	0.71, 1.83	0.574	1.96	0.62, 6.19	0.253
Cognitive function	1.00	0.95, 1.06	0.975	0.97	0.88, 1.07	0.523
Number of depressive symptoms	1.08	0.97, 1.20	0.159	1.24	1.06, 1.46	**0.009**

* Unweighted relative risk ratio

Not including diabetes

† Borderline significant

Appendices

Table S1 Prevalence of polypharmacy in ELSA 2012.

	Number of drugs	0	1−4	5−9 *	≥ 10 *
All long-term drugs	% (n)	31.1 (2093)	46.5 (3752)	19.6 (1656)	2.8 (228)
	95% CI	29.8, 32.4	45.2, 47.8	18.7, 20.7	2.5, 3.3
Long-term drugs excluding antihyperglycemic drugs	% (n)	31.2 (2109)	48.1 (3882)	18.4 (1563)	2.2 (175)
	95% CI	29.9, 32.6	46.8, 49.5	17.5, 19.4	1.9, 2.6

* The number of 5−9 was defined as polypharmacy; ≥ 10 was defined as heightened polypharmacy.

Table S2 Risk factors for polypharmacy in people without diabetes (n = 5372).

	Polypharmacy (n = 806)			Heightened polypharmacy (n = 72)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.04	1.02, 1.05	**<0.001**	1.01	0.97, 1.04	0.648
Female sex	0.81	0.66, 0.98	**0.035**	0.70	0.40, 1.22	0.210
Ethnicity non-white	0.72	0.34, 1.55	0.404	2.43	0.60, 9.85	0.215
Total wealth						
2nd	0.88	0.66, 1.17	0.393	1.32	0.64, 2.76	0.453
3rd	0.77	0.58, 1.04	0.091	0.90	0.41, 2.01	0.803
4th	0.99	0.73, 1.36	0.971	1.21	0.50, 2.96	0.669
5th quintile (richest)	0.65	0.46, 0.92	**0.015**	0.90	0.34, 2.41	0.836
No educational qualification	1.13	0.90, 1.41	0.309	1.03	0.57, 1.89	0.916
Manual social class	1.01	0.82, 1.24	0.943	0.91	0.51, 1.61	0.734
Live with a partner	1.41	1.13, 1.76	**0.003**	1.07	0.60, 1.93	0.812
Number of CVD	3.52	3.02, 4.10	**<0.001**	5.96	4.31, 8.24	**<0.001**
Hypertension	3.13	2.58, 3.80	**<0.001**	2.80	1.61, 4.85	**<0.001**
Hyperlipidemia	1.80	1.49, 2.17	**<0.001**	2.31	1.35, 3.97	**0.002**
Psychiatric conditions	2.07	1.63, 2.63	**<0.001**	3.27	1.86, 5.77	**<0.001**
Number of conditions #	2.21	2.00, 2.43	**<0.001**	3.90	3.06, 4.98	**<0.001**
Current smoker	1.81	1.31, 2.50	**<0.001**	1.90	0.82, 4.41	0.136
Alcohol consumption: daily (5−7 days per week)	1.14	0.91, 1.43	0.249	0.87	0.44, 1.75	0.705
Obesity						
High BMI and WC	1.67	1.33, 2.08	**<0.001**	1.18	0.63, 2.22	0.598
Either high BMI or WC	1.17	0.93, 1.48	0.179	1.09	0.58, 2.05	0.790
Cognitive function	0.96	0.93, 0.98	**0.003**	0.89	0.82, 0.97	**0.006**
Number of depressive symptoms	1.09	1.03, 1.15	**0.002**	1.15	1.02, 1.30	**0.024**

* Unweighted relative risk ratio

The rest of other conditions, not including diabetes

Table S3 Risk factors for polypharmacy in people with diabetes (n = 783).

	Polypharmacy (n = 397)			Heightened polypharmacy (n = 66)		
	RRR*	95% CI	*P*	RRR*	95% CI	*P*
Age	1.01	0.99, 1.04	0.313	0.98	0.93, 1.02	0.315
Female sex	0.50	0.34, 0.73	**<0.001**	0.50	0.24, 1.01	**0.053**†
Ethnicity non-white	1.05	0.48, 2.27	0.910	0.97	0.21, 4.51	0.968
Total wealth						
2nd	0.97	0.58, 1.63	0.918	1.41	0.54, 3.68	0.480
3rd	0.79	0.47, 1.33	0.374	1.88	0.70, 5.03	0.207
4th	1.29	0.72, 2.33	0.396	1.19	0.32, 4.37	0.795
5th quintile (richest)	0.60	0.32, 1.12	0.107	1.40	0.39, 4.98	0.605
No educational qualification	1.06	0.69, 1.63	0.776	0.99	0.45, 2.15	0.976
Manual social class	1.43	0.98, 2.10	0.066	1.75	0.85, 3.61	0.130
Live with a partner	0.96	0.65, 1.43	0.850	1.01	0.49, 2.10	0.969
Number of CVD	2.19	1.62, 2.96	**<0.001**	3.54	2.20, 5.70	**<0.001**
Hypertension	2.39	1.67, 3.43	**<0.001**	3.79	1.64, 8.78	**0.002**
Hyperlipidemia	1.52	1.07, 2.14	**0.019**	1.59	0.78, 3.27	0.205
Psychiatric conditions	4.35	2.54, 7.46	**<0.001**	6.35	2.81, 14.33	**<0.001**
Number of conditions #	1.56	1.28, 1.91	**<0.001**	3.88	2.76, 5.45	**<0.001**
Current smoker	1.28	0.72, 2.27	0.402	1.28	0.45, 3.66	0.641
Alcohol consumption: daily (5−7 days per week)	0.89	0.55, 1.46	0.648	0.55	0.18, 1.66	0.291
Obesity						
High BMI and WC	1.70	1.11, 2.62	**0.015**	3.58	1.26, 10.15	**0.016**
Either high BMI or WC	1.13	0.70, 1.82	0.621	2.00	0.63, 6.38	0.239
Cognitive function	1.00	0.95, 1.06	0.988	0.96	0.86, 1.06	0.421
Number of depressive symptoms	1.06	0.95, 1.18	0.316	1.24	1.05, 1.47	**0.012**

* Unweighted relative risk ratio

The rest of other conditions, not including diabetes

† Borderline significant

Table S4 Prevalence of long-term conditions, according to polypharmacy and diabetes status.

	No diabetes (n = 6629)		Diabetes (n = 1100)	
	No polypharmacy (n= 5424) % (n)	Polypharmacy* (n=1205) % (n)	No polypharmacy (n=421) % (n)	Polypharmacy* (n=679) % (n)
Number of conditions# mean ± SD	1.8 ±1.4	4.2 ±1.6	2.3 ± 1.4	4.2 ± 1.8
Cardiovascular diseases	14.6% (789)	55.2% (665)	19.2% (81)	49.3% (335)
Hypertension	29.3% (1591)	65.6% (791)	51.5% (217)	74.5% (506)
Hyperlipidemia	30.8% (1668)	56.9% (685)	46.8% (197)	65.5% (445)
Psychiatric conditions	14.2% (771)	30.0% (362)	8.8% (37)	29.9% (203)
Lung diseases (including asthma)	12.3% (665)	36.0% (434)	11.4% (48)	26.2% (178)

Not including diabetes

* Including polypharmacy and heightened polypharmacy