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Structural social relations and cognitive aging trajectories: Evidence from the Whitehall II cohort study

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Key Messages:

Baseline cognitive performance was not strongly associated with subsequent rate of cognitive decline.

Frequent social contacts and being married were associated with better cognitive performance trajectory over time.

The associations between social relations and cognitive performance trajectories were independent of age, gender, socioeconomic position, behavioral risks and cardio-metabolic factors.

Abstract

Background: Social relations are important for health, particularly at older ages. We examined the salience of frequency of social contacts and marital status for cognitive ageing trajectories over 21 years, from midlife to early old age.

Methods: Data are from the Whitehall II cohort study, including 4290 men and 1776 women aged 35-55 years at baseline (1985-1988). Frequency of social contacts and marital status were measured in 1985-1988 and 1989-1990. Assessment of cognitive function on five occasions (1991-1994, 1997-1999, 2003-2004, 2007-2009, and 2012-2013) included the following tests: short-term memory, inductive reasoning, verbal fluency (phonemic and semantic), and a combined global score. Cognitive trajectories over the study period were analyzed using longitudinal latent growth class analyses and the associations of these latent classes (trajectory memberships) with social relations were analysed using multi-nominal logistic regression.

Results: More frequent social contacts (relative risk (RRR) 0.96, 95% confidence interval (CI) 0.94 – 0.98) and being married (RRR 0.70, 95% CI 0.58 – 0.84) were associated with lower probability of being on a low- rather than high-cognitive performance trajectory over the subsequent 21 years. These associations persisted after adjustment for covariates. Of the sub-tests, social relations variables had the strongest association with phonemic fluency (RRR 0.95, 95% CI 0.94 – 0.97 for frequent contact; RRR 0.59, 95% CI 0.48 – 0.71 for being married).

Conclusions: More frequent social contacts and having a spouse were associated with more favourable cognitive aging trajectories. Further studies are needed to examine whether interventions designed to improve social connections affect cognitive ageing.

Background

People with dense, good, and supportive social relations are healthier and they live longer than those without such relations[1-3]. The effects of social relations on health are attributable to multiple pathways, including stress related cardio-metabolic changes and health risk behaviors[4]. Both better structural (the size, frequency of contacts, and structure of network, e.g. marital status) and functional (frequency or amount of social support) aspects of social relations have been associated with better cognitive performance[5] and slower cognitive decline [6 7]. More frequent social contacts have also been associated with reduced risk of dementia[6].

Although there are a number of studies that have examined the association between social support (functional aspects of social relations) and cognitive performance using cross-sectional[8-10] and longitudinal designs[8], only two time points of cognitive performance measures have typically been used. This is a limitation due to the fluctuation in cognitive performance, which could be especially marked at older age. Moreover, most longitudinal studies have used linear mixed-effects models, [11 12] which models correlated repeated measures with random effects, to allow individuals differences in both cognitive scores at baseline and rates of cognitive decline. However, this strategy does not take into account the possibility that certain groups of individuals may have different developmental trajectories. An alternative approach, namely latent class modeling (a semi-parametric specification of mixed modeling) [13] allows the underlying, unobserved characteristics of groups of individuals to be taken into account, with identification of homogeneous subgroups within the study population.

To address these limitations, the aim of the current study was to examine, using latent class modeling, the association between structural aspects of social relations, i.e., frequency of social contact and marital status, with cognitive performance. We used five

assessments of cognitive performance spanning 21 years and examined the associations with specific cognitive abilities.

Methods

Study sample

Participants were from the ongoing Whitehall II Study [14 15], which originally included 10308 London-based civil servants from 20 civil service departments who were 35–55 years of age at study baseline (phase 1: data collection took place between 1985–1988). Data from phase 1 (baseline, 1985–1988), phase 2 (1989 – 1990) and five follow-up phases 3 (1991 – 1994), 5 (1997-1999), 7 (2003-2004), 9 (2007 – 2009) and 11 (2011 - 2013) were used in this study. All participants who provided data at baseline and at the second follow-up phase (n=7578), and at any subsequent follow-up phases (n=6072; 4290 men, 1776 women) were included in the analyses. Ethical approval for the Whitehall II Study was obtained from the University College London Medical School Committee on the ethics of human research and informed consent was obtained from all study participants.

Structural aspects of social relations

Self-reported frequency of social contacts from phase 2 (1989/ 1990), and marital status were used as structural measures of social relations. Frequency of social contacts score (0-28) was adapted from the Berkman/Syme social network index [16], and is the sum of all the items assessing structural aspects of social contacts (i.e. questions on the frequency of contacts with relatives, friends, and colleagues and the frequency of participation in social or religious activities and the total number of relatives or friends seen once a month or more) and reflects amount and frequency of social connectedness. The index measures

the network structure (how many peoples are there in the individual's social network) and network interactions (how frequently the individual is in contact with people in their social network)**.** Marital status was dichotomized as married/cohabiting versus unmarried (including never married, separated, divorced or widowed).

Cognitive performance

Cognitive testing was introduced to the Whitehall study midway through Phase 3 (1991/ 1994). Consequently, cognitive data are available only for 40 percent of the participants at Phase 3 but for the entire sample at Phases 5, 7, 9 and 11. The cognitive test battery comprised four cognitive tests to assess different cognitive abilities and was administered at five clinical examinations over 21 years (1991/1994 to 2012/2013).

(a) The Alice Heim 4-I (AH4-I) [17] is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty to be completed in 10 minutes.

(b) Short-term verbal memory was assessed with a 20-word free recall test. Participants were presented with a list of 20 one or two-syllable words at 2 second intervals and then had to recall them in writing in 2 minutes.

(c) There were two tests of verbal fluency [18]. Participants were asked to recall in writing as many 'S' words (phonemic fluency) and as many animal names as they could (semantic fluency) in 1 minute.

The four cognitive tests were combined to create a global cognitive z-score (mean 0, S.D.= 1), to minimize problems due to measurement error on individual tests. First, the raw scores from each test were standardized to a z-score based on the phase 5 mean value and SD and then these z scores were averaged to obtain the global cognitive performance scores. Similar procedure has been used in previous studies [11].

Covariates

Age, sex, ethnicity (white, non-white) and socioeconomic status, measured as occupational position (low, intermediate, high) were reported at the study baseline and were used as covariates in all analyses. Occupational position has been shown to be a broad marker of socioeconomic status in the Whitehall II study as it has been associated with salary, educational level and the level of responsibility at work[15 19]. To control for potential confounding and mediating factors, we included an inflammatory marker, level of C-reactive protein (CRP); for cardiometabolic risk factors, we used diastolic and systolic blood pressure, LDL cholesterol and fasting glucose; and for behavioral risks, we included alcohol consumption and body mass index. All of these factors have been associated with cognitive function or cognitive decline previously[12 20-26]. The methods used for measuring these variables have been reported in detail elsewhere[14].

Statistical analysis

Trajectories of cognitive performance were defined using group-based trajectory models (GBTM) that identify classes of individuals (trajectory groups) with a similar trajectory over time (a special case of latent class analyses). GBTM is increasingly being applied to clinical research to map the developmental course of disease and to identify the number, shape, and size of different (latent) trajectory groups in the data. We used Bayesian Information Criteria (BIC) and Akaike's information criterion (AIC) to determine the optimal number of trajectories: lower absolute values correspond to better fit. We hypothesized *a priori* that there would be 2 to 3 latent trajectories, as suggested by previous research [27 28]. In addition to global cognitive score, the change in each individual cognitive performance test score (memory, inductive reasoning, and phonemic and semantic fluency) were analysed using GBTM. The latent class modeling is a semi-parametric specification of mixed modeling, that approximates

the underlying continuous distribution with a discrete one[13]. The underlying theory of the latent class modeling posits that individual behavior depends on observable attributes and on latent heterogeneity that varies with factors that are unobserved by the analyst and heterogeneity is analyzed through a model of discrete parameter variation. Each individual was classified as being a member of a given trajectory group based on a posterior classification index for each individual i.e. the mean probability of being assigned to the given class. The method includes participants with data from any of the data collection phases.

We used multinomial ordinal regression analysis and expressed the results as relative rate ratios (RRR) and their 95% confidence intervals (CI), where all three trajectory groups were analysed together. First we tested proportional odds assumption using the likelihood ratio chi-square test and 'high' trajectory was set as an outcome reference group against which we tested the association with social relations variables. The estimates were adjusted for (A) age and sex, (B) additionally for socioeconomic status and (C) additionally for cardiometabolic risk factors (including CRP) and health behaviours. All the analyses were performed using STATA 13.1 statistical package.

Results

When compared with those who dropped out from the original sample, participants included in the study sample were more likely to be white (79% vs. 62%; $p<0.001$), men (81% vs. 70%; $p<0.001$), slightly younger (mean age in years: 44.7 vs 45.8, $p<0.001$) and from a higher employment position (85% vs. 60%; $p<0.001$). In addition, individuals who were included into the study sample had a higher frequency of social contacts (10 vs. 9.3 $p<0.001$), were more likely to be married or cohabiting (79% vs. 73%; $p<0.001$) and their blood glucose levels were lower (5.5 mmol/L vs. 6.5 mmol/L; $p<0.001$) than those who dropped out from the study.

A three-trajectory solution of global cognitive function scores with non-linear trajectories yielded better fit (BIC=-18848.93 /AIC=-18788.28) than two-trajectory (BIC=-21667.40 / AIC=-21626.97) or linear solutions (BIC=-19139.29 / AIC=-19102.90). The four class solution was slightly better than the three class model (BIC = -17932.12 , AIC = -17883.60), but one of the classes would have been relatively small (12%) and thus we chose the three factor solution with more even distribution of the participants (**Supplement Table 1s**) . **Figure 1** shows that each trajectory had a slightly declining shape over time. Predicted probabilities of group membership totalled 20% with 'low', 49% with 'intermediate', and 31% with 'high' global cognitive function trajectory. Trajectories of cognitive performance subscales are presented in **supplement figures 1 – 4.** There were clear differences in the level (intercept) of the cognitive performance trajectories. There were also small differences in the slope between the trajectory groups; the steepest decline was in the 'low' and the mildest decline in the 'high' group. Similar pattern was found in all performance subscales; the biggest decline was found in the low performance group.

Description of the study sample according to global cognitive performance trajectory membership is shown in **Table 1**. There were clear differences in cognitive function trajectory memberships between various demographic categories, health behavior categories and most cardiometabolic risk factors. Participants in the 'high' cognitive trajectory group were younger at baseline and more likely to be male, white and have high socioeconomic status. The mean BMI, systolic blood pressure, fasting glucose, CRP and alcohol consumption was lower in the 'high' group.

The age, sex, ethnicity and socioeconomic status adjusted associations between structural social relations (network density and marital status) and cognitive function trajectory group memberships are presented in **Table 2**, first showing the risk ratio for

membership in the "low" cognitive trajectory and then showing the risk ratio for membership in the "intermediate" cognitive trajectory setting 'high' trajectory membership as a reference group in multinomial regression analyses. Higher frequency in social contacts and being married were both associated with less likelihood of being in the 'low' or 'intermediate' global cognitive function trajectory as compared to being on the "high" trajectory. These associations were robust to adjustments for health behaviours, CRP and cardiometabolic factors. The corresponding analysis in which individual cognitive function trajectory memberships were tested as outcomes, are presented in **Table 3**. Both social relations variables seemed to have a stronger association with fluency measures than with inductive reasoning. The trajectory of short-term memory performance was not associated either of the social relations measures.

We additionally tested the associations using mixed models with frequency of social contacts and marital status as predictors (separate analyses) and overall cognitive performance over all study phases as an outcome in analyses adjusted for age and sex. Both more frequent social contacts (B = 0.01, z = 4.27. p<0.001) and being married (B = 0.06, z = 3.02, p=0.002) were associated with better cognitive function over study periods and frequency of social contacts * time interaction (z = -2.39, p = 0.017) was statistically significant. This interaction remained statistically significant (z = 2.63, p = 0.010) when adjusted additionally for socioeconomic status, alcohol consumption, body mass index, CRP, diastolic and systolic blood pressure, LDL cholesterol and fasting glucose. Both the frequency of social contacts (z = 3.45, p = 0.001) and being married (z = 2.42, p = 0.016) were associated with better cognitive function over study periods when added in to the regression model simultaneously but no interaction between them was found (z = 1.56, p = 0.119).

Discussion

Three trajectory groups of global cognitive function were identified among middle-aged men and women with up to five repeated measurements of cognitive performance over a maximum follow-up of 21 years. There were clear differences in intercepts of cognitive performance between trajectory groups but relatively small differences in the steepness or shape of the slopes. Thus, the baseline level of cognitive performance didn't have a very strong association with the rate of cognitive decline. Of the participants, 20% belonged to the 'low', 49% to the 'intermediate', and 31% to the 'high' global cognitive function trajectory group. Similar trajectories have also been previously identified [28]. Our findings showed that having more frequent social contacts and being married were both associated with a better cognitive performance trajectory over time. The associations were independent of demographic, behavioral and cardiometabolic factors. Of the individual cognitive performance trajectories, all but short-term memory performance were better in people with more frequent social contacts and among those who were married. Taken together, the findings suggest that less social contacts and living without a partner predict poorer cognitive performance between midlife and old age. Particularly, availability of other people, as indicated by frequent social contacts or living with a partner, seems to be a factor associated with cognitive decline.

Current findings are in line with previous studies where structural aspects of social relations have been associated with better average levels of cognitive performance and slower cognitive decline[6 7]. Our results also show that decline in different cognitive abilities is similar, which is also in line with previous findings [29]. Associations between structural aspects of social relations and various cognitive domains were similar indicating that lack of social contacts is a risk factor for general cognitive aging. We did find a stronger association between structural aspects of social relations and verbal ability. Married people have been shown to have more frequent contact with their social

networks[30] and this engagement may directly strengthen cognitive ability through repeated practice and refinement of communication, which could explain this finding.

Our study adds new insight by using a relatively large dataset and repeat measures of cognitive performance, starting in midlife. Our approach to modelling risk factors for cognitive function using long-term trajectory modelling of cognitive performance using the GBTM is new. In previous studies, cognitive performance has been often examined using cross-sectional data, shorter follow-up time or analysing cognitive decline with mixed modelling, [11 12] which models correlated repeated measures with random effects, to allow individuals differences in both cognitive scores at baseline and rates of cognitive decline. This strategy does not take into account the possibility that certain categories of individuals may have different developmental trajectories. GBTM, a semi-parametric specification of mixed modeling,[13] allows the underlying, unobserved characteristics of groups of individuals to be taken into account, with identification of homogeneous subgroups within the study population.

The large sample size, long follow-up period and multiple waves of cognitive assessment strengthen confidence in the results. Several known confounding factors were included in the analysis. Combining four tests into a single measure of global cognition reduces measurement error. All participants were from a sample of basically white-collar employees, and that restrict the generalizability of our results. However, the cohort covers a wide socioeconomic range, with a large difference in full-time salary between the highest and lowest occupational grade. The measures of social relationships were self-reported, so the information may be biased by respondents' personality traits[31]. The shape of the trajectories suggests that there were practice effects at the second time point for all three trajectories. As the effect appeared to be of a similar magnitude in all trajectories, this was unlikely to have affected our results. Subjective perceptions of the social

environment derived from a well-validated questionnaire, are relevant indictors of social relationships and have been shown to associate with various health outcomes[32-34]. However, as this study was an observational study, further studies are needed to examine whether interventions designed to improve possibilities for social connections would affect cognition favourably. To form a comprehensive picture on the role of social relations in cognitive performance, future studies also should examine the role of both structural and functional aspects of social relations.

We studied only the associations between midlife social relationships and subsequent cognitive performance development to reduce the risk of reverse causality affecting our results. In future, the impact of social relationship changes during the time from middle age to old age on cognitive performance should be investigated. Our results emphasize the importance of structural aspects of social relations in relation to cognitive function.

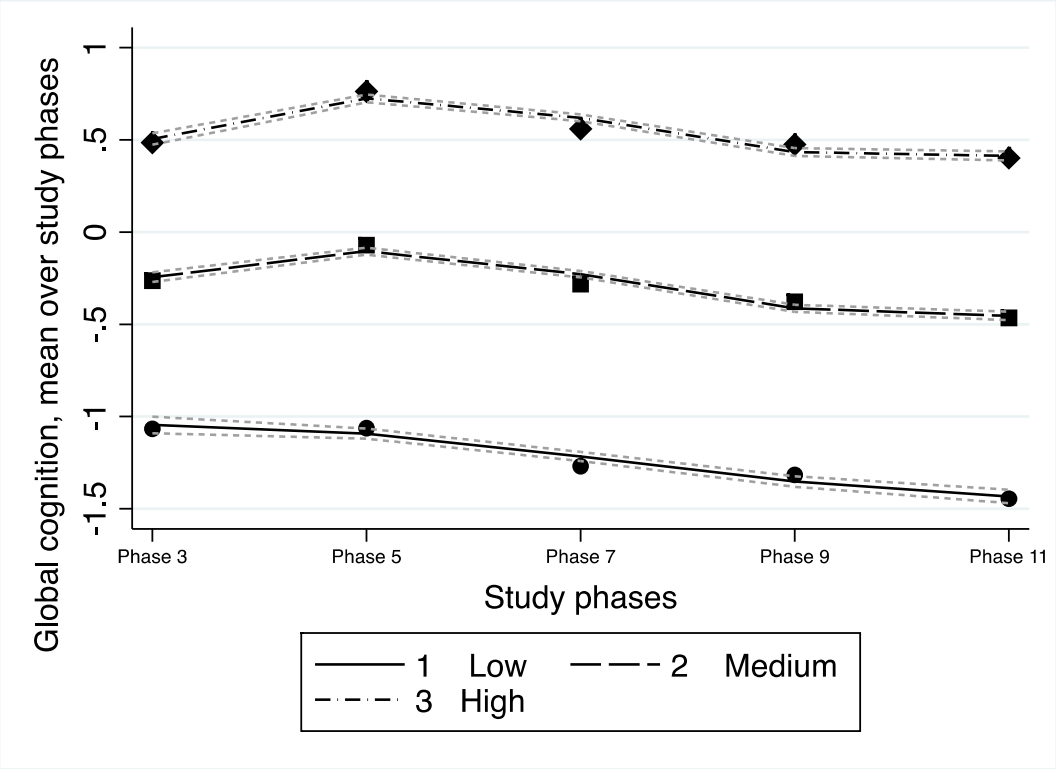

Figure 1. Trajectories of global cognitive performance score over five study phases (from 1991/1994 to 2012/2013 (n=6072).

Table 1. Descriptive characteristics of the participants by trajectories of global cognitive performance (n=6072) at the end of follow-up (Phase 7).

	Trajectory of cognitive performance			
	Low n= 1174	Intermediate n = 3030	High n= 1868	P-value for heterogeneity
	n (%)	n(%)	n(%)	
Sex: male	619 (14%)	2,284 (53%)	1,391(33%)	
Female	555 (31%)	746 (42%)	477 (27%)	<0.001
Socioeconomic status: high	79 (4%)	965 (47%)	980 (49%)	
Intermediate	494 (16%)	1701 (56%)	846 (28%)	
Low	601 (50%)	364 (36%)	42 (4%)	<0.001
Ethnicity : white	802 (15%)	2874 (52%)	1852 (33%)	
other	371 (69%)	151 (28%)	16 (3%)	<0.001
	Mean (SE)	Mean (SE)	Mean (SE)	
Age (years)	64.2 (0.2)	61.5 (0.1)	58.5 (0.1)	<0.001
Body mass index (kg /m^2)	27.4 (0.1)	26.6 (0.1)	26.3 (0.1)	<0.001
Alcohol consumption last 1 months (range 1 >2/day to 6 no)	3.7 (0.0)	2.9 (0.0)	2.6 (0.0)	<0.001
C-reactive protein (mg/l)	3.3 (0.2)	2.4 (0.1)	2.2 (0.1)	<0.001
Fasting glucose (mmol/l)	5.6 (0.0)	5.4 (0.0)	5.4 (0.0)	<0.001
LDL-cholesterol (mmol/l)	3.4 (0.0)	3.5 (0.0)	3.5 (0.0)	0.007
Diastolic blood pressure (mmHg)	69.8 (0.4)	70.9 (0.2)	70.9 (0.3)	0.012
Systolic blood pressure (mmHg)	126.5 (0.6)	125.3 (0.3)	123.4 (0.4)	<0.001

Table 2. Multinomial logistic regression analysis for the associations of social relations dimensions at Phase 2 with trajectories of global cognitive performance from phase 3 until phase 11. Figures are relative risk ratios (RRR) and 95% confidence intervals (95% CI)

	Trajectory of cognitive performance	
Social relations dimensions	'Low (ref. versus high')	'Intermediate versus high'
	RRR (95% CI)	RRR (95% CI)
Frequency of social contacts (one point increase on social network scale)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.96 (0.94 – 0.98)	0.98 (0.96 -0.99)
Adjusted additionally for health behaviors [a]	0.96 (0.93 – 0.98)	0.98 (0.96 – 0.99)
Adjusted additionally for cardiometabolic factors[b]	0.96 (0.93 – 0.99)	0.98 (0.96 - 1.00)
Marital status (married)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.70 (0.58 – 0.84)	0.77 (0.66 – 0.89)
Adjusted additionally for health behaviours [a]	0.75 (0.59 – 0.96)	0.88 (0.74 - 1.04)
Adjusted additionally for cardiometabolic factors[b]	0.76 (0.58 - 1.00)	0.88 (0.74 – 1.06)

[a]Alcohol consumption and BMI

[b] C-reactive protein, glucose, ldl-cholesterol, diastolic and systolic blood pressure

Table 3. Multinomial logistic regression analysis for the associations of social relations dimensions at Phase 2 with trajectories of individual cognitive performance tests from phase 3 until phase 11. Figures are relative risk ratios (RRR) and 95% confidence intervals (95% CI)

	Trajectory of cognitive performance	
Social relations dimensions	'Low versus high'	'Intermediate versus high'
	RRR (95% CI)	RRR (95% CI)
	Memory	
Frequency of social contacts (one point increase on social network scale)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.98 (0.95 – 1.00)	1.00 (0.98 -1.03)
Adjusted additionally for health behaviours	0.98 (0.95 – 1.01)	1.01 (0.98 – 1.01)
Adjusted additionally for cardiometabolic factors	0.99 (0.96 – 1.02)	1.01 (0.98 - 1.04)
Marital status (married)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.80 (0.64 - 1.00)	0.86 (0.69 - 1.07)
Adjusted additionally for health behaviours	0.84 (0.65 - 1.08)	0.88 (0.70 - 1.12)
Adjusted additionally for cardiometabolic factors	0.88 (0.67 - 1.16)	0.92 (0.72 - 1.18)
	Inductive reasoning	
Frequency of social contacts (one point increase on social network scale)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.97 (0.95 – 0.98)	0.99 (0.97 -1.00)
Adjusted additionally for health behaviours	0.95 (0.92 – 0.98)	0.99 (0.98 – 1.01)
Adjusted additionally for cardiometabolic factors	0.95 (0.92 – 0.98)	0.99 (0.97 - 1.01)
Marital status (married)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.80 (0.67 – 0.97)	0.80 (0.70 – 0.92)
Adjusted additionally for health behaviours	0.88 (0.69 - 1.14)	0.98 (0.84 - 1.16)
Adjusted additionally for cardiometabolic factors	0.90 (0.68- 1.19)	0.98 (0.82 - 1.16)

Table 3 continues.

Social relations dimensions	'Low versus high'	'Intermediate versus high'
	RRR (95% CI)	RRR (95% CI)
	Phonemic fluency	
Frequency of social contacts (one point increase on social network scale)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.95 (0.94 – 0.97)	0.98 (0.96 -0.99)
Adjusted additionally for health behaviours	0.95 (0.93 – 0.98)	0.98 (0.96 – 1.00)
Adjusted additionally for cardiometabolic factors	0.96 (0.94 – 0.99)	0.99 (0.97 - 1.01)
Marital status (married)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.59 (0.48 – 0.71)	0.75 (0.62 – 0.89)
Adjusted additionally for health behaviours	0.64 (0.51 – 0.80)	0.77 (0.63 – 0.94)
Adjusted additionally for cardiometabolic factors	0.60 (0.47 – 0.77)	0.78 (0.64 – 0.97)
	Semantic fluency	
Frequency of social contacts (one point increase on social network scale)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.96 (0.94 – 0.98)	0.98 (0.96 -0.99)
Adjusted additionally for health behaviours	0.96 (0.94 – 0.98)	0.98 (0.96 – 1.00)
Adjusted additionally for cardiometabolic factors	0.96 (0.94 – 0.99)	0.99 (0.97 - 1.01)
Marital status (married)		
Adjusted for age, sex, ethnicity and socioeconomic status	0.71 (0.59 – 0.86)	0.77 (0.66 – 0.91)
Adjusted additionally for health behaviours	0.79 (0.63 - 1.00)	0.89 (0.74 - 1.06)
Adjusted additionally for cardiometabolic factors	0.81 (0.63 – 1.04)	0.89 (0.74- 1.08)

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