Title: DEPRESSION AND MORTALITY: ARTIFACT OF MEASUREMENT AND ANALYSIS?

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Column Title: Depression and mortality: Measurement and analysis

ABSTRACT

Background: Previous research demonstrates various associations between depression, cardiovascular disease (CVD) incidence and mortality, possibly as a result of the different methodologies used to measure depression and analyse relationships. This analysis investigated the association between depression, CVD incidence (CVDI) and mortality from CVD (MCVD), smoking related conditions (MSRC), and all causes (MALL), in a sample data set, where depression was measured using items from a validated questionnaire and using items derived from the factor analysis of a larger questionnaire, and analyses were conducted based on continuous data and grouped data.

Methods: Data from the PRIME Study (N=9,798 men) on depression and ten year CVD incidence and mortality were analysed using Cox proportional hazards models.

Results: Using continuous data, both measures of depression resulted in the emergence of positive associations between depression and mortality (MCVD, MSRC, MALL). Using grouped data, however, associations between a validated measure of depression and MCVD, and between a measure of depression derived from factor analysis and all measures of mortality were lost.

Limitations: Low levels of depression, low numbers of individuals with high depression and low numbers of outcome events may limit these analyses, but levels are usual for the population studied.

Conclusions: These data demonstrate a possible association between depression and mortality but detecting this association is dependent on the measurement used and method of analysis. Different findings based on methodology present clear problems for the elucidation and determination of relationships. The differences here argue for the use of validated scales where possible and suggest against over-reduction via factor analysis and grouping.

Depression, cardiovascular disease, mortality, methodology, questionnaires, statistical analysis

INTRODUCTION

Various researchers report a link between depression, cardiovascular disease, and mortality, while others also report no association, or an association that results purely from confounders (see Atlantis et al, 2012; Baune et al, 2012; Leung et al, 2012; Schulz et al, 2002; Wulsin et al, 1999). These different conclusions between studies are often attributed partly to differing methodologies. Studies investigating methodological effects have largely focussed on details such as depression subtype, time course effects, and confounding variables (Atlantis et al, 2012; Baune et al, 2012; Leung et al, 2012; Schulz et al, 2002; Wulsin et al, 1999), but two purely methodological aspects of limited study include the method by which depression is assessed and the analyses subsequently conducted. Measures of depression can range from clinical interviews to self-rating scales and single questions (Nezu et al, 2000). Analyses can be conducted using continuous data, allowing the emergence of continuous patterns and effects, or data which is grouped dichotomously as depressed / not depressed, or grouped by quartiles or quintiles, which may more easily elucidate extreme differences and detect non-linear associations (Kline, 2000; Biswas et al, 2008). Use of different methods of measurement and analysis could potentially result in different outcomes. This analysis aimed to investigate the link between depression, cardiovascular disease incidence and mortality in a sample data set, when comparing the use of items from a validated questionnaire and items from the factor analysis of a larger questionnaire for the assessment of depression, and using analyses based on continuous data and grouped data.

METHODS

Analyses were conducted on the data set gained from the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study, where data on depression, cardiovascular disease incidence and mortality are available over a ten year follow-up period for 9,798 men from France and Northern Ireland. Full details of the PRIME study are provided elsewhere (The PRIME Study Group, 1998).

Depression was assessed in the PRIME study using 10 questions from a validated questionnaire – the Welsh Pure Depression Inventory (Rodda et al, 1971), plus three additional questions, all contained within a larger 70 item psychosocial questionnaire. The psychosocial questionnaire was derived by including questions from a number of validated questionnaires - the Framingham Type A scale (Haynes et al, 1978), the Cook-Medley Hostility scale (Cook & Medley, 1954) and the MONICA scales for the assessment of social support (WHO, 1989), plus additional questions derived by researchers (Sykes et al, 2002). The questionnaire was completed by all participants at the start of the study.

Data on depression via a validated questionnaire were obtained by combination of the 10 items from the Welsh Pure Depression Inventory. Questions were responded to on a 2 point scale (true / false: scored 1 / 0), then combined and divided by the number of questions to result in a single depression score (depV) per person between 0 and 1, where higher scores denote greater depression. Individual questions are provided in Table 1. All questions were responded to using the full extent of possible answers.

Data on depression via the factor analysis were obtained through principal component analysis (with varimax rotation) on 69 items from the psychosocial questionnaire. (One item was optional and due to low response rates was excluded from the analysis). This analysis revealed eight factors, explaining 37% of the variance, but inspection of individual factor loadings and composite factors, and reference to an earlier analysis of the same dataset (Sykes et al, 2005) resulted in a decision to limit the analysis outcomes to five factors, explaining 29% of the variance. These five factors utilised 58 items from the questionnaire. All items with a factor loading less than 0.30 on any factor were ignored. Based on their component questions, these factors were labelled Depression (16 items), Competitiveness (14 items), Hostility (10 items), Social Support (8 items) and Anger / Impatience (10 items). Individual questions for the Depression factor are provided in Table 2. Cronbach's alpha for

reliability = 0.71. All questions were responded to using a variety of response formats, but all response formats were subsequently re-scaled to result in a score per question of between 0 and 1. All questions were responded to using the full extent of possible answers. Scores on the depression factor were created per person by adding scores for all relevant items and dividing by the number of items, to result in a score (depFA) between 0 – 1, where higher scores again denote greater depression.

Tables 1 and 2 about here

For the analyses, either calculated continuous depression scores (depV / depFA) were used, or depression scores were grouped into approximate fifths (depVG / depFAG). Grouping into exact quintiles was not possible due to the limited gradations and responses in the depression scales.

Cardiovascular disease incidence (CVDI), mortality (MCVD), mortality from smoking related conditions (MSRC) and mortality from all causes (MALL) were assessed for a ten year period from the start of the study via hospital records. All reported cases were verified by study personnel (The PRIME Study Group, 1998).

Cox proportional hazards models were used to predict incidence or not of CVDI, MCVD, MSRC and MALL using depression scores (Model 1), depression scores plus two demographic confounders (Model 2), and depression scores, demographic confounders and ten lifestyle confounders known to be associated with mortality (Model 3) (The PRIME Study Group, 1998; Wulsin et al, 1999; Schulz et al, 2002). The two demographic confounders were age and country of residence (NI / France). The ten lifestyle confounders were: systolic blood pressure, cholesterol, HDL cholesterol, height, BMI, fruit and vegetable intakes (portions of fruit, fruit juice and vegetables / day), physical activity (metabolic equivalent scores / week), lifetime smoking (five categories: never smoked; smoked other

than cigarettes; smoked less than 15 cigarette pack-years; smoked 15 or more but less than 30 cigarette pack-years; smoked 30 or more cigarette pack-years), alcohol (five categories: none; 1-128ml/week; 129-265ml/week; 266-461ml/week; and 462ml or more/week) and diabetes (present/absent). Similar analyses were conducted using continuous data and using grouped data. The grouped analyses investigated evidence of a linear trend to allow comparison with continuous data. Analyses were also attempted using two groups (depressed / not depressed), but cut offs for depression / no depression are not available for the Welsh Pure Depression Inventory (Rodda et al, 1971), and are clearly not available for the scale derived from factor analysis. Analyses were conducted for two groups using scores of 0 vs 0.1 or more on each scale, but this resulted in classification of 60% of the sample as depressed using depV, and 84% of the sample as depressed using depFA. These proportions of depressed / not depressed are neither comparable between scales nor with other reports of depression incidence (APA, 2000). Analyses were also conducted using a cut-off score for depFA that resulted in classification of 60% of the sample as depressed, as was similar for depV, but this number of depressed individuals is again not comparable with other reports on depression incidence (APA, 2000). Analyses were conducted only on participants who were free from cardiovascular disease at the start of the study, and who provided scores for both depV and depFA variables.

RESULTS

A total of 8,138 men provided data for both depV and depFA and were included in analyses. Detailed descriptive statistics for the sample are provided in Table 3. Using the validated questionnaire, mean +/- st.dev. depV score for the sample was 0.15 +/- 0.18 ranging from 0 – 1, and using factor analysis, mean +/- st.dev. depFA score for the sample was 0.23 +/- 0.18, ranging from 0 – 1. DepV and depFA scores correlated very well ($r=0.908$, $p<0.01$) (see Figure 1), but depFA scores were consistently higher than depV scores (paired samples t-test $t(8137)=95.01$, $p<0.001$). Detailed descriptive statistics by group (depVG and depFAG) are also provided in Table 4. Number of cases of CVDI = 372,

MCVD = 59, MSRC = 177, and MALL = 419, were obtained in a total observation time of 78,493 person years. Number of events and event rate, in total and by depression category are provided in Table 5.

Tables 3 - 5 about here

Figure 1 about here

Hazards ratios, confidence intervals and significance for all depV, depFA, depVG and depFAG relationships are displayed in Tables 6 and 7, respectively.

Using continuous data, both depV and depFA were associated with CVDI independently and when demographic variables were included in the model, but not when lifestyle variables were also included. Both depV and depFA were associated with MCVD, MSRC and MALL in all three models, although effects in all models were more significant using depV than depFA.

Table 6 about here

Using grouped data, similar patterns were found with depVG as were found with depV, but no associations were found between depVG and MCVD in any model. Unlike results for depFA, depFAG was not associated with CVDI or MCVD in any model, and depFAG was only associated with MSRC and MALL, independently and when demographic variables were included in the model, but not when lifestyle variables were also included.

Table 7 about here

Using depressed / not depressed groups, similar patterns were found as were found using five categories (depVG / depFAG) (data not shown).

DISCUSSION

Different associations were found dependent on measurement of depression and analysis used.

Comparable results were found using the two depression measures when analysed using continuous data. Using both measures, depression at baseline was associated with mortality from CVD, from smoking-related conditions, and from all causes up to ten years later, where greater depression is associated with increased risk. Comparable findings from the validated questionnaire and the scale derived by factor analysis are reassuring and suggest the derivation and use of a single 'depression' concept by factor analysis, despite the use of eight items from the validated questionnaire plus an additional eight items derived by researchers. The scale derived by factor analysis clearly depends on the other items used in the whole questionnaire, both in terms of inclusion (items that are included in one scale) and exclusion (items that become more associated with other scales), plus the interpretation of the analyst (Kline, 2000; Coaley, 2010). It shouldn't be forgotten that factor analysis is a statistical method for grouping questionnaire items that are subsequently described by a label, and the accuracy of the label is far from guaranteed (Kline, 2000; Coaley,2010). Compared to this, a questionnaire or questionnaire items that have been validated against a clinical diagnosis, agreed clinical symptoms or using clinical treatments may offer increased accuracy, reliability and validity (Kline, 2000).

Different findings, however, emerged when data were grouped. Using data from the validated questionnaire, associations between depression and MCVD were lost with the use of grouped data, although all other relationships remained. Using data from the factor analysis, grouping (depFAG) resulted in the loss of all associations between depression and CVDI and MCVD, and of the

associations between depression and MSRC and MALL once lifestyle variables were taken into account. These results suggest that the reduction of data, via both factor analysis and grouping, can result in the loss of relationships that are apparent using analyses of continuous data. Loss of associations may have occurred for a number of statistical reasons, including the coherence of the factor, the strength of the association, and the variance in the data (Kline, 2000). MCVD results based on grouped data are also likely to have been affected by the small number of cases available, and some of the differences between depVG and depFAG results may have arisen as a result of differences in categorization. It is noticeable that the depVG data was more difficult to categorize evenly, due to the presence of fewer gradations in this scale.

The stronger associations using depV and depVG than using depFA and depFAG scales may also demonstrate the provision of a cleaner or purer measure of depression using the items from the validated measure than the scale derived by factor analysis, or a more complete capture of the aspects of depression most pertinent to mortality. The difference in question items in the two scales are provided in Tables 1 and 2, and it is noteworthy that almost half of those in the scale derived by factor analysis were not originally provided by a questionnaire purporting to measure depression. The majority of the remaining questions are sleep-related, and disruptions to sleep are symptomatic of a number of conditions other than depression (APA, 2000).

The potential implications of these differing conclusions from the same data set, as a result purely of measurement and analyses, are obvious. Based on the same questionnaire responses, analyses using continuous data result in the demonstration of a relationship between depression and mortality from cardiovascular disease, smoking related conditions and all causes, whereas analyses using grouped data result in the reporting of no association. Associations and no associations between depression and mortality have previously been reported elsewhere (Atlantis et al, 2012; Baune et al, 2012; Leung et al, 2012; Schulz et al, 2002; Wulsin et al, 1999). The findings of this study however

suggest that no associations may have previously been reported, purely as a result of an over-reduction of data. These conclusions may suggest greater need or prefential use of analyses conducted on continuous data.

Limitations

The results of this analysis clearly depend on the factor analysis, which in turn depends on the questionnaire used and our interpretation of results. Different questionnaires and interpretations could result in different conclusions, but this is the point of this paper. The analysis may also be limited however, by the low levels of depression, the low number of people suffering from severe depression, and the low levels of outcome events. Levels in this study however are usual for the populations studied.

Conclusions

These data demonstrate possible associations between depression and mortality, but the detection of these associations is dependent on the measurement used and method of analysis. To allow relationships to be accurately reported, there is a clear need here for the use of standardised methods and analyses. The objectivity, reliability and validity of validated measures argue for the use of validated scales where possible. The increased appearance and clarity of associations where these exist argue for the use of continuous data and suggest against over-reduction.

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Table 1: Question items from the Welsh Pure Depression Inventory (Rodda et al, 1971)

Item	
1	I get tired for no reason
2	Life seems dull to me
3	I do not seem to have the energy to do things
4	I have a good appetite
5	I am usually bored
6	I feel that others would be better off if I were dead
7	I awake in the morning feeling tired
8	I have trouble sleeping at night
9	In thinking of my life I often wonder why I exist
10	I feel useless

Table 2: Question items for the Depression scale derived by Factor Analysis from the 70 item Psychosocial Questionnaire

Item	
1	I get tired for no reason
2	Life seems dull to me
3	I do not seem to have the energy to do things
4	I am usually bored
5	I awake in the morning feeling tired
6	I have trouble sleeping at night
7	In thinking of my life I often wonder why I exist
8	I feel useless
9	I feel powerless to effect changes in my life
10	I feel helpless
11	I often feel uncertain, uncomfortable or dissatisfied with how well I am doing
12	How often in the last month, did you have trouble falling asleep?
13	How often in the last month, did you have trouble staying asleep (e.g. waking up too early)?
14	How often in the past month, did you wake up two or more times per night?
15	How often in the past month, did you wake up after your usual amount of sleep feeling tired and worn out?
16	How many hours of sleep do you usually get each night?

Table 3: Descriptive statistics (mean, st.dev., minimum, maximum, or %) for depression, demographic and lifestyle variables for the whole sample (N=8138).

	Mean	St. Dev.	Minimum	Maximum
DepV score (0-1)	0.15	0.18	0	1
DepFA score (0-1)	0.23	0.18	0	1
Age (years)	54.8	2.9	48	64
Systolic blood pressure (mm Hg)	133.6	18.8	79	226
Cholesterol (mg/dl)	2.22	0.38	0.79	6.15
HDL cholesterol (mg/dl)	0.49	0.13	0.10	1.50
Height (m)	1.73	0.07	1.43	2.00
BMI (kg/m^2)	26.5	3.4	15.8	47.6
Fruit and vegetable intakes (portions of fruit, fruit juice and vegetables / day)	2.6	1.4	0	21
Physical activity (metabolic equivalent scores / week)	96	66	0	528
Country of residence (%)	France - 74; Northern Ireland - 26			
Lifetime smoking (% per category)	never smoked - 30; smoked other than cigarettes - 8; smoked less than or equal to 15 cigarette pack-years -22; smoked 16 - 30 cigarette pack-years - 19; smoked 31 or more cigarette pack-years –21.			
Alcohol (% per category)	none - 17; 1-128ml/week - 22; 129-265ml/week - 22; 266-461ml/week - 19; and 462ml or more/week –20.			
Diabetes (% present)	3			
Disease or mortality (N of cases)	CVDI = 372; MCVD = 59; MSRC = 177; MALL = 419			

Table 4: Descriptive statistics (mean and standard deviation or %) for depression, demographic and lifestyle variables in five categories of DepVG and DepFAG.

	DepVG N=3283 (40%)	DepVG1 N=1880 (23%)	DepVG2 N=1193 (15%)	DepVG3 N=761 (9%)	DepVG4 N=1021 (13%)	
DepV score (0-1)	0.00 (0.00)	0.10 (0.00)	0.20 (0.00)	0.30 (0.00)	0.52 (0.14)	<0.001
DepFA score (0-1)	0.09 (0.05)	0.19 (0.08)	0.29 (0.08)	0.37 (0.09)	0.56 (0.15)	<0.001
Age (years)	54.8 (2.9)	54.8 (2.9)	54.8 (2.9)	54.8 (2.8)	54.5 (2.8)	0.06
Systolic blood pressure (mm Hg)	133 (19)	134 (19)	134 (19)	134 (19)	132 (18)	0.05
Cholesterol (mmol/L)	2.22 (0.36)	2.21 (0.38)	2.24 (0.39)	2.22 (0.36)	2.20 (0.40)	0.06
HDL cholesterol (mmol/L)	0.49 (0.12)	0.49 (0.13)	0.48 (0.13)	0.48 (0.13)	0.48 (0.14)	0.27
Height (cm)	173 (7)	173 (6)	173 (7)	173 (6)	172 (6)	0.01
BMI (kg/m^2)	26.5 (3.1)	26.6 (3.4)	26.7 (3.4)	26.4 (3.5)	26.5 (3.9)	0.42
Fruit and vegetable intake (portions / day)	2.7 (1.4)	2.6 (1.4)	2.6 (1.4)	2.5 (1.3)	2.4 (1.4)	<0.001
Physical activity (metabolic equivalent scores / week)	97 (63)	99 (65)	94 (67)	91 (71)	89 (69)	<0.001
Country of residence (%)						0.22
France	73	76	75	72	75	
Northern Ireland	27	24	25	28	25	
Lifetime smoking (%)						<0.001
never smoked	32	31	29	30	25	
smoked other than cigarettes	9	9	7	7	6	
less than 15 cigarette pack-years	22	21	23	20	19	
15 - 30 cigarette pack-years	18	20	18	20	20	
30 or more cigarette pack-years	18	20	23	22	30	
Alcohol (%)						<0.001
none	17	15	15	19	20	
1-128ml/week	23	21	21	21	21	
129-265ml/week	22	23	21	20	19	
266-461ml/week	20	21	21	19	16	
462ml plus/week	18	20	23	21	23	
Diabetes (%)	3	2	3	4	4	0.003

	DepFAG N=1789 (22%)	DepFAG1 N=1630 (20%)	DepFAG2 N=1561 (19%)	DepFAG3 N=1618 (20%)	DepFAG4 N=1540 (19%)	
DepV score (0-1)	0.01(0.02)	0.04 (0.05)	0.10 (0.08)	0.20 (0.09)	0.42 (0.18)	<0.001
DepFA score (0-1)	0.05 (0.02)	0.11 (0.02)	0.19 (0.03)	0.30 (0.04)	0.52 (0.13)	<0.001
Age (years)	54.8 (3.0)	54.7 (2.9)	54.9 (2.9)	54.9 (2.8)	54.6 (2.8)	0.01
Systolic blood pressure (mm Hg)	134 (19)	132 (18)	134 (19)	135 (19)	133 (18)	0.002
Cholesterol (mmol/L)	2.22 (0.37)	2.22 (0.36)	2.21 (0.37)	2.23 (0.39)	2.21 (0.39)	0.28
HDL cholesterol (mmol/L)	0.48 (0.12)	0.49 (0.12)	0.49 (0.13)	0.48 (0.13)	0.49 (0.13)	0.13
Height (cm)	173 (7)	173 (6)	173 (7)	173 (7)	173 (6)	0.03
BMI (kg/m^2)	26.5 (3.1)	26.4 (3.3)	26.6 (3.3)	26.6 (3.4)	26.6 (3.8)	0.41
Fruit and vegetable intake (portions / day)	2.7 (1.3)	2.7 (1.5)	2.6 (1.4)	2.6 (1.4)	2.4 (1.3)	<0.001
Physical activity (metabolic equivalent scores / week)	100 (65)	96 (62)	97 (64)	94 (68)	89 (69)	<0.001
Country of residence (%)						0.17
France	28	25	26	26	25	
Northern Ireland	72	75	74	74	75	
Lifetime smoking (%)						<0.001
never smoked	32	31	32	29	27	
smoked other than cigarettes	8	9	8	8	7	
less than 15 cigarette pack-years	22	22	20	22	21	
15 - 30 cigarette pack-years	20	18	19	19	19	
30 or more cigarette pack-years	18	20	21	22	26	
Alcohol (%)						<0.001
none	19	14	16	15	19	
1-128ml/week	24	22	21	21	21	
129-265ml/week	20	24	22	22	20	
266-461ml/week	19	20	20	20	18	
462+ ml/week	18	19	21	22	21	
Diabetes (%)	2	3	3	3	4	0.07

Table 5: Number of events and event rates in total, and by categories of depression.

	n	Person years	CVD Incidence		Mortality from CVD		Mortality from Smoking related conditions		Mortality from All Causes	
			Events	Rate per 1,000 person years	Events	Rate per 1,000 person years	Events	Rate per 1,000 person years	Events	Rate per 1,000 person years
Total	8138	78493	372	4.7	59	0.8	177	2.3	419	5.3
DepV Category										
1	3283	31929	121	3.8	15	0.5	54	1.7	137	4.3
2	1880	18185	97	5.3	14	0.8	32	1.8	84	4.6
3	1193	11501	51	4.4	11	1.0	35	3.0	67	5.8
4	761	7225	44	6.1	7	1.0	21	2.9	54	7.5
5	1021	9654	59	6.1	12	1.2	35	3.6	77	8.0
DepFA Category										
1	1789	17344	73	4.2	14	0.8	36	2.1	88	5.1
2	1630	15811	65	4.1	4	0.3	25	1.6	63	4.0
3	1561	15134	72	4.8	11	0.7	26	1.7	75	5.0
4	1618	15558	79	5.1	14	0.9	46	3.0	92	5.9
5	1540	14646	83	5.7	16	1.1	44	3.0	101	6.9

Table 6: Hazards Ratios, Confidence Intervals and significance for depression and disease or mortality relationships using continuous data

	Unadjusted			Adjusted for demographic variables[1]			Adjusted for demographic and lifestyle variables[2]		
	HR	CI	Sig.	HR	CI	Sig.	HR	CI	Sig.
DepV									
CVDI	2.18	1.29,3.70	<0.01	2.36	1.39,4.00	<0.01	1.73	0.99,2.99	0.06
MCVD	4.97	1.55,15.91	0.01	5.83	1.80,18.93	<0.01	4.16	1.22,14.25	0.02
MSRC	3.64	1.78,7.43	<0.01	4.02	1.96,8.23	<0.01	2.56	1.23,5.34	0.01
MALL	3.50	2.20,5.56	<0.01	3.86	2.42,6.14	<0.01	2.71	1.68,4.35	<0.01
DepFA									
CVDI	1.79	1.04,3.11	0.04	1.93	1.12,3.35	0.02	1.50	0.86,2.64	0.15
MCVD	4.37	1.27,15.11	0.02	5.06	1.47,17.44	0.01	3.60	1.01,12.77	0.04
MSRC	2.83	1.32,6.07	0.01	3.11	1.45,6.65	<0.01	2.25	1.04,4.87	0.04
MALL	2.41	1.46,3.97	<0.01	2.63	1.59,4.33	<0.01	2.01	1.21,3.35	0.01

[1] Model adjusted for age and country of residence (NI / France).

[2] Model adjusted for age, country of residence (NI/France), systolic blood pressure, cholesterol, HDL cholesterol, height, BMI, fruit and vegetable intakes (portions of fruit, fruit juice and vegetables / day), physical activity (metabolic equivalent scores / week), lifetime smoking (five categories: never smoked; smoked other than cigarettes; smoked less than 15 cigarette pack-years; smoked 15 or more but less than 30 cigarette pack-years; smoked 30 or more cigarette pack-years), alcohol (five categories: none; 1-128ml/week; 129-265ml/week; 266-461ml/week; and 462ml plus/week) and diabetes (present/absent).

Table 7: Hazards Ratios, Confidence Intervals and significance for depression and disease or mortality relationships using grouped data

		Unadjusted			Adjusted for demographic variables[1]			Adjusted for demographic and lifestyle variables[2]		
		HR	CI	Sig.	HR	CI	Sig.	HR	CI	Sig.
depVG										
CVDI	Q[3]			0.01			0.01			0.08
	Q1[4]	1.41	1.08,1.85	0.01	1.44	1.10,1.88	0.01	1.40	1.07,1.83	0.02
	Q2	1.16	0.83,1.61	0.39	1.18	0.84,1.64	0.34	1.11	0.79,1.55	0.56
	Q3	1.60	1.13,2.28	0.01	1.62	1.14,2.30	0.01	1.45	1.02,2.06	0.04
	Q4	1.54	1.12,2.12	0.01	1.60	1.16,2.20	<0.01	1.35	0.97,1.87	0.07
MCVD	Q			0.12			0.08			0.22
	Q1	1.65	0.80,3.42	0.18	1.70	0.82,3.52	0.15	1.66	0.80,3.46	0.18
	Q2	2.06	0.95,4.48	0.07	2.13	0.98,4.64	0.06	1.98	0.90,4.35	0.09
	Q3	2.11	0.86,5.16	0.10	2.17	0.88,5.31	0.09	1.87	0.76,4.62	0.18
	Q4	2.66	1.24,5.68	0.01	2.84	1.33,6.08	0.01	2.42	1.11,5.31	0.03
MSRC	Q			<0.01			<0.01			0.04
	Q1	1.07	0.69,1.66	0.77	1.09	0.70,1.68	0.72	1.04	0.67,1.61	0.87
	Q2	1.80	1.17,2.77	0.01	1.84	1.20,2.83	0.01	1.68	1.09,2.58	0.02
	Q3	1.70	1.02,2.85	0.04	1.73	1.04,2.90	0.04	1.49	0.88,2.49	0.14
	Q4	2.01	1.29,3.11	<0.01	2.11	1.36,3.27	<0.01	1.69	1.08,2.65	0.02
MALL	Q			<0.01			<0.01			<0.01
	Q1	1.07	0.82,1.41	0.61	1.09	0.83,1.43	0.55	1.05	0.80,1.39	0.72
	Q2	1.37	1.02,1.84	0.04	1.40	1.04,1.88	0.03	1.31	0.98,1.76	0.07
	Q3	1.77	1.29,2.44	<0.01	1.81	1.32,2.49	<0.01	1.60	1.16,2.20	<0.01
	Q4	1.82	1.37,2.42	<0.01	1.92	1.45,2.55	<0.01	1.63	1.22,2.18	<0.01
DEPFAG										

CVDI	Q			0.43			0.31			0.76
	Q1	0.96	0.69,1.35	0.82	0.99	0.70,1.38	0.93	1.06	0.76,1.48	0.74
	Q2	1.09	0.78,1.52	0.60	1.11	0.80,1.54	0.54	1.13	0.82,1.58	0.46
	Q3	1.18	0.86,1.63	0.32	1.20	0.87,1.65	0.27	1.14	0.83,1.58	0.42
	Q4	1.27	0.93,1.75	0.14	1.34	0.97,1.84	0.08	1.24	0.90,1.71	0.20
MCVD	Q			0.13			0.10			0.23
	Q1	0.31	0.10,0.95	0.04	0.33	0.11,0.99	0.05	0.36	0.12,1.11	0.08
	Q2	0.90	0.41,1.99	0.80	0.93	0.42,2.06	0.87	0.95	0.43,2.12	0.91
	Q3	1.13	0.54,2.38	0.74	1.18	0.56,2.47	0.67	1.14	0.54,2.40	0.74
	Q4	1.36	0.66,2.78	0.40	1.49	0.73,3.06	0.28	1.37	0.65,2.86	0.41
MSRC	Q			0.03			0.02			0.08
	Q1	0.78	0.47,1.31	0.35	0.80	0.48,1.34	0.40	0.81	0.48,1.35	0.41
	Q2	0.82	0.49,1.38	0.46	0.83	0.50,1.39	0.49	0.81	0.49,1.36	0.43
	Q3	1.46	0.94,2.27	0.10	1.48	0.95,2.30	0.08	1.37	0.88,2.14	0.16
	Q4	1.39	0.89,2.19	0.15	1.48	0.94,2.32	0.09	1.30	0.83,2.06	0.26
MALL	Q			0.01			<0.01			0.06
	Q1	0.80	0.58,1.11	0.19	0.82	0.59,1.13	0.23	0.82	0.59,1.13	0.23
	Q2	0.96	0.71,1.32	0.82	0.97	0.71,1.33	0.86	0.94	0.69,1.29	0.72
	Q3	1.20	0.89,1.61	0.23	1.21	0.90,1.63	0.21	1.14	0.85,1.53	0.38
	Q4	1.36	1.02,1.81	0.04	1.43	1.07,1.92	0.02	1.29	0.96,1.73	0.09

[1] Model adjusted for age and country of residence (NI / France).

[2] Model adjusted for age, country of residence (NI/France), systolic blood pressure, cholesterol, HDL cholesterol, height, BMI, fruit and vegetable intakes (portions of fruit, fruit juice and vegetables / day), physical activity (metabolic equivalent scores / week), lifetime smoking (five categories: never smoked; smoked other than cigarettes; smoked less than 15 cigarette pack-years; smoked 15 or more but less than 30 cigarette pack-years; smoked 30 or more cigarette pack-years), alcohol (five

categories: none; 1-128ml/week; 129-265ml/week; 266-461ml/week; and 462ml plus/week) and diabetes (present/absent).

[3] significance value for a linear trend

[4] coefficient, confidence intervals and significance values for each group compared to the reference group – no depression.

Figure 1: Scatterplots demonstrating the relationship between DepV and DepFA in France and Northern Ireland.