AGING & MENTAL HEALTH
https://doi.org/10.1080/13607863.2018.1531368

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The impact of social networks and *APOE* ε4 on dementia among older adults: tests of possible interactions

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ABSTRACT

Objectives: Emerging evidence suggests that social networks may protect against the development of dementia among older adults. In this study we analysed the association between social networks, the apolipoprotein E (*APOE*) ε4 allele, and dementia. We also investigated whether there were gender-specific patterns in this respect.

Method: The analyses used population-based longitudinal data from Gothenburg, Sweden: the *H70 Birth Cohort Study* and the *Prospective Population Study on Women* (PPSW). A total of 580 individuals born in 1930 underwent semi-structured neuropsychiatric examinations in 2000–2001. Follow-up examinations were carried out in 2005–2006 and 2009–2010. The timing of dementia onset was analysed using Cox proportional hazards regression.

Results: The presence of the *APOE* ε4 allele affected the risk of developing dementia in both genders. Among women, distant social networks had a protective effect on dementia, while among men the significant associations between close social networks and dementia did not remain after controlling for covariates. Significant interactions between social networks and the *APOE* ε4 allele were not found.

Conclusion: Strong social networks do not seem to moderate the increased risk of dementia implied by the *APOE* ε4 allele. Nevertheless, our results underline the importance of strong social networks in postponing dementia onset and indicate that their impact may differ among men and women.

ARTICLE HISTORY
Received 15 February 2018
Accepted 30 September 2018

KEYWORDS
Social networks; *APOE* ε4; dementia; gender; longitudinal study

Introduction

Are lonely people more likely to develop dementia? Conversely, can strong social networks protect individuals from developing dementia and reduce the impact of genetic risk factors? In this article we analyse the association between social networks, the apolipoprotein E (*APOE*) ε4 allele, and dementia. The question of interest is whether the impact of this well-known genetic risk factor could be reduced by the existence of strong social networks.

The APOE *ε4 allele and dementia*

Dementia is a formidable public health problem with an estimated prevalence of 6.2 percent among adults older than 60 years in Europe (Martínez et al., 2016). The most common form of dementia is Alzheimer's disease. The *APOE* ε4 allele accounts for a large share of the genetic risk in sporadic Alzheimer's disease (Blennow, de Leon, & Zetterberg, 2006; Corder et al., 1993; Poirier et al., 1993; Raber, Huang, & Ashford, 2004). Its effect on dementia is mediated by Alzheimer neuropathology (Mortimer, Snowdon, & Markesbery, 2009; Wang et al., 2012), and cerebral amyloid β pathology in particular (Jansen et al., 2015). Recent studies have further suggested that the *APOE* ε4 allele is also a genetic risk factor (albeit a weaker one) for other forms of dementia, such as vascular dementia (Liu et al., 2012; Martínez et al., 2017; Rohn, 2014) and dementias with synucleinopathy (Martínez et al., 2017; Tsuang et al., 2013), even if it is not settled to which degree such associations exist since patients with these disorders have concomitant cerebral amyloid β pathology (Lim et al., 1999; Lopez et al., 2002; Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study, 2001). However, not all people carrying the *APOE* ε4 allele develop Alzheimer's disease or dementia, whereas some people without the *APOE* ε4 allele do (Blennow, Hampel, Weiner, & Zetterberg, 2010; Blennow et al., 2006; Prince, Zetterberg, Andreasen, Marcusson, & Blennow, 2004). By extension, this might imply the existence of social and environmental characteristics that could either 'buffer' or 'trigger' the harmful effects of this genetic risk factor (Rizzuto & Fratiglioni, 2014).

The different dimensions of social networks

The complexity of an individual's social network is difficult to capture. Kahn and Antonucci (1980) identified three

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Table 1. Characteristics of the study population, *n* (%).

Characteristics	All *n* (%)	Men *n* (%)	Women *n* (%)
Gender			
Men	224 (39.72)		
Women	340 (60.28)		
Cohabiting	365 (65.18)	177 (79.02)	188 (55.95)
Socio-economic status			
Blue collar	229 (43.43)	89 (39.91)	140 (46.20)
Lower white collar	139 (26.48)	31 (13.90)	108 (35.64)
White collar and self-employed	158 (30.10)	103 (46.19)	55 (18.15)
Education			
Primary	340 (60.82)	125 (56.05)	215 (63.99)
Lower secondary	118 (21.11)	39 (17.49)	79 (23.51)
Secondary/university	101 (18.07)	59 (26.46)	42 (12.50)
Presence of APOE ε4	151 (28.17)	62 (28.44)	89 (27.99)
Diagnosed with dementia 2000–2012	53 (19.40)	22 (9.82)	31 (9.12)

dimensions of social networks: (1) structure, which includes network size, proximity and frequency of contact; (2) function, which refers to the exchange of different kinds of support between network members; and (3) subjective evaluations of quality, which provide insight into individuals' experiences of their networks (Fiori, Smith, & Antonucci, 2007). Furthermore, social networks among men and women vary across the life span (Glass, de Leon Mendes, Seeman, & Berkman, 1997). In general, women have larger and more diverse social networks than men (Ajrouch, Blandon, & Antonucci, 2005), as well as a wider range of sources for emotional support (Fuhrer & Stansfeld, 2002). There are a number of studies focusing on the potentially positive effect of having strong social networks on decreasing the risk of dementia (Amieva et al., 2010; Anme et al., 2013; Beland, Zunzunegui, Alvarado, Otero, & del Ser, 2005; Crooks, Lubben, Petitti, Little, & Chiu, 2008; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Kuiper et al., 2015, 2016; Zunzunegui, Alvarado, del Ser, & Otero, 2003). For instance, structural aspects of social networks, such as larger network size (James, Boyle, Buchman, Barnes, & Bennett, 2011; Saczynski et al., 2006) and higher frequency of social contact (Crooks et al., 2008; Gureje et al., 2011; Saczynski et al., 2006; Scarmeas et al., 2001), have been found to decrease the risk of developing the disease. As to the quality of social networks, previous studies show divergent results. Amieva et al. (2010) reported an association between low satisfaction with social networks and incident dementia, while a meta-analysis by Kuiper et al. (2015) concluded that there was no association between these variables.

In general, the size of an individual's network reflects his/her possibility to receive emotional and material support. A variety of behavioural, psychological, and physiological mechanisms have thus been investigated to explain the above-mentioned effects of social networks on dementia risk (Fratiglioni, Paillard-Borg, & Winblad, 2004; Qiu, Xu, & Fratiglioni, 2010). First, the support and intellectual stimulation provided by social networks is hypothesized to have a positive impact on the individual's emotional state by, for instance, reducing stress (Fratiglioni et al., 2004) which in turn has been suggested to decrease disease susceptibility (Andel et al., 2012; Johansson et al., 2010, 2013), possibly because of its inverse relationship with vascular disorders and other risk factors linked to dementia and Alzheimer's disease (Kivipelto et al., 2001, 2002; Launer et al., 2000; Skoog & Gustafson, 2002). Second, in line with the *cognitive reserve hypothesis,* the intellectual stimulation provided by social interaction is thought to impede degenerative brain changes by improving resilience and compensatory abilities in the neuronal networks (Kuiper et al., 2015; Stern, 2002, 2012).

Social networks and the APOE ε4 allele

As discussed above, the impact of the *APOE* ε4 allele on dementia onset is well established and there are several studies that have investigated the relationship between social networks and the risk of developing dementia. However, studies that jointly examine the influence of the *APOE* ε4 allele and social networks are scarce (Heser et al., 2014; Saczynski et al., 2006; Salinas et al., 2017). Furthermore, to our knowledge there are relatively few studies that explicitly examine the possible interaction effect between aspects of social networks and genetic risk factors on the development of dementia. Among those, neither Brenowitz, Kukull, Beresford, Monsell, and Williams (2014), who investigated the incidence of mild cognitive impairment, nor Zuelsdorff et al. (2013), who examined a sample of individuals with a family history of AD, could verify interactions between aspects of social relationships and the *APOE* ε4 allele. In contrast, Poey, Burr, and Roberts (2017) found that living arrangements and perceived social support could moderate the association between the *APOE* ε4 allele and cognitive function. Moreover, Niti, Yap, Kua, Tan, and Ng (2008) found that different kinds of leisure activities (including social activities) protected against cognitive decline and that the protective impact was particularly strong among individuals carrying the *APOE* ε4 allele.

The overarching aim of the study was to analyse the association between social networks, the *APOE* ε4 allele and dementia. Special attention was paid to the question of whether strong social networks could moderate the effect of the *APOE* ε4 allele on dementia and, additionally, whether gender specific patterns existed in this respect.

Data and operationalisation

Participants

The analyses are based on data from the *H70 Birth Cohort Study* and the *Prospective Population Study on Women* (PPSW), both conducted in Gothenburg, Sweden. All participants in the study were sampled from the Swedish population register and systematically selected on the basis of birth dates. Both persons living in private households and in residential care were included. The present analyses were based on a sample of 580 individuals born in 1930, all living in Sweden on 1 September 2000. When studying the relation between social networks and cognitive decline, the possibility of reverse causality needs to be taken into consideration (Kuiper et al., 2016). In order to minimize the possibility of such bias, respondents with cognitive impairments or dementia at baseline were excluded from the analysis (Amieva et al., 2008, 2010; Kuiper et al., 2015, 2016; Pillai & Verghese, 2009; Starkstein, Petracca, Chemerinski, & Kremer, 2001), leaving a total sample of 564 respondents. Information on the presence/absence of the *APOE* ε4 allele was available for 536 of these individuals. Follow-up examinations were carried out in 2005–2006 (n = 443) and in 2009–2010 (n = 368). Informed consent was obtained from all participants or their relatives, and

Table 2. Background information on social network variables, *n* (%).

	All *n* (%)	Men *n* (%)	Women *n* (%)
Do you have an intimate person with whom you can talk about anything?			
Yes, spouse	184 (34.85)	109 (52.40)	75 (23.44)
Yes, child	59 (11.17)	10 (4.81)	49 (15.31)
Yes, relative	17 (3.22)	4 (1.92)	13 (4.06)
Yes, friend	65 (12.31)	22 (10.58)	43 (13.44)
Yes, another person	3 (0.57)	2 (0.96)	1 (0.31)
Yes, combination	153 (28.98)	45 (21.63)	108 (33.75)
No	47 (8.90)	16 (7.69)	31 (9.69)
Do you have more than one intimate person?			
Yes	320 (62.38)	104 (51.49)	216 (69.45)
No	193 (37.62)	98 (48.51)	95 (30.55)
Do you and your neighbours visit each other to say hello?			
Yes, often	41 (7.85)	13 (6.28)	28 (8.89)
Yes, sometimes	280 (53.64)	118 (57.00)	162 (51.43)
No, never	201 (38.51)	76 (36.71)	125 (39.68)
Do you stop and talk with your neighbours when you meet?			
Yes, often	308 (58.67)	125 (60.39)	183 (57.55)
Yes, sometimes	200 (38.10)	73 (35.27)	127 (39.94)
No, never	17 (3.24)	9 (4.35)	8 (2.52)
Do you think you have enough, too much, or too little contact with your neighbours?			
Too much	0 (0)	0 (0)	0 (0)
Enough	487 (92.94)	190 (91.35)	297 (93.99)
Too little	37 (7.06)	18 (8.65)	19 (6.01)
How often do you receive visits from or visit people other than your children or neighbours?			
Every day	12 (2.28)	4 (1.93)	8 (2.51)
At least once per week	124 (23.57)	63 (30.43)	61 (19.12)
Once per week/once per month	206 (39.16)	69 (33.33)	137 (42.95)
Once per month/once per quarter	126 (23.95)	48 (23.19)	78 (24.45)
Less than once per quarter	39 (7.41)	17 (8.21)	22 (6.90)
Never	19 (3.61)	6 (2.90)	13 (4.08)
Do you think you have enough, too much, or too little contact with people other than your children or neighbours?			
Too much	1 (0.19)	0 (0)	1 (0.31)
Enough	460 (87.45)	180 (86.54)	280 (88.05)
Too little	65 (12.36)	28 (13.46)	37 (11.64)

the study was approved by the regional Ethics Review Board for medical research in Gothenburg (Skoog et al., 2015). A more detailed description of the full baseline sample can be found in previous studies (see Karlsson et al., 2009, 2010). Table 1 shows the characteristics of the study population.

Neuropsychiatric examinations, diagnoses, and genotyping

Clinical examinations were conducted at an outpatient department or in the participant's home and included comprehensive social, functional, physical, neuropsychiatric and neuropsychological examinations. Semi-structured neuropsychiatric examinations were performed by trained psychiatric research nurses. These examinations included ratings of common symptoms and signs of dementia (e.g. assessments of memory, orientation, general knowledge, apraxia, visuospatial function, understanding proverbs, following commands, naming ability and language) and has been described in detail previously (Guo et al., 2007; Skoog, Nilsson, Palmertz, Andreasson, & Svanborg, 1993). Close informant interviews were also performed as part of the clinical examinations. These interviews were semi-structured and contained questions about 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 both on symptoms rated during the neuropsychiatric examinations and on information from the close informant interviews. A more detailed description of the diagnostic procedures can be found in previous studies (see Guo et al., 2007; Skoog et al., 1993). For participants lost during follow-up, incident dementia cases (until 2012) were diagnosed based on information from medical records, and evaluated by geriatric psychiatrists, or from the Swedish Hospital Discharge Register (Guo et al., 2007). Information about the age of dementia onset was gathered from the Swedish Hospital Discharge Register, the neuropsychiatric examinations, or the close informant interviews. Blood samples were collected to establish genotyping for the single nucleotide polymorphisms (SNPs) rs7412 and rs429358 in *APOE* (gene map locus 19q13.2) using a KASPar® PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK), or by mini-sequencing (Blennow et al., 2000). Genotype data for these two SNPs were used to define ε2, ε3, and ε4 alleles. Statistical analyses focused upon ε4 as this is the only allelic variant clearly associated with and increased risk of Alzheimer's disease.

Assessment of social networks

Since the *H70/PPSW studies* did not include questions relating to functions of social networks (specifically support and reciprocity) during 2000–2001, the respondents were only asked about the structure and quality of their social networks (Table 2). With regard to structure the questions included the number of intimate person(s) as well as the frequency of visits to and from neighbours, greeting neighbours, and visits to and from acquaintances. Regarding network quality, the questions focused on whether the levels of contact with neighbours and acquaintances were perceived as satisfactory. Here we excluded the variables

Table 3. Factor loadings of the seven manifest indicators on the two factors representing social networks at baseline.

Variable	Factor 1 (distant social networks)	Factor 2 (close social networks)	Uniqueness
Intimate(s) (1)	0.241	0.839	0.238
Intimate(s) (2)	0.019	0.823	0.322
Neighbours (1)	0.612	0.092	0.617
Neighbours (2)	0.522	0.298	0.639
Neighbours (3)	0.682	0.184	0.501
Acquaintances (1)	0.586	0.133	0.639
Acquaintances (2)	0.737	0.176	0.426

Extraction method: Principal-factor. Rotation: Varimax orthogonal.

Abbreviations: Intimate(s) (1): Do you have an intimate person with whom you can talk about anything? Intimate(s) (2): Do you have more than one intimate person? Neighbours (1): Do you and your neighbours visit each other to say hello? Neighbours (2): Do you stop and talk with your neighbours when you meet? Neighbours (3): Do you think you have enough contact with your neighbours? Acquaintances (1): Do you think you have enough contact with people other than your children or neighbours? Acquaintances (2): Do you receive visits from or visit people other than your children or neighbours?

about family (e.g. contacts with children and grandchildren) for two reasons. First, the beneficial association between social networks and survival among older people might be restricted to relationships with friends and confidants rather than those with children and relatives (Giles, Glonek, Luszcz, & Andrews, 2005; Rizzuto & Fratiglioni, 2014). Moreover, it is common for childless old people to have more contact with friends and relatives (Albertini & Kohli, 2009; Deindl & Brandt, 2017). Second, since around 13 percent of the respondents reported that they had no children, information on the frequency and satisfaction of contact with children was missing for a large part of the study population. Consequently, these questions were not included in the factor analysis (see below); instead, 'have no child/childless' was added as a control variable.

Covariates

The socio-demographic variables (cohabiting, childlessness, occupational class, and education) were considered as potential confounding factors and controlled for in the analyses. The 'cohabiting' variable indicated whether an individual was either married or living together with someone without being formally married. Information on occupational class was recoded in accordance with the Swedish SEI standards for socioeconomic classification (MIS, 1982:4). Three socio-economic groups were categorized: *blue collar*, *lower white collar*, and *white collar and self-employed*. *Blue collar* corresponded to manual workers (unskilled, semi-skilled, and skilled). *Lower white collar* corresponded to assistant, non-manual employees, with or without subordinates, in occupations requiring a maximum of three years of post-comprehensive schooling. *White collar and self-employed* included intermediate/higher non-manual workers and professionals in occupations requiring three to six years of post-comprehensive education, as well as upper-level executives, self-employed persons, and farmers. In the present study, which was based on a sample gathered in an urban area, only one respondent reported 'farmer' to be their main occupation. Educational attainment was classified as *primary*, *lower secondary*, and *secondary/university*, based primarily on information obtained from the clinical examination in 2000–2001. *Primary* corresponded to elementary school/vocational school, *lower secondary* to girls' school/junior secondary school/folk high school, and *secondary/university* to high school/university. A more detailed description of the covariates can be found in the literature (see Hasselgren et al., 2018). While education and occupational class are often highly correlated, it has been suggested that these indicators could be linked to health via partly different mechanisms (Lahelma, Martikainen, Laaksonen, & Aittomaki, 2004; Torssander & Erikson, 2010). Additionally, while some studies propose that occupational class is associated with dementia only when education is not taken into account (Evans et al., 1997; Fratiglioni & Wang, 2007; Karp et al., 2004), others found that these variables have separate effects (Sattler, Toro, Schönknecht, & Schröder, 2012). Consequently, we controlled for occupational class and education separately in our models.

Statistical methods

Four of the seven social network variables were recoded as binary. The number of intimate persons was dichotomized on the basis of the question: 'Do you have an intimate person with whom you can talk about anything?' (Table 2). The responses 'yes, spouse', 'yes, child', 'yes, relative', 'yes, friend', 'yes, another person', 'yes, combination' were coded as 'yes', while 'no' was coded as 'no'. The quality of contact with neighbours and people other than children or neighbours was dummy coded into 'yes' or 'no' on the basis of the questions: 'Do you think you have enough, too much, or too little contact with your neighbours/people other than your children or neighbours?' (Table 2). The response 'enough' was coded as 'yes', to indicate satisfaction, while 'too little' and 'too much' were coded as 'no' to reflect dissatisfaction. Due to overlapping response alternatives, the quantity of contact with people other than children or neighbours was dichotomized on the basis of the question: 'How often do you receive visits from or visit people other than your children or neighbours?' (Table 2). The responses 'every day', 'at least once per week', 'once per week/once per month', 'once per month/once per quarter', and 'less than once per quarter' were coded as 'yes', while 'never' was coded as 'no'.

Exploratory factor analysis was performed in order to identify potential latent constructs in the data and hence enable a better conceptual understanding of correlations among the seven social network variables (Fabrigar et al., 1999). In our study as all seven manifest variables were categorical (binary or ordinal scale) we began by computing a polychoric correlation matrix which is suitable for factor analysis with discrete data (Kolenikov & Angeles, 2004). From this matrix, two factors were retained (both with

eigenvalues >1). Furthermore, following Ledesma, Valero-Mora, and Macbeth (2015), we also took the factor loadings, the percentage of variance accounted for by the factors, and the factors' theoretical interpretability into consideration in the selection process. The first retained factor could be defined as *presence of one or more intimate person(s)* (close social networks) and the second as *frequency of, and satisfaction with, contact with neighbours and acquaintances* (distant social networks). The factors were rotated using varimax orthogonal rotation, and accordingly constrained from being correlated (Table 3). Subsequently, the factor scores were saved as covariates in the regression; for ease of interpretation, they were standardized to have a mean of zero and a standard deviation of one.

The timing of dementia onset was estimated using Cox regression (Guo, 2010, p. 73). The continuous component of the dependent variable measured years-at-risk for dementia from baseline (i.e. from age 70) while the dichotomous component indicated whether the participant had developed dementia during the study period (up to 2012). The Cox proportional hazards model is a distribution-free model which assumes that the hazard for any individual in a sample is a fixed proportion of the hazard for any other individual; that is, that the ratio of the two hazards is constant over time (Guo, 2010, pp. 73–75). A post-estimation test based on Schoenfeld residuals was conducted for all models in order to assess the proportionality of hazards (Allison, 2014). The tests showed no signs of violations (test statistics not shown here but can be requested from the first author). The analysis was conducted using partial-likelihood estimation in version 14.0 of the Stata software package (Stata Corp LP, College Station, TX). We report hazard ratios and 95 percent confidence intervals, and also mark 0.01 and 0.05 significance levels for two-tailed test for the variables included.

Analytic approach

Our analysis began by testing the basic bivariate associations between the *APOE* ε4 allele and the risk of dementia, and by examining whether weak social networks were associated with increased risk of dementia. As expected (see Table 4), gender differences were observed in this respect. Even though no significant interaction between gender and social networks could be detected in the full sample, presumably due to lack of power, the observed tendency of a difference was similar to that revealed in the stratified analyses (results not shown here but can be requested from the author). Thus, in the continued analysis, we presented separate results for men and women in addition to those obtained from the full sample. In the second step, we analysed whether the expected positive association between dementia and social networks remained after controlling for the effect of the *APOE* ε4 allele. Finally, we explored whether strong social networks could 'buffer' the negative effect of the *APOE* ε4 allele. Our main focus was on this final analysis, and we hypothesized that strong social networks would decrease the impact of the *APOE* ε4 allele on the risk of dementia. Thus, we assumed that the negative effect of the *APOE* ε4 allele on dementia would be lower among individuals with strong social networks.

Table 4. Bivariate analysis between social networks, *APOE* ε4, and dementia.

	All	Men	Women
Close social networks	0.781*	0.678*	0.869
	[0.621–0.981]	[0.483–0.952]	[0.631–1.197]
Distant social networks	0.760*	0.861	0.683*
	[0.593–0.974]	[0.580–1.279]	[0.493–0.946]
APOE ε4	2.327**	2.087	2.522*
	[1.334–4.059]	[0.879–4.954]	[1.217–5.225]

*$p < 0.05$, **$p < 0.01$.

Results

Table 4 shows the bivariate relationships between social networks (close and distant), the *APOE* ε4 allele, and dementia. In the total sample, close and distant social networks were negatively associated with dementia (HR = 0.781, 95% CI = [0.621–0.981]; HR = 0.760, 95% CI = [0.593–0.974]), whereas the *APOE* ε4 allele had a positive relationship with dementia (HR = 2.327, 95% CI = [1.334–4.059]). Close social networks were significantly associated with dementia among men (HR = 0.678, 95% CI = [0.483–0.952]), while distant social networks had a significant relationship with dementia among women (HR = 0.683, 95% CI = [0.493–0.946]). The risk of developing dementia was more than double among carriers of the *APOE* ε4 allele compared to non-carriers. However, the estimated effect was only significant in the total sample and among women.

Table 5 shows Cox regression models for the impact of the *APOE* ε4 allele, social networks, and their interaction on dementia in the total sample as well as among men and women, respectively. Models 1-3 gave estimates for close social networks. With regards to the total sample, the estimates for close social networks were statistically significant except in Model 2, and the hazard ratios for the *APOE* ε4 allele were above 2. Among men, the estimate for close social networks was significant only in Model 1, but none of the estimates for the *APOE* ε4 allele was found to be significant. Among women, the hazard ratios for close social networks were non-significant. The *APOE* ε4 allele, on the other hand, had a strong effect with estimated hazard ratios above 2.7. The estimates for the interaction effects were non-significant in all groups (Model 3).

Models 4-6 gave the corresponding estimates for distant social networks. While the *APOE* ε4 allele had a strong effect with estimated hazard ratios above 2, the estimates for distant social networks in the total sample were non-significant. Among men, there were no significant effects found for distant social networks. This held true also for the effect of the *APOE* ε4 allele. Among women, a strong distant social network had an inverse relationship with dementia in all three models. Increasing the distant social network index by one standard deviation decreased the hazard rate by about one third. Meanwhile, the *APOE* ε4 allele had estimated hazard ratios above 3 in model 4. The estimates for the interaction effects were again non-significant in all groups (Model 6).

In order to draw the correct substantial conclusions from the interaction models (models 3 and 6) we also computed and compared the marginal effects of *APOE* ε4 allele at different values for social networks (Brambor, Clark, & Golder, 2006). However, no such effects were detected (results not shown here but can be requested from the first

Table 5. Cox regression models for the impact of social networks and *APOE* ε4 on dementia.

		All	Men	Women
Model 1[a]	Close social networks	0.778* [0.617–0.981]	0.684* [0.475–0.987]	0.855 [0.618–1.181]
	APOE ε4	2.345** [1.279–4.299]	1.599 [0.616–4.148]	3.064** [1.356–6.921]
	N	452	192	260
Model 2[b]	Close social networks	0.831 [0.656–1.054]	0.757 [0.518–1.105]	0.910 [0.659–1.257]
	APOE ε4	2.315** [1.296–4.134]	2.023 [0.791–5.172]	2.780** [1.317–5.865]
	N	477	191	286
Model 3[c]	Close social networks	0.688* [0.500–0.946]	0.605 [0.357–1.025]	0.733 [0.485–1.110]
	APOE ε4	2.388** [1.333–4.278]	1.778 [0.663–4.774]	2.765** [1.305–5.858]
	Close social networks**APOE* ε4	1.322 [0.846–2.064]	1.239 [0.626–2.454]	1.484 [0.778–2.833]
	N	479	193	286
Model 4[a]	Distant social networks	0.808 [0.618–1.056]	0.999 [0.625–1.598]	0.653* [0.468–0.911]
	APOE ε4	2.418** [1.327–4.407]	1.890 [0.751–4.762]	3.159** [1.404–7.105]
	N	452	192	260
Model 5[b]	Distant social networks	0.813 [0.624–1.059]	0.921 [0.572–1.484]	0.695* [0.507–0.952]
	APOE ε4	2.357** [1.325–4.195]	2.148 [0.853–5.411]	2.897** [1.375–6.102]
	N	477	191	286
Model 6[c]	Distant social networks	0.843 [0.568–1.252]	1.016 [0.512–2.017]	0.730 [0.446–1.195]
	APOE ε4	2.221** [1.245–3.960]	1.845 [0.745–4.571]	2.649* [1.229–5.710]
	Distant social networks**APOE* ε4	0.900 [0.536–1.513]	0.968 [0.384–2.436]	0.844 [0.446–1.598]
	N	479	193	286

[a]Adjusted for cohabiting, childlessness, and socio-economic status.
[b]Adjusted for cohabiting, childlessness, and education.
[c]Not adjusted for covariates.
*$p < 0.05$, **$p < 0.01$.

author). We also tested the inclusion of confounders in the interaction models, but the results did not change in any substantial way.

Discussion

The aim of this study was to examine whether social networks and the *APOE* ε4 allele were associated with dementia onset. Special attention was paid to the question of whether strong social networks could moderate the effect of the *APOE* ε4 allele on dementia and, additionally, whether gender specific patterns existed in this respect.

As expected, and in line with previous research, we found that individuals carrying the *APOE* ε4 allele had an increased risk of developing dementia (e.g. Blennow et al., 2006; Corder et al., 1993; Mortimer et al., 2009; Poirier et al., 1993; Raber et al., 2004; Skoog et al., 2015; Wang et al., 2012). Moreover, we observed that the impact of the *APOE* ε4 allele on dementia increased in the total sample and among women, after controlling for all covariates, including occupational class and education, which might imply that these factors moderate its effect (Ferrari et al., 2013; Hasselgren et al., 2018; Rizzuto et al., 2016). For men, the slightly lower estimate for the *APOE* ε4 allele (approximately 1.6 and 2.2 in the multivariate analysis) could possibly reflect a selection bias, as white-collar and self-employed respondents were over-represented in our male sample (n = 103, 46.19%). Previous findings suggesting that high socio-economic status reduces the risk of dementia related to the *APOE* ε4 allele among men (Hasselgren et al., 2018) may therefore partially explain our results. Furthermore, the *APOE* ε4 allele estimates were consistently statistically non-significant for men, which could be explained by the combination of a smaller sample size and the fact that the coefficient was smaller. However, as pointed out by Ziliak and McCloskey (2008), it is important also to take into account the estimate size when interpreting results. Thus, it is worthwhile to draw attention to the fact that the coefficients for the *APOE* ε4 allele were above 2 for both genders in the bivariate analysis. This means that among women and men, the hazard rate of *APOE* ε4 carriers in the sample was twice as high as that of non-carriers, which is in agreement with earlier studies (Ganguli et al., 2000; Kivipelto et al., 2008; Skoog et al., 2015). It is also likely that the effect size for the *APOE* ε4 allele would have been higher for individuals with Alzheimer's disease, or positive for cerebral amyloidosis.

We chose to distinguish between close and distant social networks. In line with earlier results (Caetano, Silva, & Vettore, 2013; McLaughlin, Vagenas, Pachana, Begum, & Dobson, 2010), our bivariate analyses in Table 4 indicated that there could be gender-specific patterns in the effect of social networks on dementia among older adults. Previous studies have pointed out that older women have more confidants, while older men rely mainly on their spouses for emotional intimacy (Bildtgård & Öberg, 2017; McLaughlin et al., 2010). This is also in line with studies of bereavement that show spousal loss emotionally affects men more than women, while women suffer more economically (Halleröd, 2013). It has also been shown that although women generally have larger networks and more close friends compared to men, women also to a higher extent report that they are lonely and perceive loneliness as a problem (Halleröd, 2009; Halleröd & Seldén, 2013).

Our bivariate analysis in Table 4 and multivariate analysis in Table 5 showed that close and distant social networks had an inverse relationship with dementia in the total sample, which generally supported the main assumption that weak social networks are associated with an increased risk of dementia. Thus, in line with previous findings, the present study indicates that strong social networks may have a positive influence on cognition and a protective function in relation to disease development (Crooks et al., 2008; Fratiglioni et al., 2000; Fratiglioni & Wang, 2007; Wang, Karp, Winblad, & Fratiglioni, 2002), even after adjustment for potential confounders such as age and education (Beland et al., 2005; Crooks et al., 2008; Zunzunegui et al., 2003).

Our study indicates that for women, distant social networks (i.e. those involving frequent and satisfying contact with neighbours and acquaintances) are important for preventing or postponing dementia onset. This is in line with

previous studies that report an association between social networks and incident dementia (Amieva et al., 2010; Crooks et al., 2008; Gureje et al., 2011; James et al., 2011; Saczynski et al., 2006; Scarmeas et al., 2001). Additionally, our findings show that the positive effect of having strong social networks remains even after controlling for the *APOE* ε4 allele (Heser et al., 2014; Saczynski et al., 2006; Salinas et al., 2017). For men, we found significant associations between close social networks and dementia onset. This result held true also after controlling for the *APOE* ε4 allele and other covariates but not after controlling for education. In our analysis, close social networks consist of the presence and the number of intimate person(s) to whom the older adults can talk about everything. Here, talking with an intimate persons(s) is not only related to the structural dimension of social networks but is also characterized as emotional support which can be included in the functional aspects of social networks. Taken together, this might imply that there are gender-specific patterns of social networks that need to be taken into consideration when studying the effect of social networks on dementia and health in general (Fuhrer & Stansfeld, 2002).

Contrary to our expectations social networks and the *APOE* ε4 allele were unrelated and no interactions between them were found to be significantly associated with dementia. Hence, in line with the results presented by Brenowitz et al. (2014) and Zuelsdorff et al. (2013), but in contrast to those of Niti et al. (2008) and Poey et al. (2017), strong social networks do not seem to moderate the increased risk of dementia implied by the *APOE* ε4 allele.

The main contribution of the present study is twofold. First, it adds to the current state of knowledge by underlining the importance of social interaction in postponing dementia onset. Second, it highlights the fact that there might be gender-specific patterns in this respect. By extension, this suggests that special attention should be paid to individuals' social settings in preventive efforts undertaken by healthcare professionals and others.

Limitations

The limitations of the measures must be considered in relation to the findings of the study. It was impossible to include more functional aspects of social networks, especially social support, emotional closeness, and instrumental reciprocity, since the *H70/PPSW studies* did not ask about these aspects in 2000–2001. Due to both theoretical reasons and missing data, neither social networks with children and/or grandchildren nor social networks with acquaintances were included in the analysis. Another limitation was lack of biomarker data on cerebral β-amyloidosis and neurodegeneration (cerebrospinal fluid- or positron emission tomography-based markers) on the included individuals. Moreover, reverse causality is an important issue in terms of the association between social networks and dementia as dementia may result in poorer or more restricted social networks (Rizzuto & Fratiglioni, 2014). Although we excluded the respondents who were diagnosed with dementia before baseline in order to limit such bias, it is difficult to exclude the possibility of reverse causality, and this may still play a role in the relation between social networks and cognitive decline (Gallacher, Bayer, & Ben-Shlomo, 2005; Kuiper et al., 2016). Furthermore, other non-genetic confounders, such as mid-life hypertension, more severe late-life cardiovascular disease and obesity, which could also give rise to reverse causality, were not included in our study. Finally, as the sample size was relatively small and a significant interaction effect between gender and social networks could not be corroborated, the observed gender differences must be interpreted with caution.

Conclusions

The present study offers insight into the relationship between social networks and dementia onset. Our results provide further evidence to support the idea that gender-specific patterns in social networks exist in older adulthood and that social networks could play a different role in dementia among men and women. Future research should therefore take into consideration how social networks influence dementia through social support, emotional closeness, and instrumental help, and investigate whether this influence varies between genders.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by [the Stena Foundation]; [the Swedish Research Council] under Grants [2015-02830, 2013-8717]; [the Swedish Research Council for Health, Working Life and Welfare] under Grants [2004-0145, 2006-0596, 2008-1111, 2010-0870, 2013-1202, AGECAP 2013-2300, 2013-2496]; [the Alzheimer's Association Zenith Award] under Grant [ZEN-01-3151]; [the Alzheimer's Association Stephanie B. Overstreet Scholars] under Grant [IIRG-00-2159]; [Sahlgrenska University Hospital (ALF)]; [Alzheimerfonden]; [Hjärnfonden]; [Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse]; [Eivind och Elsa K:son Sylvans Stiftelse]; [Stiftelsen Söderström-Königska Sjukhemmet]; [Stiftelsen för Gamla Tjänarinnor]; [Handlanden Hjalmar Svenssons Forskningsfond]; [Stiftelsen Professor Bror Gadelius' Minnesfond]; [the Swedish Brain Foundation]; [the Swedish Alzheimer Foundation]; [the Torsten Söderberg Foundation]; and [the Swedish Society of Medicine]. HZ is a Wallenberg Academy Fellow. KB holds the Torsten Söderberg Professorship in Medicine.

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