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Socioeconomic status, gender and dementia: The influence of work environment exposures and their interactions with *APOE* ϵ 4

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ABSTRACT

It is a well-established fact that unfavourable social and economic conditions have a negative impact on health and longevity. Recent findings suggest that this is also true of age-related dementias. Yet most common indicators of socioeconomic status (SES) say very little about the actual mechanisms at play in disease development. The present paper explores five work exposure characteristics, all of which have a clear social gradient, that could potentially shed further light on the relationship between SES and dementia. Specifically, it investigates whether these exposures could moderate the impact of a well-known genetic risk factor: the *APOE* ϵ 4 allele. The empirical analyses are based on data from a Swedish population study ($n = 1019$). Main occupation was linked to The Job Exposure Matrix to estimate the individuals' exposure to the following work environment factors: *work control*, *support*, *psychological demands*, *physical demands* and *job hazards*. All analyses were conducted using binary logistic regression and focused specifically on gene-work exposure interactions. A significant main effect of *work control* on dementia risk was detected for males ($OR = 0.68$; $p < 0.05$), but not for females. However, control was found to significantly moderate the effect of *APOE* ϵ 4 in both genders, albeit in different ways. These findings do not only underscore the importance of considering interactions between social and genetic risk factors to better understanding multifactorial diseases such as dementia. They also propose that gender- and class-based inequities interact, and hence must be considered simultaneously, also in relation to this particular disease.

1. Introduction

The present study seeks to shed further light on the complex relationship between socioeconomic status (SES) and health or, more specifically, old-age dementia. It draws on the idea that SES differences in health are, at least partly, attributable to differences in work environment (Borg & Kristensen, 2000; Marmot, Ryff, Bumpass, Shipley, & Marks, 1997; Nilsen et al., 2014) and adds to the current state of research by exploring whether work exposures can in fact moderate genetic risk. With the increase in longevity all across the world, dementia has become a public health issue of major concern to all ageing societies (Winblad et al., 2016; World Health Organization, 2012). The most common cause of dementia is Alzheimer's disease (AD), accounting for 50–70 per cent of all cases, and the majority of elderly

people have multimorbidity involving Alzheimer-related changes in combination with other pathologies, especially cerebrovascular changes (Attems & Jellinger, 2013; James et al., 2016; Winblad et al., 2016). The major genetic risk factor for AD is the apolipoprotein E (*APOE*) ϵ 4 allele – a non-causative mutation known to increase disease risk by between three and 15 times (Blennow, de Leon & Zetterberg, 2006; Scheltens et al., 2016). Further, dementia follows a *social gradient* (Marmot, 2004). Low educational attainment stands out as a prominent risk factor (Meng & D'Arcy, 2013; Ngandu et al., 2007; Wang et al., 2012; Winblad et al., 2016), and previous findings suggest that low occupational class is associated with increased disease risk (Hasselgren et al., 2018; Qiu et al., 2003; Sattler, Toro, Schoenknecht, & Schroeder, 2012). Still, current knowledge is limited concerning whether and how social inequities interact with individual genetic endowments in the

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development of disease. Additionally, most common indicators of SES, including those mentioned above, say very little about the actual mechanisms at play in disease development. Given that most individuals spend a vast amount of time at work throughout life, it is hardly surprising that work environment exposures seem to partly explain SES differences in a variety of health outcomes, including cognitive decline (Borg & Kristensen, 2000; Marmot et al., 1997; Nilsen et al., 2014; Toivanen & Hemström, 2006). In the present paper, we explore a range of work exposures that could potentially shed further light on the relationship between SES and dementia. Additionally, we set out to investigate if any of these exposures could moderate the impact of the APOE ε4 allele, and whether gender differences exist in this respect.

1.1. Dementia and work environment exposures

Some of the most important psychosocial work exposures include demand characteristics of work tasks, job demands (e.g., work load), decision latitude (e.g., control over the work process/intellectual discretion) and social support (Johnson & Hall, 1988; Karasek, 1979; Stansfeld & Candy, 2006; Then et al., 2014). Many of these factors have previously been linked to cognitive decline in general (Andel, Crowe, Kåreholt, Wastesson, & Parker, 2011; Elovainio et al., 2009) as well as to prospective cognitive complaints (Stenfors, Hanson, Oxenstierna, Theorell, & Nilsson, 2013). In relation to dementia specifically, a number of studies suggest that psychosocial factors such as high levels of control, social demands/support (Andel et al., 2012; Seidler et al., 2004) and challenge at work (Seidler et al., 2004) serve a potentially protective function, also when controlling for APOE ε4 allelic status (Wang, Wahlberg, et al., 2012). Likewise, high job strain¹ and work-related stress in midlife have been suggested to increase the risk of dementia late in life (Sindi et al., 2016). However, it still remains unclear whether work environment exposures could moderate genetic risk in dementia, as they have been suggested to do in relation to, e.g., atherosclerosis (Hintsanen et al., 2008, 2007). With regard to having a physically demanding job, the evidence is still limited, although associations between physical demands and occurrence of AD (Smyth et al., 2004), as well as indicators of AD pathology (Stern et al., 1995), have been reported. In relation to job hazards, this is, to our knowledge, the first study to explore the potential association between dementia and hazardous work using an index that combines a range of adverse exposures (see Section 2.3). Two suggested physiological mechanisms seem to dominate previous studies dealing with the association between psychosocial work exposures and dementia. First, with regard to occupations in which decision latitude, skill discretion and/or psychological demands are high, the *cognitive reserve hypothesis* (Stern, 2002, 2012) proposes that activities containing intellectual stimulation could increase compensatory abilities in the neuronal networks and hence improve the brain's resilience to degenerative changes (Qiu, Kivipelto, & von Strauss, 2009; Then et al., 2017). The second explanation is related to *stress and vascular mechanisms* (Johansson et al. 2010; Johansson et al., 2013; Wang et al., 2012). For example, stress is known to be associated with cardiovascular risk factors such as hypertension (Kivimäki et al., 2002; Vrijkotte, Van Doornen, & De Geus, 2000) that, in turn, increases the risk of developing dementia (Kivipelto et al., 2001; Skoog et al., 1996). Further, it is hypothesized to heighten levels of glucocorticoid hormones in the blood, which could cause damage to the hippocampus (Bremner, 2006; Lupien et al., 1999; Sapolsky, 1996) and, possibly, increase buildup of beta-amyloid (Aβ) peptide and tau-protein in the brain (both of which are involved in the development of AD) (Dong et al., 2004; Green, Billings, Roozendaal, McGaugh, & LaFerla, 2006).

¹ Job strain is a composite measure and widely used definition of psychosocial stress at work, characterized by the combination of high psychological demands and low decision latitude (control) (Karasek, 1979).

1.2. On the importance of 'contextualizing risk'

As suggested by Stansfeld and Candy (2006, p. 442), 'social hierarchies and the implicit power relationships contained therein influence the distribution of work-related stressors'. In the context of the present study, it should therefore be underlined that there are considerable gender and SES differences in exposure to various work characteristics. It has repeatedly been reported that white-collar workers have a higher degree of work control than blue collar workers, and that women in both of these occupational classes report lower levels of control compared to their male counterparts. Similarly, high occupational physical demands are associated with lower SES, and men are, on average, more exposed than women in this respect (Hall, 1989; Matthews, Hertzman, Ostry, & Power, 1998; Rovio et al., 2007; Swedish Work Environment Authority, 2016). Furthermore, stressors such as emotional demands and violence/threats of violence are known to be widespread in human service professions where women predominate (Brotheridge & Grandey, 2002; Swedish Work Environment Authority, 2016; Hochschild, 2003), and a number of studies have reported higher risks of affective and stress related complaints in these occupational groups (see for example; Johnson et al., 2005; Stansfeld, Rasul, Head, & Singleton, 2011; Wieclaw, Agerbo, Mortensen, & Bonde, 2006). For women, the possible 'double burden' of professional and domestic engagements must also be acknowledged. During the 20th century, women's labour market participation has increased substantially in large parts of the world, including Sweden (Statistics Sweden, 2011). While men have gradually come to spend more time on domestic chores, there have been, and still are, large gender differences in this respect (Statistics Sweden, 1992, 2012). In terms of health outcomes, the combination of high workloads in both paid and unpaid work among women has previously been linked to various indicators of psychological strain and ill-health (Floderus, Hagman, Aronsson, Marklund, & Wikman, 2009; Krantz, Berntsson, & Lundberg, 2005), also in older cohorts (Arber, Gilbert, & Dale, 1985; Hall, 1992).

2. Material and methods

2.1. Study population

The study sample is derived from two longitudinal studies from Gothenburg, Sweden, that were merged to become one in 2000; the *H70 Birth Cohort Study* and the *Prospective Populations Study of Women* (PPSW) (Karlsson et al., 2009). The present sample consists of 1019 individuals (229 men and 790 women), all living in Sweden on September 1, 2000 (Table 1). Of the 790 women, 691 had previously been part of the *Prospective Populations Study of Women* (PPSW). All participants were sampled from the Swedish population register and systematically selected on the basis of birth dates. The women were born in 1908, 1914, 1918, 1922 or 1930, while all men were born in 1930. Of these individuals, 923 (90.6%) consented to donate blood for genetic analyses. A more detailed description of the baseline sample can be found elsewhere (Karlsson et al., 2009; Karlsson et al., 2010). Follow-up examinations were carried out in 2005-06 (n = 724) and 2009-10 (n = 368). Informed consent was acquired from all participants or their relatives, and the studies were approved by the regional Ethics Review Board for medical research in Gothenburg (Skoog et al., 2015).

2.2. Neuropsychiatric examinations, diagnoses and genotyping

The clinical examination, conducted at an outpatient department or in the participant's home, comprised comprehensive social, functional, physical, neuropsychiatric and neuropsychological assessments as well as an interview with a close informant. The semi-structured neuropsychiatric examinations included ratings of common symptoms and signs of dementia (e.g., assessments of memory, orientation, general knowledge, apraxia, visuospatial function, understanding proverbs,

Table 1
Characteristics of the study population, n(%) / mean(sd).

	All	Males	Females
Presence of APOE $\epsilon 4$	262 (28.4)	65 (29.2)	197 (28.1)
Education			
Primary	597 (62.2)	130 (57.0)	467 (63.8)
Lower secondary	220 (22.9)	39 (17.1)	181 (24.7)
Upper secondary/university	143 (14.9)	59 (25.9)	84 (11.5)
Occupational class			
Blue collar	408 (48.9)	93 (40.8)	315 (52.0)
Lower white collar	220 (26.8)	31 (13.6)	189 (31.2)
White-collar/self-employed	206 (24.7)	104 (45.6)	102 (16.8)
Sex			
Male	229 (22.5)	–	–
Female	790 (47.5)	–	–
Year of birth			
1908	8 (0.8)	–	8 (1.0)
1914	44 (4.3)	–	44 (5.6)
1918	171 (16.8)	–	171 (21.7)
1922	216 (21.2)	–	216 (27.3)
1930	580 (56.9)	229 (100.0)	351 (44.4)
Job exposures			
Work control	5.0 (1.1)	5.6 (1.3)	4.7 (1.0)
Psychological demands	4.7 (1.2)	4.9 (1.4)	4.6 (1.2)
Support	8.5 (0.9)	9.0 (0.9)	8.3 (1.0)
Job hazards	2.2 (1.1)	3.0 (1.5)	1.8 (0.5)
Physical demands	3.0 (1.5)	3.6 (1.9)	2.8 (1.3)
Diagnosed with dementia at baseline	94 (9.2)	5 (2.2)	89 (11.3)
Diagnosed with dementia 2000–2012	246 (24.1)	27 (11.8)	219 (27.7)
Age at baseline	75.3 (5.8)	70.5 (0.2)	76.7 (5.9)

Comment: N = 1019.

following commands, naming ability and language) and were performed by trained psychiatric research nurses. For a more detailed description of the procedures, see Guo et al. (2007) and Skoog, Nilsson, Palmertz, Andreasson & Svanborg (1993). In addition, semi-structured interviews with a close informant were performed and comprised questions regarding changes in behaviour and intellectual function, psychiatric symptoms, activities of daily living, and, in cases of dementia, age of onset and disease course (Karlsson et al., 2009, Skoog et al., 2015). Dementia was diagnosed by geriatric psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised (DSM-III-R) (APA, 1987). The diagnoses were based on symptoms rated during the neuropsychiatric examinations as well as on information from the close informant interviews, as previously described in detail (Guo et al., 2007, Skoog, Nilsson, Palmertz, Andreasson & Svanborg, 1993). For individuals lost to follow-up, incident dementia cases (until 2012) were diagnosed on the basis of information from medical records, evaluated by geriatric psychiatrists, or from the Swedish Hospital Discharge Register (Guo et al., 2007). Blood samples were collected and the SNPs (single nucleotide polymorphisms) rs7412 and rs429358 in APOE (gene map locus 19q13.2) were genotyped using the KASPar® PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK) or by mini-sequencing, as previously described in detail (Blennow et al., 2000). Genotype data for these two SNPs were used to define $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles. Because $\epsilon 4$ is the only allele associated with an increased risk of AD, the subsequent analyses focused solely on this variant.

2.3. Assessment of work environment exposures

Information on occupation was obtained through interviews at baseline and/or in conjunction with the follow-up examinations. All participants were asked to specify their main occupation in free text. Individuals (women only, approx. 12.5 per cent) who stated that they had primarily engaged in domestic work/had not been employed during working age were excluded from further analyses. Using these data, in combination with the validated Job Exposure Matrix (JEM) (Johnson, Stewart, Fredlund, Hall, & Theorell, 1990; Johnson &

Stewart, 1993), we were able to estimate each participant's exposure to the following work environment factors: *work control*, *support*, *psychological demands*, *physical demands* and *job hazards*. The data on which the JEM is based were originally sampled through the annual Swedish Survey of Living Conditions (ULF) for 1977 and 1979, respectively. In order to construct the JEM, Johnson et al. (1990) used factor analysis to combine sets of items. Five factors/scales, corresponding to the work environment exposures listed above, were retained. With regard to work control, the scale comprises items such as degree of influence over the planning of work, flexible working hours, possibility of learning new things and degree of variation in task content. The support scale was constructed from questions regarding the possibility of social interaction with co-workers, at the workplace as well as outside work. Psychological demands refer to whether the job is perceived as hectic and/or psychologically demanding, while the physical demands scale includes items such as exposure to accident risk and heavy lifting. Finally, the job hazards scale indicates the individual's level of exposure to, e.g., noise, heavy shaking and inadequate ventilation. Based on the matrix, each individual received a score, ranging from 0 to 10, for each of the five factors, where higher scores indicate higher levels of the factor. For ease of interpretation, the exposure indicators were later mean centred. Given the substantial gender differences in work content, the JEM includes separate scales for men and women (see also Hall, 1989; Johnson et al., 1990). In practice, this means that a man and a woman holding the same occupation are assigned different JEM scores. A final remark on retrospectively estimating work exposure is necessary. As noted by Johnson et al. (1990), the activities and exposures associated with a certain occupation are likely to change over time. In this respect, it is advantageous that the version of the JEM used in the present paper was constructed from data sampled during the 1970s, i.e., when the majority of our study population was still active on the labour market.

2.4. Covariates

In order to distinguish between different occupational groups, all occupations in free text were coded in accordance with the Swedish SEI standards for socioeconomic classification (Statistics Sweden, 1982), which has many commonalities with the Eriksson-Goldthorpe scheme (Goldthorpe, 2007). Based on the initial, two-digit classifications, three aggregated socioeconomic groups were specified: *Blue collar* (BC) corresponds to manual workers, *Lower white collar* (LWC) to assistant, non-manual employees and *Upper white collar* (UWC) includes intermediate/higher non-manual workers and professionals in occupations as well as upper-level executives, self-employed and farmers (for a more detailed description of these groups, see Hasselgren et al., 2018). The education variable was mainly constructed from responses gathered in conjunction with the baseline examination in 2000–01, when all respondents were asked to specify the level/type of their educational attainment. In cases where information was missing at baseline, it was, if available, obtained from the follow-up examinations. The variable has three values: where *Primary* corresponds to elementary school/vocational school, *Lower secondary* to girls' school/junior secondary school/folk high school and *Secondary/university* to high school/university. Although the most commonly used SES indicators, e.g., income, education and occupational class, are largely overlapping, they are also likely to be linked to health via partly different mechanisms (Lahelma, Martikainen, Laaksonen, & Aittomäki, 2004; Torssander & Erikson, 2010). Therefore, in the subsequent analyses, we chose to control for both education and occupational class, albeit in separate models.

2.5. Statistical analyses

Due to issues of non-normality, the non-parametric Mann-Whitney U test and the The Kruskal-Wallis H test, with a Bonferroni correction for multiple group comparisons (Dunn, 1964; Laerd Statistics, 2015,

2016), were used to confirm previous findings on the bivariate associations between SES/gender and work environment exposures. Because the distributions of scores were not similar across the compared groups, as assessed by visual inspection, all comparisons refer to differences in mean ranks, where higher ranks indicate greater exposure (Laerd Statistics, 2015, 2016). In order to assess the potential associations between dementia and the five job exposure indicators, we used bivariate logistic regression, because the dependent variable is dichotomous, indicating whether an individual had been diagnosed with dementia prior to, or during, 2012 (Long & Freese, 2006). Logistic regression was hence used in the multivariate analyses as well, and we report odds ratios with 95% CIs. All models were stratified by gender, as the JEM contains separate scales for men and women (see Section 2.3). To facilitate the exploration of potential interaction effects, separate models were computed for each job exposure indicator. Because interaction models differ from additive regression models in the sense that the coefficient of any constitutive term X cannot be interpreted as an un-conditional marginal effect, it is not possible to draw any substantial conclusions based on the estimates shown in the results table. Hence, for the interaction models, we computed, and graphically illustrate, the conditional marginal effect of APOE ε4 at different levels of each work exposure indicator (Brambor, Clark, & Golder, 2006).

3. Results

3.1. Bivariate and descriptive analyses

As expected, significant differences were observed between the different SES groups for all of the five job exposure indicators: control, support, psychological demands, physical demands and job hazards (Table 2a). In general, lower SES corresponded to lower levels of control and psychological demands, but higher physical demands and more exposure to hazardous conditions. Further, men scored significantly higher than women in all these dimensions (Table 2b). With regard to dementia, a significant (negative) association was observed only for work control (OR = 0.76; $p < 0.01$) (Table 2c). A summary of the main occupational categories, stratified by gender, in which control was reported to be high revealed that, among men, occupations such as engineer, private sector manager and academic professional were most common. In contrast, the most common professions among women who reported high control were clerical worker, teacher and public-sector care worker (Table 4).

Table 2

Bivariate analyses of (a) job exposures by SES, (b) job exposures by gender and (c) dementia by job exposure.

JOB EXPOSURE ^a	BC (n = 398) Mean rank	LWC (n = 214) Mean rank	UWC (n = 197) Mean rank	Kruskal-Wallis H Chi ² (df), sig	BC vs. LWC Adj. sig	BC vs. UWC Adj. sig	LWC vs. UWC Adj. sig
Work control	245.4	497.1	627.4	398.9 (2) ***	***	***	***
Psychological demands	328.1	389.9	576.8	151.0 (2) ***	**	***	***
Support	312.4	498.1	490.9	123.5 (2) ***	***	***	ns.
Job hazards	489.4	282.5	367.6	116.1 (2) ***	***	***	***
Physical demands	579.5	178.1	298.9	466.1 (2) ***	***	***	***

JOB EXPOSURE ^{b and c}	Males (n = 222) Mean rank	Females (n = 587) Mean rank	Mann-Whitney U U, sig	Dementia (n = 809) OR [CI]	Sig.
Work control	525.0	359.6	38508.5 ***	0.76 [0.65-0.89]	**
Psychological demands	439.0	392.1	57609.0 ***	0.97 [0.84-1.11]	ns.
Support	551.4	349.6	32649.0 ***	0.86 [0.73-1.02]	ns.
Job hazards	545.9	351.7	33876.0 ***	0.97 [0.82-1.15]	ns.
Physical demands	473.0	379.3	50055.0 ***	1.11 [0.99-1.24]	ns.

Comment: * $p < 0.05$. BC = Blue collar; LWC = Lower white collar; UWC = Upper white collar.

** $p < 0.01$;

*** $p < 0.001$.

3.2. Multivariate analysis

Results from the multivariate analyses are displayed in Table 3, where we report odds ratios with 95% CIs. In Fig. 1 (males) and Fig. 2 (females), we report the results for the interaction models.

A significant relationship between work control and dementia was detected for males (OR = 0.68, i.e., the more work control, the lower risk of dementia), but not for females (OR = 0.92) (Table 3, Model 1). With regard to the interaction models, the APOE ε4-control interaction term was significant among both men and women (Table 3, Model 2). In order to draw the correct substantial conclusions from these models, we computed the conditional marginal effect of APOE ε4 at different levels of control, which confirmed the presence of significant interaction effects. Among males, the estimated effect of APOE ε4 on the probability of dementia was only significant (the CIs did not overlap zero) at lower levels of control. However, at higher levels of control (> mean), the corresponding effect was found to be non-significant (Fig. 1a). The pattern observed among women was directly opposed to that among men. The effect of APOE ε4 was only significant at higher levels of control (Fig. 2a). Finally, for both women and men, these results remained significant when controlling for both occupational class (Model 3) and education (Model 4).

For psychological demands, social support and job hazards (Table 3, Model 1), no significant effects on dementia risk were observed among either men or women. As regards the interaction models, the CIs overlapped zero and/or each other at all levels of the exposure variables (Figs. 1b-d and 2b-d). This held true also with a confidence level of 84% (MacGregor-Fors & Payton, 2013; Payton, Greenstone, & Schenker, 2003) (results not shown here but can be requested from the first author). Additionally, Pseudo R² remained virtually unchanged after inclusion of the interaction terms. Consequently, the presence of interaction effects could not be confirmed in either of the two groups, and we did not proceed to compute models with further adjustments.

For both men and women, the estimated effects of physical demands were non-significant (Table 3, Model 1). For males, no significant interaction effect between support and APOE ε4 was observed (Fig. 1e). For females, the CIs only overlap zero at high levels of physical demands, which indicates that some sort of interaction could exist (Fig. 2e). Further, with a confidence level of 84%, there was a small non-overlap in the effect of APOE ε4 between the highest and lowest level of physical demands (results not shown here but can be requested from the first author). However, the difference in effect was much smaller than for work control, and Pseudo R² remained unchanged after the interaction term was added. Thus, the fully adjusted models were not considered. Finally, drawing on Karasek's (1979) job strain model,

Table 3
Logistic regression for dementia risk. Odds ratios [95% CI].

	Model 1		Model 2		Model 3 ^b		Model 4 ^c	
	Males	Females ^a	Males	Females ^a	Males	Females ^a	Males	Females ^a
CONTROL								
control	0.68* [0.48, 0.97]	0.92 [0.73, 1.15]	0.95 [0.61, 1.46]	0.76 [0.58, 1.00]	0.81 [0.47, 1.40]	0.76 [0.55, 1.06]	0.84 [0.50, 1.39]	0.86 [0.64, 1.17]
apoe	2.35 [0.98, 5.63]	1.82* [1.13, 2.95]	1.56 [0.56, 4.30]	1.88** [1.16, 3.05]	1.55 [0.56, 4.29]	1.88* [1.16, 3.05]	1.93 [0.68, 5.48]	1.96** [1.17, 3.26]
control*apoe			0.37* [0.16, 0.85]	1.88* [1.12, 3.13]	0.37* [0.16, 0.86]	1.88* [1.12, 3.13]	0.39* [0.17, 0.89]	2.02* [1.15, 3.57]
constant	0.09	1.10e-06	0.10	6.60e-07	0.07	7.10e-07	0.07	8.37e-07
Pseudo R ²	0.05	0.13	0.09	0.14	0.09	0.14	0.12	0.14
N	217	536	217	536	217	536	216	517
PSYCHOLOGICAL DEMANDS								
dempsy	0.78 [0.58, 1.05]	1.12 [0.93, 1.36]	0.84 [0.56, 1.25]	1.06 [0.84, 1.34]	–	–	–	–
apoe	2.32 [0.98, 5.53]	1.83* [1.13, 2.95]	2.23 [0.93, 5.37]	1.82* [1.12, 2.94]	–	–	–	–
dempsy*apoe			0.86 [0.48, 1.56]	1.20 [0.79, 1.82]	–	–	–	–
constant	0.09	8.23e-07	0.10	7.96e-07	–	–	–	–
Pseudo R ²	0.04	0.13	0.04	0.14	–	–	–	–
N	217	536	217	536	–	–	–	–
SUPPORT								
support	0.89 [0.55, 1.44]	0.96	1.16 [0.57, 2.35]	0.99	–	–	–	–
apoe	2.08 [0.89, 4.89]	1.81*	1.99 [0.82, 4.79]	1.81*	–	–	–	–
support*apoe			0.53 [0.19, 1.49]	0.89	–	–	–	–
constant	0.10	9.29e-07	0.10	9.70e-07	–	–	–	–
Pseudo R ²	0.02	0.13	0.03	0.13	–	–	–	–
N	216	536	216	536	–	–	–	–
JOB HAZARDS								
hazards	1.20 [0.92, 1.57]	1.22 [0.81, 1.85]	1.15 [0.80, 1.66]	1.40 [0.87, 2.27]	–	–	–	–
apoe	2.18 [0.92, 5.14]	1.81* [1.12, 2.93]	2.12 [0.89, 5.08]	1.86* [1.15, 3.01]	–	–	–	–
hazards*apoe			1.09 [0.64, 1.86]	0.61 [0.25, 1.53]	–	–	–	–
constant	0.10	1.13e-06	0.10	9.88e-07	–	–	–	–
Pseudo R ²	0.03	0.13	0.03	0.14	–	–	–	–
N	217	536	217	536	–	–	–	–
PHYSICAL DEMANDS								
demphys	1.19 [0.96, 1.48]	1.18 [0.99, 1.39]	1.18 [0.89, 1.57]	1.32** [1.07, 1.63]	–	–	–	–
apoe	2.21 [0.93, 5.21]	1.76* [1.09, 2.85]	2.19 [0.91, 5.27]	1.89** [1.16, 3.07]	–	–	–	–
demphys*apoe			1.02 [0.65, 1.59]	0.72 [0.50, 1.03]	–	–	–	–
constant	0.09	1.17e-06	0.09	8.62e-07	–	–	–	–
Pseudo R ²	0.03	0.14	0.03	0.14	–	–	–	–
N	217	536	217	536	–	–	–	–

Comment: **p* ≤ 0.05; ***p* ≤ 0.01; ****p* ≤ 0.001.

^a Adjusted for age (only applicable for women).

^b Adjusted for occupational class.

^c Adjusted for education.

Table 4
Main occupational categories (high/low control) for males and females (%).

	Males	Females
Control > mean^a	Engineers (28.9) Private sector managers/executives (16.7) Academic professionals, e.g., doctors, architects, researchers, lecturers (11.4)	Clerical workers (41.9) Care workers, e.g., nurses, home- and childcare workers (18.1)
Control < mean^b	Craftsmen/mechanics/machine-menders (38.0) Factory-/construction-/dock workers (18.5) Transportation workers, e.g., drivers, railroad workers (9.3)	Teachers (7.6) Retail workers/shop assistants (29.2) Assistant nurses (14.4) Cleaners (8.9)

^a N (males) = 120, N (females) = 315.

^b N (males) = 108, N (females) = 271.

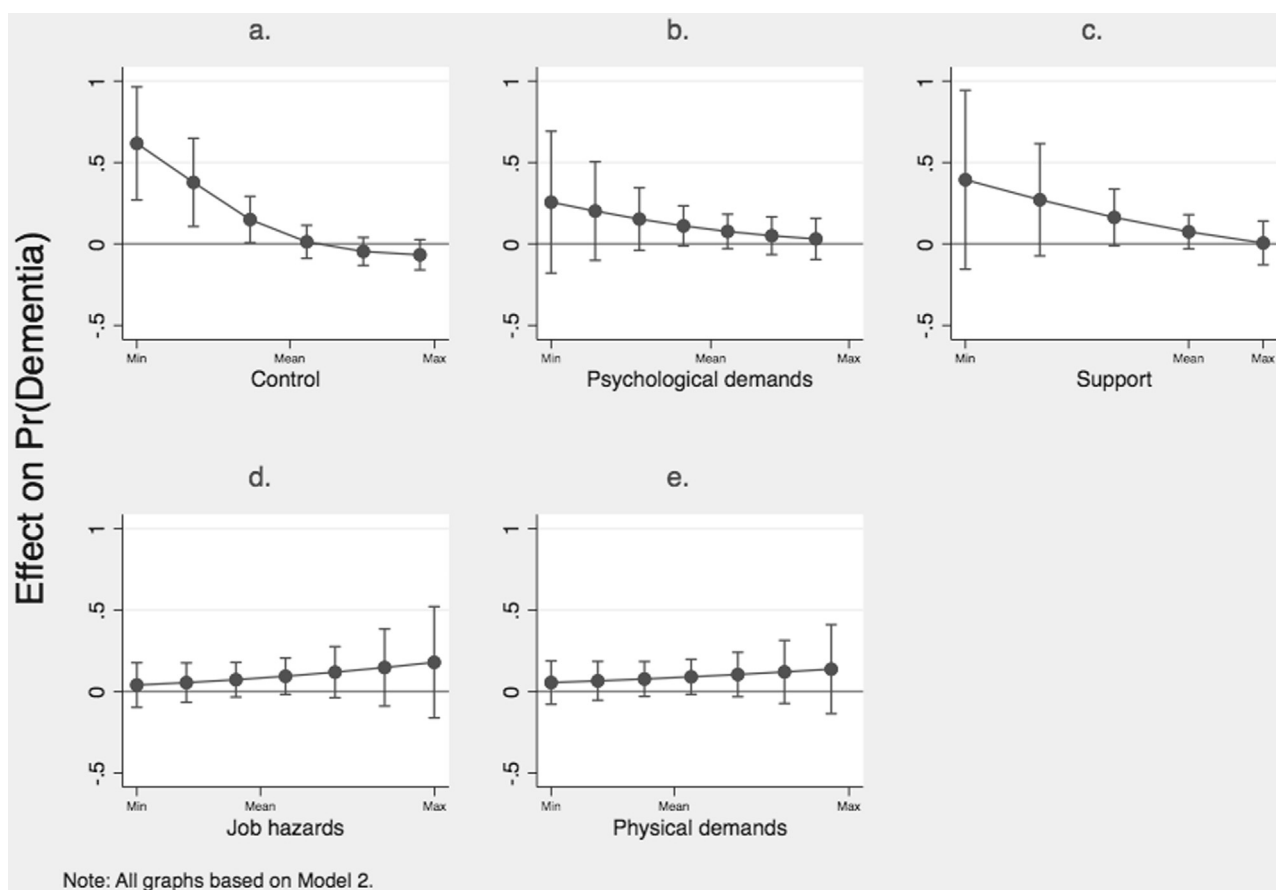


Fig. 1. Conditional marginal effects of APOE $\epsilon 4$ at different levels of (a) control, (b) psychological demands, (c) support, (d) job hazards and (e) physical demands, for males. 95% CIs.

we combined the control and psychological demand variables into continuous strain variable where high values indicate high strain. As this indicator did not reveal any significant results, neither main effects nor interactions, the analyses are not reported here (but can be requested from the first author).

4. Discussion

In the present paper, we investigated whether a number of work environment exposures, all known to be closely related to SES, could moderate the effect of the APOE $\epsilon 4$ allele, which is the major genetic risk factor for dementia. The overall results suggest that work control is the most influential indicator in moderating the effect of the gene variant, although it seems to do so differently among men than among women.

The initial bivariate analyses (Table 2) revealed positive and significant associations between work control and dementia. Further, they confirmed previous research on socioeconomic and gender differences in all of the five work exposure factors, which underlines that the distribution of work-related stressors is closely related to occupational hierarchies as well as to gender segregation in the labour market (Eriksson & Karlsson, 2009; Hall, 1989; Matthews et al., 1998; Rovio et al., 2007; Stansfeld & Candy, 2006; Swedish Work Environment Authority, 2016).

The findings from the multivariate analyses could not corroborate previously detected associations between *physical demands* (Smyth et al., 2004; Stern et al., 1995), *social support* (Andel et al., 2012) and occurrence of dementia. Likewise, no significant effects were observed for *job hazards*. In contrast to the findings of Sindi et al. (2016), yet in line with those of Seidler et al. (2004), high *psychological demands* were

not found to significantly increase the risk of developing dementia late in life.² Moreover, none of these four work exposure characteristics was found to moderate the increased risk of dementia implied by APOE $\epsilon 4$. For high *work control*, on the other hand, the results of our analysis supported previous findings on its protective effect (Andel et al., 2012; Seidler et al., 2004; Wang, Wahlberg, et al., 2012). More specifically, it was revealed that, for men, the estimated effect of APOE $\epsilon 4$ on the probability of dementia was relatively sizeable, but only significant at lower levels of control (approx. increase = 50 per cent) (Fig. 1a). This implies that control could actually moderate the effect of APOE $\epsilon 4$, such that men who carry this gene variant are ‘protected’ if they have held professions in which they could exert control over their own work situation. The pattern observed among women was directly opposed to that among men, indicating that the effect of APOE $\epsilon 4$ was only significant, and again quite sizeable (approx. increase = 50 per cent), at higher levels of control. Finally, for both women and men, these effects remained significant while controlling for both occupational class (Model 3) and education (Model 4). With reference to previously suggested pathological pathways between work exposures and dementia, it is not surprising that work control stands out, at least among men, as the most protective factor. This is the case, we argue, because the control indicator derived from the JEM includes two separate components: skill discretion and decision authority (Van der Doef & Maes, 1999), both of which could be related to the main pathological mechanisms proposed in the literature as well as to other known risk

² The lack of significant associations in this respect could possibly be attributed to the fact that the indicator of psychological demands found in the JEM is ‘weaker’ (constructed from two items only) than, e.g., the one assessing control (12 items).

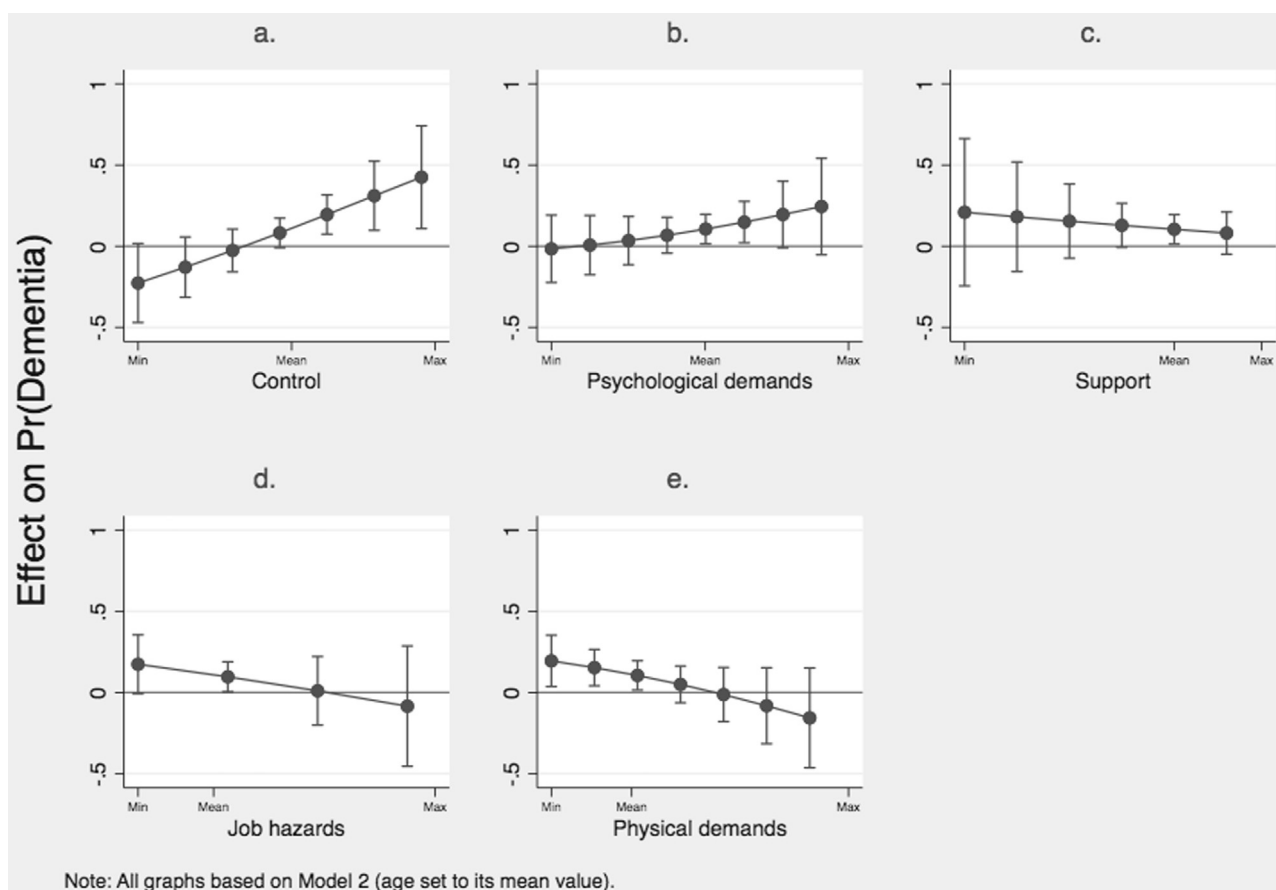


Fig. 2. Conditional marginal effects of APOE $\epsilon 4$ at different levels of (a) control, (b) psychological demands, (c) support, (d) job hazards and (e) physical demands, for females. 95% CIs.

factors. First, the control indicator includes items such as ‘possibility of learning new things’ and ‘variation in task content’, which, in line with the *cognitive reserve hypothesis* (Stern, 2002, 2012), are likely to provide intellectual stimulation that could improve the brain’s resilience to degenerative changes (Qiu et al., 2009; Then et al., 2017). Second, it comprises items such as ‘influence over the planning of work’ and ‘flexible working hours’, i.e., factors that could reduce stress and, consequently, the occurrence of cardiovascular risk factors (Kivimäki et al., 2002; Kivipelto et al., 2001; Skoog et al., 1996; Theorell et al., 2016; Vrijkotte et al., 2000) and/or augmented glucocorticoid hormone levels (Bremner, 2006; Dong et al., 2004; Green et al., 2006; Lupien et al., 1999; Sapolsky, 1996). Finally, lack of work control is a known risk factor for depressive symptoms (for a review, see; Theorell et al., 2015), which in turn is hypothesized increase dementia risk (Livingston et al., 2017; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Interpreting the interaction model for women is less straightforward, although a few things are clear at this stage. First, ‘male’ high control jobs are likely to be very different from ‘female’ high control jobs, especially in previous generations. In the present sample, human service workers make up a large proportion of the women in the ‘high control’ group’ (see Table 4). According to previous findings, affective and stress related disorders are particularly common in such professions (Johnson et al., 2005; Stansfeld et al., 2011; Wieclaw et al., 2006). However, reportedly important stressors contributing thereto, e.g., emotional demands, are not included in the JEM. It is thus possible that even though these women were exposed to certain favourable workplace conditions, they were also exposed to unmeasured negative ones. By extension, this could explain why they actually seem to be ‘worse off’ compared to their low control counterparts. Finally, for women, the ‘double burden’ of professional and domestic engagements could cause

a sort of role strain that adversely affects health. Given historical differences in the gendered division of labour, it is reasonable to assume that the women in the present sample (born in or before 1930) may have encountered more traditionalist expectations on themselves as women. Thus, even if they worked full-time in a professional occupation, they might still have been expected to shoulder the main responsibility for childcare and domestic chores. Ultimately, this would result in a greater total workload and hence in elevated stress levels (Arber et al., 1985; Floderus et al., 2009; Hall, 1992; Krantz et al., 2005). Naturally, the present study has a number of limitations. For reasons related to selective survival/mortality, it is often preferable to use years-to-diagnosis as the dependent variable, but such a design was not chosen because differences in ‘age when diagnosed’ exist between cohorts in the present sample. Instead, we measured dementia at one specific point in time. This choice also maximized the number of cases, which was important because the number of dementia cases was relatively small. Owing to the small number of cases, we did not distinguish between dementia subtypes. This is a significant limitation in the sense that APOE $\epsilon 4$ is generally considered to be a major risk factor for AD, while for other dementia subtypes, associations are less well-established. However, AD is the most common form of dementia, accounting for approximately 50–70 per cent of all cases, and recent studies suggest that the $\epsilon 4$ allele could also be associated with other forms of dementia such as VaD, which is the second most common form (Liu et al. 2012; Rohn, 2014). Finally, information on lifetime occupation was collected retrospectively, which is a potential source of measurement uncertainty.

5. Conclusions

The present study suggests that work control is the most influential indicator in moderating the effect of the *APOE* $\epsilon 4$ allele on dementia, although it seems to do so differently among men than among women. While holding a high control profession appears to ‘protect’ men, in the sense that it buffers the increased risk implied by the gene variant, the opposite pattern was observed for women. These findings not only underscore the importance of considering interactions between social and genetic risk factors in better understanding multifactorial diseases such as dementia. They also highlight that factors which are more ‘proximate’ to the individual, such as work environment characteristics, must not be studied as if distinct from the underlying systems that ‘put [] people at risk of risks’ (Link & Phelan, 1995, p. 80), e.g., gender- and class-based inequities. In line with this, we encourage intersectional studies targeting the potential health-effects of job exposures other than those examined here, as well as home-work interactions and historical changes in work content.

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The authors confirm that all funding sources have been acknowledged and that none of them were involved in: 1) the design of the study, 2) the collection, analysis and interpretation of data or 3) writing the manuscript.

Conflict of interest statement

The authors have no conflicting interests to report.

Statement of ethical approval

Informed consent was acquired from all participants or their relatives. The regional Ethical Review Board for medical research in Gothenburg, Sweden approved the H70/PPSW examination waves in 2000 (ref: Ö402-99), 2004 (ref: T453 04) and 2009 (ref: 075-09).

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