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Complete List of Authors:	Slater, Natasha; Keele University School of Pharmacy Rowley, Charlotte; Keele University School of Pharmacy, Pharmacy Venables, Rebecca; Keele University, School of Pharmacy White, Simon; Keele University, School of Pharmacy Frisher, Martin; Keele University, School of Pharmacy
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Evaluating the associations between metabolic health, obesity and depressive symptoms: A prospective analysis of data from The English Longitudinal Study of Ageing (ELSA) with a two-year follow-up

Authors:
Natasha Slater, Charlotte Rowley, Rebecca Venables, Simon White, Martin Frisher

School of Pharmacy, Keele University, Staffordshire, ST5 5BG, United Kingdom Natasha Slater PhD Student School of Pharmacy, Keele University Charlotte Rowley MPharm graduate School of Pharmacy, Keele University Rebecca Venables Lecturer School of Pharmacy, Keele University Simon White Reader School of Pharmacy, Keele University Martin Frisher Reader School of Pharmacy, Keele University

Correspondence to: n.slater@keele.ac.uk

ABSTRACT

OBJECTIVES: Recent publications suggest that metabolic syndrome is associated with psychological conditions; however, conflicting results have been reported when the associations between metabolic health, obesity and depression were examined previously. The aim of this study is to determine whether metabolic health or obesity are independently associated with depressive symptoms, among a representative sample of older people living in England.

DESIGN: Prospective study with a two-year follow-up

SETTING: The English Longitudinal Study of Ageing Wave 6 (2012-2013) and Wave 7 (2014-2015)

PARTICIPANTS: 6804 participants aged over 50 years

DATA SYNTHESIS: Multivariate models were used to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up. Unadjusted and adjusted odds ratios with corresponding 95% confidence intervals (CI) were calculated after adjusting for baseline depression, gender, age, wealth, obesity and poor metabolic health.

RESULTS: Before adjusting for covariates, poor metabolic health was associated with depressive symptoms at two-year follow-up (OR 1.20;95% CI, 1.07-1.35, p<0.01). After adjusting for covariates, the association was no longer statistically significant (OR 1.11; 95% CI, 0.94-1.31, p=0.22). Similarly, obesity was associated with depressive symptoms at two-year follow-up before adjusting for covariates (OR 1.65;95% CI, 1.46-1.87, p<0.01). However, after adjusting for covariates the association between obesity and depressive symptoms at two-year follow-up became statistically insignificant (OR 1.16; 95% CI, 0.98-1.38, p=0.09). The strongest predictor for future depression is baseline depression (OR 9.55; 95% CI, 8.11-11.25, p<0.01).

CONCLUSION: Neither poor metabolic health nor obesity are associated with a risk of depressive symptoms at two-year follow-up, after adjusting for covariates. Baseline depression and lower wealth are strong predictors for the risk of depressive symptoms at two-year follow-up.

Key words: depression, obesity, metabolic health, ELSA

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A representative sample (n=6,804) of older people living in England provided data for this prospective analysis.
- Standardised data collection methods and validated data collection tools were used to obtain data for ELSA Wave 6 and Wave 7.
- All multivariate models were adjusted for baseline depression, gender, age, wealth, obesity and poor metabolic health to reduce the impact of confounders.
- Participants were required to truthfully and accurately recall information about their mood to prevent study bias.

INTRODUCTION

Dyslipidaemia, hypertension, obesity and hyperglycaemia are central to the development of metabolic syndrome. [1,2,3] Individuals diagnosed with metabolic syndrome are at an increased risk of developing cardiovascular diseases, type 2 diabetes mellitus and other potentially life-threatening conditions. [4] In recent years, there has been a significant increase in the number of individuals diagnosed with metabolic syndrome, and this has been attributed to the diabetes and obesity epidemics. [5].

Previous research has predominantly focused on the association between metabolic syndrome and the onset of cardiovascular diseases. [6] However, there is emerging evidence which suggests that metabolic syndrome is associated with psychological conditions. [7-11] Several studies have examined the individual components of metabolic syndrome to determine whether there is an association with depression. [7,9,10,11] The findings from a study by Lustman et al [12] showed an association between hyperglycaemia and the development of depressive symptoms; whereas a statistically significant association between dyslipidaemia and depressive symptoms was reported by Akbaraly et al [7]. However, inconsistent findings were reported when the association between obesity and depression was examined.

Findings from a prospective cohort study suggested that obesity increases an individual's risk of developing depression by 55.0%, while other studies have either failed to establish an association between obesity and depression, or an inverse association has been reported. [10,13,14] When Hamer et al [15] examined the association between obesity and depression the authors concluded that "the association appears to be partly dependent on metabolic health, although further work is required to confirm these findings".

The aim of this study is to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up, using the latest data from the English Longitudinal Study of Ageing.

METHOD

Sample and participants

A prospective study was conducted using Wave 6 and Wave 7 data gathered from the English

Longitudinal Study of Ageing (ELSA). Since inception in 2002, ELSA has gathered socio-economic, lifestyle and health data from a representative sample of the English population, who are aged over 50 years. Every two years, a new 'wave' of ELSA data are collected. [16] This study used data collected between 2012 and 2013 (Wave 6) as baseline data. Data collected between 2014-2015 (Wave 7) was used for follow-up. Overall, 6,804 participants successfully provided data in both Wave 6 and Wave 7, and this group are the focus of the current study. [16]

Patient involvement and ethics

All ELSA waves have been ethically approved by the National Research and Ethics Committee under the National Research and Ethics Service. Only participants who provided informed written consent were enrolled into ELSA. These data are anonymised and freely accessible from the UK Data Service Discover. [17] No patients were involved in the development of the research question, study design or data interpretation; therefore, further ethical approval was not required for this study.

Data collection

Three methods of data collection were utilised during ELSA Wave 6: a paper-based questionnaire, a face-to-face interview and a nurse interview. In Wave 7, the nurse interview did not take place; instead, data was collected during a face-to-face interview and using a paper-based questionnaire.

Nurse interview

During the nurse interview in Wave 6, demographic information, including gender and age, was recorded for each participant. Subsequent stages of the nurse interview involved participants having their blood pressure, pulse rate, lung function and grip strength measured, in addition to providing hair samples and fasting blood samples. Fasting blood test results and blood pressure readings were analysed to determine a participant's metabolic health status. In this study, a participant with two or more metabolic risk factors was described as having poor metabolic health. The following were defined as metabolic risk factors: glycated haemoglobin (HbA1c) greater than 6.0% (42mmol/mol); C-reactive protein (CRP) greater than or equal to 3mg/L; high density lipoprotein (HDL) less than 1.03 mmol/L for men or less than 1.30 mmol/L for women; triglycerides greater than or equal to 1.7mmol/L and blood pressure readings greater than 130/85 mmHg. [15]

The nurse interviewer also recorded a number of anthropometric measurements including height, weight and waist circumference for each participant. Using a participant's weight and height values, it was possible to calculate their body mass index (BMI). A participant was classified as obese if their calculated BMI was $\geq 30 kg/m^2$.

Face-to-face interviews

In both Wave 6 and Wave 7, face-to-face interviews were conducted by trained interviewers, at the participant's residential address. During the interviews, participants were asked questions about their physical and mental health status. To determine whether participants were experiencing depressive symptoms, they were asked to answer eight questions which

had been adapted from the Center for Epidemiologic Studies depression (CESD) scale. [18] One point was awarded for each depressed answer given. Each participant received a total score between 0 and 8. In accordance with previous studies, a score ≥ 4 was used to define participants with elevated depressive symptoms. [15,19]

Following the questions about health status, the interviewer asked the participants to provide information about everyone who resided within their property, including information about their financial situation, employment status, assets and whether they were in receipt of any benefits. Based upon this information, wealth index scores for each participant were calculated. Participants were allocated to one of five wealth quintiles, with quintile 1 being the poorest and quintile 5 being the wealthiest.

Data analysis

Descriptive statistics were used initially to summarise the prevalence of depressive symptoms among Wave 6 participants (baseline). These data were subsequently stratified according to participant demographics and chi-squared tests were performed. Multivariate models were used to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up (Wave 7). Unadjusted and adjusted odds ratios with corresponding 95% confidence intervals (CI) for the risk of depressive symptoms at two-year follow-up were calculated. The following factors were covariates: baseline depression, gender, age, wealth, obesity and poor metabolic health. Missing data was coded as "missing" and presented as a separate category in the multivariate models. All p values generated from the models were considered to be statistically significant if $p<0.05$. Analyses were undertaken using SPSS version 24.0.

RESULTS

Participant characteristics

Overall, 6,804 participants successfully provided data in both Wave 6 and Wave 7. Baseline participant characteristics are presented in Table 1. The mean age of the participants was 67.6 years, 44.5% (n=3030/6804) of the participants were male and 16.8% (n= 1145/6804) of the participants had elevated depressive symptoms at baseline (Table 1).
Baseline data were stratified according to participant characteristics, including gender, age, metabolic health status and body mass index (BMI). The prevalence of depressive symptoms was higher among females (20.3%), compared to males (12.5%) (Table 1). Results from the chi-squared statistical test showed an association between gender and depressive symptoms ($\chi^2(1) = 65.64$, $p <0.01$). There was also a significant association between age and depressive symptoms ($\chi^2(3) = 57.04$, $p <0.01$). A greater proportion of individuals with poor metabolic health (17.9%) had elevated depressive symptoms, compared to participants with good metabolic health (15.5%) (Table 1). The association between metabolic health and depressive symptoms was significant ($\chi^2(1) = 9.15$, $p <0.01$). Similarly, there was a significant association between obesity (BMI ≥ 30kg/m^2) and depressive symptoms ($\chi^2(2) = 127.28$, $p <0.01$).

Table 1: Wave 6 participant characteristics and associated depressive symptoms (n=6,804)

	Depressive symptoms (CESD 4+)	
Participant characteristics	**No (0-3)**	**Yes (≥4)**

All participants (n=6,804)	83.2%	16.8%
Gender		
Male (n=3030)	87.5%	12.5%
Female (n=3774)	79.7%	20.3%
Age		
50-59 years (n=1492)	79.6%	20.4%
60-69 years (n=2720)	86.1%	13.9%
70-84 years (n=2313)	82.9%	17.1%
85+ years (n=279)	76.0%	24.0%
Metabolic Health		
Good metabolic health (n=3123)	84.5%	15.5%
Poor metabolic health (n=3681)	82.1%	17.9%
Body Mass Index (BMI)		
Non-obese (BMI < 30kg/m^2) (n=4488)	86.1%	13.9%
Obese (BMI ≥ 30kg/m^2) (n=2058)	78.6%	21.4%

Examining the association between poor metabolic health and the risk of depressive symptoms at two-year follow-up (Wave 7)

The unadjusted logistical regression analysis showed that participants with poor metabolic health were 20.0% more likely to experience depressive symptoms at two-year follow-up, compared to those with good metabolic health. This finding was statistically significant (p<0.01) (Table 2). The odds ratio for the risk of depressive symptoms at two-year follow-up reduced to 1.12 (0.99-1.27, p= 0.06), after the model was adjusted for obesity. The odds ratio for the risk of depressive symptoms at two-year follow-up was 1.13 (0.96 -1.33, p=0.14), after the model was adjusted for obesity and baseline depression (Table 2). After adjusting for participant characteristics and baseline depression, the odds ratio for the risk of depressive symptoms at two-year follow-up decreased further to 1.11 (0.94-1.31, p=0.22) (Table 2). All adjusted models failed to produce any statistically significant results.

Table 2: Odds ratios for the association between poor metabolic health and the risk of depressive symptoms at two-year follow-up (Wave 7)

Independent variable	Odds ratio	95% C.I. for OR		Sig. level
		Lower	Upper	
Metabolic health	1.20	1.07	1.35	<0.01
Metabolic health Adjusted for obesity	1.12	0.99	1.27	0.06
Metabolic health Adjusted for obesity and baseline depression (Wave 6)	1.13	0.96	1.33	0.14
Metabolic health Adjusted for obesity, baseline depression (Wave 6), gender, age and wealth	1.11	0.94	1.31	0.22

Examining the association between obesity and the risk of depressive symptoms at two-year follow-up (Wave 7)

The unadjusted logistical regression analysis showed that obese participants were 65.0% more likely to experience depressive symptoms at two-year follow-up, compared to participants who had a body mass index <30kg/m^2 (Table 3). This finding was statistically significant (p<0.01) (Table 3). The odds ratio for the risk of depressive symptoms at two-year follow-up reduced to 1.62 (1.43-1.84, p<0.01), after adjusting for poor metabolic health (Table 3). The odds ratio for the risk of depressive symptoms at two-year follow-up decreased further to 1.29 (1.09- 1.53, p<0.01), after adjustments for poor metabolic health and baseline depression were made (Table 3). After adjusting for participant characteristics and baseline depression the odds ratio for the risk of depressive symptoms at two-year follow-up was 1.16 (0.98-1.38, p=0.09) (Table 3). The latter finding was not statistically significant.

Table 3: Odds ratios for the association between obesity and the risk of depressive symptoms at two-year follow-up (Wave 7)

Independent variable	Odds ratio	95% C.I. for OR		Sig. level
		Lower	Upper	
Obesity	1.65	1.46	1.87	<0.01
Obesity Adjusted for poor metabolic health	1.62	1.43	1.84	<0.01
Obesity Adjusted for poor metabolic health and baseline depression (Wave 6)	1.29	1.09	1.53	<0.01
Obesity Adjusted for poor metabolic health, baseline depression (Wave 6), gender, age and wealth	1.16	0.98	1.38	0.09

Examining the associations between gender, age, wealth, baseline depression (Wave 6) and the risk of depressive symptoms at two-year follow-up (Wave 7)

Results showed that females were 42.0% more likely experience depressive symptoms at two-year follow-up compared to males (Table 4). This finding was statistically significant (p<0.01) (Table 4). The association between age and depression was examined. The adjusted odds ratio for the risk of depressive symptoms at two-year follow-up was 0.88 (0.71-1.09, p=0.25) in participants aged between 60 and 69 years (Table 4). This value increased to 1.14 (0.92-1.42, p=0.23) in participants aged between 70 and 84 years (Table 4). For participants aged above 85 years, the adjusted odds ratio increased further to 1.39 (0.94-2.07, p=0.10) (Table 4). All findings, in relation to age, were not statistically significant. The association between wealth and depression was also examined. The adjusted odds ratio for the risk of depressive symptoms at follow-up reduced from 0.78 (0.61-0.99, p=0.04) in wealth quintile 2 to 0.33 (0.25-0.44, p<0.01) in wealth quintile 5 (Table 4). This suggests that individuals living in affluent areas are less likely to experience depressive symptoms at two-year follow-up, compared to individuals living in poorer areas. Finally, the association between baseline depression and future depression was examined. The adjusted odds ratio for the risk

of depressive symptoms at two-year follow-up was 9.55 (8.11-11.25, p<0.01).

Table 4: Adjusted odds ratios for the association between the independent variables and the risk of depressive symptoms at two-year follow-up (Wave 7) (n=6,084)

		95% C.I. for OR		
Independent variables	Adjusted OR	Lower	Upper	Sig. level
Gender				
Male **(Reference)** (n=3030)	1			
Female (n=3774)	1.42	1.20	1.68	<0.01
Age				
50-59 years **(Reference)** (n=1492)	1			
60-69 years (n=2720)	0.88	0.71	1.09	0.25
70-84 years (n=2313)	1.14	0.92	1.42	0.23
85+ years (n=279)	1.39	0.94	2.07	0.10
Wealth				
Wealth Quintile 1 (poorest) **(Reference)** (n=1005)	1			
Wealth Quintile 2 (n=1214)	0.78	0.61	0.99	0.04
Wealth Quintile 3 (n=1372)	0.49	0.38	0.64	<0.01
Wealth Quintile 4 (n=1464)	0.43	0.33	0.56	<0.01
Wealth Quintile 5 (wealthiest) (n=1619)	0.33	0.25	0.44	<0.01
Missing Wealth Data (n=130)				
Baseline depression				
Baseline depression (n=1145)	9.55	8.11	11.25	<0.01
No baseline depression (n=5659)				

Adjusted for obesity, poor metabolic health, baseline depression (Wave 6), gender, age and wealth

DISCUSSION

This study evaluated the associations between metabolic health, obesity and depressive symptoms. Initially, the unadjusted logistical regression model showed that poor metabolic health was associated with depressive symptoms at two-year follow-up; however, after adjusting for covariates, including baseline depression, obesity, gender, age and wealth, this finding was no longer statistically significant, and the previously elevated adjusted odds ratios diminished. Similar findings were generated when the association between obesity and depressive symptoms was examined. The unadjusted logistical regression model initially showed that obesity was associated with depressive symptoms at two-year follow-up, but after adjusting for covariates, the finding became statistically insignificant.

These findings differ when compared to the findings reported by Hamer et al [15]. Both studies analysed ELSA data, with Hamer et al [15] analysing data gathered between 2004 and 2007, and this study analysing data gathered between 2012 to 2015. It is possible that a period effect may have contributed towards the differing findings; however, the timeframe between the two studies is relatively short. [20] Another possible explanation for the differing results is that Hamer et al [15] identified medical factors as confounders; whereas this study included social and economic factors, in addition to medical factors, as confounders.

Findings from this study show that baseline depression and lower wealth are strong predictors for the risk of depressive symptoms at two-year follow-up. Patten et al [21] supports our latter

finding, concluding that an increased prevalence of major depression was associated with lower personal wealth. Similarly, Martikainen et al [22] analysed data collected during the Whitehall II study and reported that depression was most common among individuals in the lowest wealth categories, after adjusting for age and ill health at baseline. This finding is important because wealth inequalities are continuing to rise across England; therefore, the risk of experiencing depressive symptoms at two-year follow up is likely to be elevated in individuals living in the lower wealth quintiles. [23]

Our multivariate model was also used to determine whether gender or age were independently associated with a risk of depressive symptoms at two-year follow-up. Findings showed that females were more likely to experience depressive symptoms at two-year follow-up compared to males. This finding was statistically significant and consistent with the existing literature. [24,25,26] Albert [24] suggests that 'biological sex differences' are fundamentally responsible for the differing prevalence of depression between males and females, but the author also acknowledges that further research is necessary to develop our understanding about this complex finding. Whilst a critical review by Piccinelli and Wilkinson [26] identified that a lack of social integration, reduced social support and an increased vulnerability to adverse life events were social factors which may potentially contribute towards a higher incidence of depression among females.

Individuals aged over 70 years were at least 14.0% more likely to experience depressive symptoms at two-year follow-up compared to individuals aged between 50 and 59 years. Findings also showed that participants aged between 60 and 69 years were 12.0% less likely to experience depressive symptoms at two-year follow-up, compared to individuals aged between 50 and 59 years. This U-shaped curve in depression prevalence has been reported previously by Wild et al. [27] An explanation for this finding could be that retirement is beneficial for an individual's mental well-being. [28,29]

The size and representativeness of our sample are the primary strengths of this study, and therefore, our findings are generalisable to the English population, who are aged over 50 years. Standardised data collection methods and validated data collection tools were used to obtain data for ELSA, for example the Center for Epidemiologic Studies depression scale (CES-D) was used to gather data about depressive symptoms. The CES-D scale required participants to accurately and truthfully recall information about depressive symptoms, to prevent study bias. [30] Using this scale provided an insight into an individual's risk of depressive symptoms at two-year follow-up; however, it was not possible to determine how many participants had received a depression diagnosis from a clinician. [19] The cause of depressive symptoms is often multifactorial, and although many covariates were used in the analyses to minimise study bias, there may be other contributory factors which have not been examined in ELSA, and thus, these factors could have influenced our findings. While this study indicated that neither metabolic health or obesity predict depressive symptoms at two-year follow-up, there could nevertheless be associations which are obscured by the study design. As the study only included respondents aged over 50, it is possible that metabolic health and/or obesity could predict depression earlier in the life course.

CONCLUSION

This study has identified that neither poor metabolic health nor obesity are associated with a risk of depressive symptoms at two-year follow-up. Findings from this study also showed that baseline depression and lower wealth are strong predictors for the risk of depressive

symptoms at two-year follow-up. Previous research has predominantly identified medical factors as confounders; however, this study highlights the importance of considering social and economic factors, in addition to medical factors, as confounders in future research.

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CONTRIBUTORSHIP STATEMENT
MF, CR, SW, RV contributed to the study idea. MF led the study. Data analysis was conducted by MF and CR. All authors had full access to ELSA Wave 6 and Wave 7 data, supplied by the UK Data Service and they take full responsibility for the integrity and accurate analysis of data. All authors contributed to data interpretation. NS drafted the manuscript with contributions from MF, CR, SW and RV. NS and MF are the Guarantors for this study.

TRANSPARENCY STATEMENT
NS and MF confirm that the manuscript is an honest, accurate and transparent account of the study being reported. No important aspects of this study have been omitted.

COMPETING INTERESTS All authors have completed the ICMJE form for disclosure of potential conflicts of interest available from www.icmje.org/coi_disclosure.pdf and declare that there is nothing to disclose.

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DATA SHARING STATEMENT No additional data are available for this study; however, all ELSA data are anonymised and publicly available from https://discover.ukdataservice.ac.uk/ [16]

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	5-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-8
		(*b*) Report category boundaries when continuous variables were categorized	5-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			9
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluating the associations between metabolic health, obesity and depressive symptoms: A prospective analysis of data from The English Longitudinal Study of Ageing (ELSA) with a two-year follow-up

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Evaluating the associations between metabolic health, obesity and depressive symptoms: A prospective analysis of data from The English Longitudinal Study of Ageing (ELSA) with a two-year follow-up

Authors:
Natasha Slater, Charlotte Rowley, Rebecca Venables, Simon White, Martin Frisher

School of Pharmacy, Keele University, Staffordshire, ST5 5BG, United Kingdom Natasha Slater PhD Student School of Pharmacy, Keele University Charlotte Rowley MPharm graduate School of Pharmacy, Keele University Rebecca Venables Lecturer School of Pharmacy, Keele University Simon White Reader School of Pharmacy, Keele University Martin Frisher Reader School of Pharmacy, Keele University

Correspondence to: n.slater@keele.ac.uk

ABSTRACT

OBJECTIVES: Conflicting results have been reported when the associations between metabolic health, obesity and depression were examined previously. The primary aim of this study was to determine whether metabolic health or obesity are independently associated with depressive symptoms, among a representative sample of older people living in England. Independent associations between covariates and depression were also examined.

DESIGN: Prospective study with a two-year follow-up

SETTING: The English Longitudinal Study of Ageing Wave 6 (2012-2013) and Wave 7 (2014-2015)

PARTICIPANTS: 6804 participants aged over 50 years

DATA SYNTHESIS: Multivariate models were used to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up. Unadjusted and adjusted odds ratios with corresponding 95% confidence intervals (CI) were calculated after adjusting for baseline depression, gender, age, wealth, obesity and poor metabolic health.

RESULTS: Before adjusting for covariates, poor metabolic health was associated with depressive symptoms at two-year follow-up (OR 1.24;95% CI, 1.07-1.44, p<0.01). After adjusting for covariates, the association was no longer statistically significant (OR 1.17; 95% CI, 0.99-1.38, p=0.07). Similarly, obesity was associated with depressive symptoms at two-year follow-up before adjusting for covariates (OR 1.54;95% CI, 1.33-1.79, p<0.01). However, after adjusting for covariates the association between obesity and depressive symptoms at two-year follow-up became statistically insignificant (OR 1.19; 95% CI, 1.00-1.41, p=0.06). The strongest predictor for future depression was baseline depression (OR 10.59; 95% CI, 8.90-12.53, p<0.01).

CONCLUSION: Neither poor metabolic health nor obesity were associated with a risk of depressive symptoms at two-year follow-up, after adjusting for covariates. As wealth inequalities continue to rise across England; the risk of depressive symptoms at two-year follow-up is likely to be elevated in individuals living in the lower wealth quintiles.

Key words: depression, obesity, metabolic health, ELSA

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A representative sample (n=6,804) of older people living in England provided data for this prospective analysis.
- Standardised data collection methods and validated data collection tools were used to obtain data for ELSA Wave 6 and Wave 7.
- All multivariate models were adjusted for baseline depression, gender, age, wealth, obesity and poor metabolic health to reduce the impact of confounders.
- Participants were required to truthfully and accurately recall information about their mood to prevent study bias.

INTRODUCTION

Obesity and depression are significant public health issues in the United Kingdom (UK). At present 26% of adults are classified as obese (defined as a body mass index of 30kg/m^2 or above), and this percentage is anticipated to rise in future years. [1] Obesity is associated with adverse outcomes including the development of cardiovascular diseases, type 2 diabetes and other potentially life-threatening conditions. [2] However, further research is needed to determine whether obesity is associated with psychological conditions, particularly depression, because this condition is now the leading cause of disability and ill health within the UK. [3]

Inconsistent findings have been reported when the association between obesity and depression has been examined previously. Conclusions drawn from early studies suggested that there was no association between obesity and depression [4] However, Crisp et al [5] reported an inverse association between obesity and depression in men; while other studies have shown that obesity is positively associated with depressive symptoms in women only. [6,7] Participant characteristics (age and gender) and sample sizes vary significantly in the aforementioned studies which may offer some explanation for the differing results. To address this limitation, a large-scale study involving a representative sample of the population is required.

Few studies have prospectively examined the association between obesity and the risk of future depression, as previous studies have been predominantly cross-sectional. [8] Findings from the existing prospective studies were evaluated in a meta-analysis. Pooled odds ratios showed that obesity significantly increased an individual's risk of developing depression during follow-up (OR 1.55, 95% CI; 1.22-1.98, p<0.01), in both men and women. [9] Meta-analytic data was adjusted for age and gender; however, there may be other confounding factors involved in this association. [9]

Metabolic health has been identified as a potential confounder in the association between obesity and the risk of future depression in several studies. [10,11] Partial support for this finding is provided from analyses conducted on eight cohort studies. [12] Jokela et al [12] reported that obese individuals with poor metabolic health were 23% more likely to experience depression, compared to obese individuals with a favourable metabolic profile; however, the risk of depression for the latter group remained elevated when compared to non-obese individuals who had good metabolic health. [12] Furthermore, findings from a prospective cohort study with 16-year follow-up showed that metabolic health was a better

predictor of future depression, compared to obesity. [13] No association between metabolic health and depression has been reported in other studies. Various definitions of metabolic health exist within the literature which may offer some explanation for the differing study findings; however, further research into the relationship between metabolic health, obesity and depression is required. [14]

The primary aim of this study was to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up, using the latest data from the English Longitudinal Study of Ageing. In addition, we determined whether the covariates used in our analyses were independently associated with depressive symptoms at follow-up.

METHOD

Sample and participants

A prospective study was conducted using Wave 6 and Wave 7 data gathered from the English Longitudinal Study of Ageing (ELSA). Since inception in 2002, ELSA has gathered socio-economic, lifestyle and health data from a representative sample of the English population, who are aged over 50 years. Every two years, a new 'wave' of ELSA data are collected. [15] This study used data collected between 2012 and 2013 (Wave 6) as baseline data. Data collected between 2014-2015 (Wave 7) was used for follow-up. Overall, 6,804 participants successfully provided data in both Wave 6 and Wave 7, and this group are the focus of the current study (Supplementary Material Figure 1). [15]

Patient and public involvement

No patients were involved in the development of the research question, study design or data interpretation in this study.

Ethical approval

All ELSA waves have been ethically approved by the National Research and Ethics Committee under the National Research and Ethics Service. Only participants who provided informed written consent were enrolled into ELSA. These data are anonymised and freely accessible from the UK Data Service Discover. [16] No patients were involved in this study; therefore, further ethical approval was not required.

Data collection

Three methods of data collection were utilised during ELSA Wave 6: a paper-based questionnaire, a face-to-face interview and a nurse interview. In Wave 7, the nurse interview did not take place; instead, data was collected during a face-to-face interview and using a paper-based questionnaire.

Face-to-face interviews

In both Wave 6 and Wave 7, face-to-face interviews were conducted by trained interviewers, at the participant's residential address. The interviewers recorded demographic information

for each participant, in addition to asking the participants questions about their physical and mental health status. To determine whether participants were experiencing depressive symptoms, they were asked to answer eight questions which had been adapted from the Center for Epidemiologic Studies depression (CESD) scale. [17] One point was awarded for each depressed answer given. Each participant received a total score between 0 and 8. In accordance with previous studies, a score ≥ 4 was used to define participants with elevated depressive symptoms. [10,18]

The interviewers also asked the participants to provide information about everyone who resided within their property, including information about their financial situation, employment status, assets and whether they were in receipt of any benefits. Participants were allocated to one of five wealth quintiles, with quintile 1 being the poorest and quintile 5 being the wealthiest. Wealth quintiles refer to household wealth (financial assets, physical assets and housing wealth) but not pension wealth. [19] Wealth was calculated less debts and included the value of owner-occupied housing (less mortgage); all assets held in bank accounts in England; the value of any business properties or holiday homes (less mortgage) and the value of physical assets such as antiques, artwork and jewellery. [20]

Nurse interview

Demographic information for each participant was also collected during the nurse interview in Wave 6. Subsequent stages of the nurse interview involved participants having their blood pressure, pulse rate, lung function and grip strength measured, in addition to providing hair samples and fasting blood samples. Fasting blood test results and blood pressure readings were analysed to determine a participant's metabolic health status. In this study, a participant with two or more metabolic risk factors was described as having poor metabolic health. The following were defined as metabolic risk factors: glycated haemoglobin (HbA1c) greater than 6.0% (42mmol/mol); C-reactive protein (CRP) greater than or equal to 3mg/L; high density lipoprotein (HDL) less than 1.03 mmol/L for men or less than 1.30 mmol/L for women; triglycerides greater than or equal to 1.7mmol/L and blood pressure readings greater than 130/85 mmHg. [10]

The nurse interviewer also recorded a number of anthropometric measurements including height, weight and waist circumference for each participant. Using a participant's weight and height values, it was possible to calculate their body mass index (BMI). A participant was classified as obese if their calculated BMI was ≥30kg/m^2.

Data analysis

Descriptive statistics were used initially to summarise the prevalence of depressive symptoms among participants. These data were subsequently stratified according to participant demographics and chi-squared tests were performed. Multivariate models were used to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up (Wave 7). The minimum sample size required for our multivariate models was 319. [21] Unadjusted and adjusted odds ratios with corresponding 95% confidence intervals (CI) for the risk of depressive symptoms at two-year follow-up were calculated. Following the main analysis, a secondary analysis was conducted excluding cases with depressive symptoms at Wave 6. The following factors were covariates: baseline depression, gender, age, wealth, obesity and poor metabolic health. Missing data was coded

as "missing" and presented as a separate category in the multivariate models. All p values generated from the models were considered to be statistically significant if $p<0.05$. Analyses were undertaken using SPSS version 24.0.

RESULTS

Participant characteristics

Overall, 6,804 participants successfully provided data in both Wave 6 and Wave 7. Baseline participant characteristics are presented in Table 1. The mean age of the participants was 67.6 years, 44.5% (n=3030/6804) of the participants were male and 12.8% (n=872/6804) of the participants had elevated depressive symptoms at baseline. At follow up (Wave 7), 12.5% (n=851/6,804) of the participants had elevated depressive symptoms (Table 1). Baseline data were stratified according to participant characteristics, including gender, age, metabolic health status and body mass index (BMI). The prevalence of depressive symptoms was higher among females (15.1%), compared to males (9.2%) at Wave 7 (Table 1). Results from the chi-squared statistical test showed an association between gender and depressive symptoms ($\chi^2(1) = 53.26$, $p <0.01$). There was also a significant association between age and depressive symptoms ($\chi^2(3) = 36.24$, $p <0.01$). A greater proportion of individuals with poor metabolic health (13.6%) had elevated depressive symptoms at Wave 7, compared to participants with good metabolic health (11.2%) (Table 1). The association between metabolic health and depressive symptoms was significant ($\chi^2(1) = 8.48$, $p <0.01$). Similarly, there was a significant association between obesity (BMI $\geq 30 kg/m^2$) and depressive symptoms ($\chi^2(2) = 32.63$, $p <0.01$).

Table 1: Wave 6 participant characteristics and associated depressive symptoms at Wave 7 (n=6,804)

	Depressive symptoms (Wave 7) (CESD 4+)	
Participant characteristics	**No (0-3) (n=5953)**	**Yes (≥4) (n=851)**
All participants (n=6,804)	87.5%	12.5%
Gender		
Male (n=3030)	90.8%	9.2%
Female (n=3774)	84.9%	15.1%
Age		
50-59 years (n=1492)	85.4%	14.6%
60-69 years (n=2720)	90.0%	10.0%
70-84 years (n=2313)	86.6%	13.4%
85+ years (n=279)	81.7%	18.3%
Metabolic Health		
Good metabolic health (n=3123)	88.8%	11.2%
Poor metabolic health (n=3681)	86.4%	13.6%
Body Mass Index (BMI)		
Non-obese (BMI $< 30 kg/m^2$) (n=4737)	89.0%	11.0%
Obese (BMI $\geq 30 kg/m^2$) (n=2058)	84.0%	16.0%
Missing BMI data (n=9)		

Baseline Depression (Wave 6)		
Baseline depression (n=872)	50.8%	49.2%
No baseline depression (n=5932)	92.9%	7.1%
Wealth		
Wealth Quintile 1 (poorest) (n=1005)	76.4%	23.6%
Wealth Quintile 2 (n=1214)	81.7%	18.3%
Wealth Quintile 3 (n=1372)	88.6%	11.4%
Wealth Quintile 4 (n=1464)	91.4%	8.6%
Wealth Quintile 5 (wealthiest) (n=1619)	94.4%	5.6%
Missing Wealth Data (n=130)		

Examining the association between poor metabolic health and the risk of depressive symptoms at two-year follow-up (Wave 7)

The unadjusted logistical regression analysis showed that participants with poor metabolic health were 24.0% more likely to experience depressive symptoms at two-year follow-up, compared to those with good metabolic health. This finding was statistically significant ($p<0.01$) (Table 2). The odds ratio for the risk of depressive symptoms at two-year follow-up reduced to 1.17 (1.01-1.35, p= 0.04), after the model was adjusted for obesity. The odds ratio for the risk of depressive symptoms at two-year follow-up was 1.19 (1.01 -1.40, p=0.04), after the model was adjusted for obesity and baseline depression (Table 2). After adjusting for participant characteristics and baseline depression, the odds ratio for the risk of depressive symptoms at two-year follow-up decreased to 1.17 (0.99-1.38, p=0.07) (Table 2). The latter finding was not statistically significant.

Table 2: The association between poor metabolic health and the risk of depressive symptoms at two-year follow-up (Wave 7) (n= 6,084)

Independent variable	Odds ratio	95% C.I. for OR		Sig. level
		Lower	Upper	
Metabolic health	1.24	1.07	1.44	<0.01
Metabolic health Adjusted for obesity	1.17	1.01	1.35	0.04
Metabolic health Adjusted for obesity and baseline depression (Wave 6)	1.19	1.01	1.40	0.04
Metabolic health Adjusted for obesity, baseline depression (Wave 6), gender, age and wealth	1.17	0.99	1.38	0.07

Examining the association between obesity and the risk of depressive symptoms at two-year follow-up (Wave 7)

The unadjusted logistical regression analysis showed that obese participants were 54.0% more likely to experience depressive symptoms at two-year follow-up, compared to participants who had a body mass index <30kg/m^2 (Table 3). This finding was statistically

significant (p<0.01) (Table 3). The odds ratio for the risk of depressive symptoms at two-year follow-up reduced to 1.50 (1.29-1.75, p<0.01), after adjusting for poor metabolic health (Table 3). The odds ratio for the risk of depressive symptoms at two-year follow-up decreased further to 1.32 (1.11- 1.56, p<0.01), after adjustments for poor metabolic health and baseline depression were made (Table 3). After adjusting for participant characteristics and baseline depression the odds ratio for the risk of depressive symptoms at two-year follow-up was 1.19 (1.00-1.41, p=0.06) (Table 3). The latter finding was not statistically significant.

Table 3: The association between obesity and the risk of depressive symptoms at two-year follow-up (Wave 7) (n=6,084)

Independent variable	Odds ratio	95% C.I. for OR		Sig. level
		Lower	Upper	
Obesity	1.54	1.33	1.79	<0.01
Obesity Adjusted for poor metabolic health	1.50	1.29	1.75	<0.01
Obesity Adjusted for poor metabolic health and baseline depression (Wave 6)	1.32	1.11	1.56	<0.01
Obesity Adjusted for poor metabolic health, baseline depression (Wave 6), gender, age and wealth	1.19	1.00	1.41	0.06

Examining the associations between gender, age, wealth, baseline depression (Wave 6) and the risk of depressive symptoms at two-year follow-up (Wave 7)

Results showed that females were 48.0% more likely experience depressive symptoms at two-year follow-up compared to males (Table 4). This finding was statistically significant (p<0.01) (Table 4). The association between age and depression was examined. The adjusted odds ratio for the risk of depressive symptoms at two-year follow-up was 0.91 (0.73-1.13, p=0.38) in participants aged between 60 and 69 years (Table 4). This value increased to 1.27 (1.02-1.58, p=0.03) in participants aged between 70 and 84 years (Table 4). For participants aged above 85 years, the adjusted odds ratio increased further to 1.43 (0.97-2.11, p=0.07) (Table 4). Most findings, in relation to age, were not statistically significant. The association between wealth and depression was also examined. The adjusted odds ratio for the risk of depressive symptoms at follow-up reduced from 0.80 (0.63-1.02, p=0.07) in wealth quintile 2 to 0.31 (0.23-0.41, p<0.01) in wealth quintile 5 (Table 4). This suggests that individuals in the higher wealth quintiles are less likely to experience depressive symptoms at two-year follow-up, compared to individuals in the lower wealth quintiles. Finally, the association between baseline depression and future depression was examined. The adjusted odds ratio for the risk of depressive symptoms at two-year follow-up was 10.59 (8.90-12.53, p<0.01).

Table 4: The association between the independent variables and the risk of depressive symptoms at two-year follow-up (Wave 7) (n=6,084)

		95% C.I. for OR		
Independent variables	Adjusted OR	Lower	Upper	Sig. level

Gender				
Male **(Reference)** (n=3030)	1			
Female (n=3774)	1.48	1.25	1.75	<0.01
Age				
50-59 years **(Reference)** (n=1492)	1			
60-69 years (n=2720)	0.91	0.73	1.13	0.38
70-84 years (n=2313)	1.27	1.02	1.58	0.03
85+ years (n=279)	1.43	0.97	2.11	0.07
Wealth				
Wealth Quintile 1 (poorest) **(Reference)** (n=1005)	1			
Wealth Quintile 2 (n=1214)	0.80	0.63	1.02	0.07
Wealth Quintile 3 (n=1372)	0.50	0.39	0.64	<0.01
Wealth Quintile 4 (n=1464)	0.43	0.33	0.56	<0.01
Wealth Quintile 5 (wealthiest) (n=1619)	0.31	0.23	0.41	<0.01
Missing Wealth Data (n=130)				
Baseline depression (Wave 6)				
Baseline depression (n=872)	10.59	8.90	12.53	<0.01
No baseline depression (n=5932)				

Adjusted for obesity, poor metabolic health, baseline depression (Wave 6), gender, age and wealth

DISCUSSION

This study evaluated the associations between metabolic health, obesity and depressive symptoms. Initially, the unadjusted logistical regression model showed that poor metabolic health was associated with depressive symptoms at two-year follow-up; however, after adjusting for covariates, including baseline depression, obesity, gender, age and wealth, this finding was no longer statistically significant, and the previously elevated adjusted odds ratios diminished. Similar findings were generated when the association between obesity and depressive symptoms was examined. The unadjusted logistical regression model initially showed that obesity was associated with depressive symptoms at two-year follow-up, but after adjusting for covariates, the finding became statistically insignificant.

Our findings are different to those reported in previous studies. Studies which report an association between metabolic health, obesity and depression often attribute the association to biological changes. For example, obesity is commonly associated with metabolic abnormalities such as insulin resistance and raised inflammatory markers, and previous research has shown that these abnormalities are independently associated with the development of depression. [22,23,24] Another explanation offered for the association is that poor metabolic health and obesity have both been linked to a reduction in serotonergic activity in the brain, thus increasing the likelihood of depression. [25,26] However, the biological mechanisms underlying the association are complex and not fully understood.

To our knowledge, only one prospective study has been conducted previously to determine "whether the association of obesity with depressive symptoms is dependent on the individual's metabolic health", using ELSA data. [10] Hamer et al [10] created four participant models: 'metabolically healthy non-obese'; 'metabolically unhealthy non-obese'; 'metabolically healthy obese' and 'metabolically unhealthy obese'. Using participants in the 'metabolically healthy non-obese' group as controls, the adjusted odds ratios showed that 'metabolically unhealthy obese' participants were 50% more likely to experience depression

at follow-up. For 'metabolically unhealthy non-obese' participants, the likelihood of experiencing depression at follow-up was 44%. This value reduced to 38% for 'metabolically healthy obese' participants. [10] Based upon their findings, the authors concluded that "the association between obesity and risk of depression symptoms appears to be partly dependent on metabolic health". [10] However, in this study, we found that neither poor metabolic health nor obesity are associated with a risk of depressive symptoms at two-year follow-up. It is possible that a period effect may have contributed towards the differing findings because Hamer et al [10] analysed ELSA data gathered between 2004 and 2007, and this study analysed ELSA data gathered between 2012 to 2015; however, the timeframe between the two studies is relatively short. [27] Another possible explanation for the differing findings is that Hamer et al [10] identified medical factors as confounders; whereas this study included wealth, in addition to medical factors as confounders.

This study shows that lower wealth, along with baseline depression, are strong predictors for the risk of depressive symptoms at two-year follow-up. Patten et al [28] support our wealth finding, concluding that an increased prevalence of major depression was associated with lower personal wealth. Similarly, Martikainen et al [29] analysed data collected during the Whitehall II study and reported that depression was most common among individuals in the lowest wealth categories, after adjusting for age and ill health at baseline. This finding is important because wealth inequalities are continuing to rise across England; therefore, the risk of experiencing depressive symptoms at two-year follow up is likely to be elevated in individuals living in the lower wealth quintiles. [30]

Our multivariate model was also used to determine whether gender or age were independently associated with a risk of depressive symptoms at two-year follow-up. Findings showed that females were more likely to experience depressive symptoms at two-year follow-up compared to males. This finding was statistically significant ($p<0.01$) and consistent with the existing literature. [31,32,33] Albert [31] suggests that 'biological sex differences' are fundamentally responsible for the differing prevalence of depression between males and females, but the author also acknowledges that further research is necessary to develop our understanding about this complex finding. Whilst a critical review by Piccinelli and Wilkinson [33] identified that a lack of social integration, reduced social support and an increased vulnerability to adverse life events were social factors which may potentially contribute towards a higher incidence of depression among females.

Individuals aged over 70 years were at least 27.0% more likely to experience depressive symptoms at two-year follow-up compared to individuals aged between 50 and 59 years. Findings also showed that participants aged between 60 and 69 years were 9.0% less likely to experience depressive symptoms at two-year follow-up, compared to individuals aged between 50 and 59 years. This U-shaped curve in depression prevalence has been reported previously by Blanchflower and Oswald. [34] An explanation for this finding could be that retirement is beneficial for an individual's mental well-being. [35]

The size and representativeness of our sample are the primary strengths of this study, and therefore, our findings are generalisable to the English population, who are aged over 50 years. Standardised data collection methods and validated data collection tools were used to obtain data for ELSA, for example the Center for Epidemiologic Studies depression scale (CES-D) was used to gather data about depressive symptoms. The CES-D scale requires participants to accurately and truthfully recall information about their depressive symptoms to prevent study bias. [36] The cause of depressive symptoms is often multifactorial, and

although many covariates were used in the analyses to minimise study bias, there may be other contributory factors which have not been examined in ELSA, and thus, these factors could have influenced our findings. While this study indicated that neither metabolic health nor obesity predict depressive symptoms at two-year follow-up, there could nevertheless be associations which are obscured by the study design. As the study only included respondents aged over 50, it is possible that metabolic health and/or obesity could predict depression earlier in the life course.

CONCLUSION

This study has identified that neither poor metabolic health nor obesity are associated with a risk of depressive symptoms at two-year follow-up. Findings from this study also showed that baseline depression and lower wealth are strong predictors for the risk of depressive symptoms at two-year follow-up. Previous research has predominantly identified medical factors as confounders; however, this study highlights the importance of considering wealth, in addition to medical factors, as confounders in future research.

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CONTRIBUTORSHIP STATEMENT
MF, CR, SW, RV contributed to the study idea. MF led the study. Data analysis was conducted by MF, CR and NS. All authors had full access to ELSA Wave 6 and Wave 7 data, supplied by the UK Data Service and they take full responsibility for the integrity and accurate analysis of data. All authors contributed to data interpretation. NS drafted the manuscript with contributions from MF, CR, SW and RV. MF and NS are the Guarantors for this study.

TRANSPARENCY STATEMENT
NS and MF confirm that the manuscript is an honest, accurate and transparent account of the study being reported. No important aspects of this study have been omitted.

COMPETING INTERESTS All authors have completed the ICMJE form for disclosure of potential conflicts of interest available from www.icmje.org/coi_disclosure.pdf and declare that there is nothing to disclose.

FUNDING This study received no specific funding

DATA SHARING STATEMENT No additional data are available for this study; however, all ELSA data are anonymised and publicly available from https://discover.ukdataservice.ac.uk/ [16]

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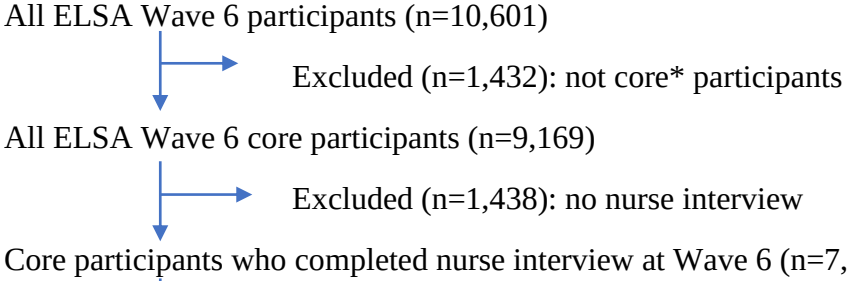
Supplementary Material

Figure 1: Flowchart illustrating participation in this study



*Core participants in ELSA are individuals who met the following three criteria [15]:

- Individuals who were living in the household at the time of the Health Survey for England
- Individuals who met the age criteria of a given ELSA cohort (≥50 years)
- Individuals who provided data in the first wave of ELSA, once invited to participate in the study.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Supplementary File
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	5-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-8
		(*b*) Report category boundaries when continuous variables were categorized	5-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			9
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.