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Regular Research Article

Genetic Liability for Depression, Social Factors and Their Interaction Effect in Depressive Symptoms and Depression Over Time in Older Adults

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ABSTRACT

Objectives: *The objectives of this study were to investigate the effect of genetic and social factors on depressive symptoms and depression over time and to test whether social factors moderate the relationship between depressive symptoms and its underlying genetics in later life.* ***Methods:*** *The study included 2,279 participants with a mean follow-up of 15 years from the Longitudinal Aging Study Amsterdam with genotyping data. The personal genetic loading for depression was estimated for each participant by calculating a polygenic risk scores (PRS-D), based on 23,032 single nucleotide polymorphisms associated with major depression in a large genome-wide association study. Partner status, network size, received and given emotional support were assessed via questionnaires and depressive symptoms were assessed using the CES-D Scale. A CES-D Scale of 16 and higher was considered as clinically relevant depression.* ***Results:*** *Higher PRS-D was associated with more depressive symptoms whereas having a partner and having a larger network size were independently associated with less depressive symptoms. After extra adjustment for education, cognitive function and*

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functional limitations, giving more emotional support was also associated with less depressive symptoms. No evidence for gene-environment interaction between PRS-D and social factors was found. Similar results were found for clinically relevant depression. ***Conclusion:*** *Genetic and social factors are independently associated with depressive symptoms over time in older adults. Strategies that boost social functioning should be encouraged in the general population of older adults regardless of the genetic liability for depression.* (Am J Geriatr Psychiatry 2020; 28:844–855)

INTRODUCTION

Depressive symptoms are a common problem in older adults with consequences for the quality of life, morbidity, mortality, and heath care costs.[1–3] A systematic review of community based studies of the prevalence of depression in later life reported that 13.5% of people aged 55 years or older have clinically relevant depressive symptoms (also known as subthreshold depression, minor depression, or subsyndromal depression) and 1.8% fulfill the criteria of major depression.[4]

Depression is a complex trait with many risk factors including genetic and social factors. It is well-established that depression has a polygenic architecture with many genetic loci with small effects scattered across the entire genome .[5] The liability of depression influenced by this polygenic architecture might lay over a continuum in the population, with the clinical disorder representing the extreme of this distribution and not being an entirely separate entity from symptoms of lower intensity.[6] Recently developed tools such as polygenic risk scores (PRS-D) (a cumulative measure of the genetic burden for one trait carried by an individual, calculated as the sum of the risk alleles weighted for their effect size) are better suited compared to single candidate genes to capture the underlying genetic liability of depression. A recent genome-wide association study (GWAS) from Psychiatric Genomic Consortium (PGC)[7] confirmed that a substantial proportion of major depression trait variance is captured by the joint effect of all measured genetic variants (single nucleotide polymorphisms [SNPs]). PRS-D derived from these results have shown to be associated with depression in independent samples.[7,8]

Social relationships and support are among the main protective factors for depressive symptoms in older adults. Literature suggests that social support reduces the risk for depression.[9] Several mechanisms on how social relationships and social support influence mental health have been suggested such as stress-buffering through social connectedness and coping.[10] A review from Schwarzbach et al.[11] identified social support, quality of relations and presence of confidants as associated with reduced risk of depression in late life.

The prevalence of depression in old adults in the Netherlands has increased in the last 20 years and social factors can partially explain these changes.[12] This is likely due to the buffer effect of social factors on the genetic liability given that genetic variants are highly unlikely to have changed. Therefore, this study aims to assess the effect of PRS-D and social factors as well as their interaction effect in depressive symptoms and depression over time in older adults. Identifying such interactions is especially important in applying personalized prevention strategies by targeting interventions that boost social relationships and support to subgroups of the population based on their genetic liability.

METHODS

The current study includes data from Longitudinal Aging Study of Amsterdam (LASA), an ongoing, population-based, cohort study of individuals 55 years and older living in Amsterdam, Zwolle and Oss in the Netherlands. The design and rationale are described by Huisman et al and Hoogendijk et al.[13,14] In short, 3,017 participants (55–84 years old) were included at baseline (1992–1993) and two additional cohorts were added in 2002–2003 and 2012–2013 with respectively 1,002 and 1,023 participants (55–64 years old). Follow-up visits were conducted every 3 years and the follow-up period was 23, 13

and 3 years respectively for the first, second and third cohort. Trained interviewers collected data on cognitive, emotional, physical, and social functioning during a home interview. Subsequently, all participants were invited for a medical interview during which further diagnostic examinations were done and blood samples were drawn.

LASA has been approved by the Medical Ethics Committee of VU University Medical Center and all participants gave written informed consent.

Genotyping, quality control (QC) and imputation procedure are described in details elsewhere.[15] Genotyping was performed using the Axiom-NL array[16] from Affymetrix (Avera Institute for Human Genetics, Sioux Falls, SD) for 623 participants from cohort 1 and Infinium Global Screening Array-24 v.1.0 (GSA) from Illumina (Human Genomics Facility, Erasmus MC, Rotterdam, the Netherlands) for 1,779 participants from cohort 1, 2, and 3. QC was performed using the Rapid Imputation for COnsortias PIpeLIne[17] developed by the PGC . Duplicate samples, samples with sex mismatch, excess heterozygosity, and call rate less than 0.98 were removed. SNPs with call rate less than 0.98 and minor allele frequency less than 0.01 were also excluded. After QC, data was imputed using as reference the Haplotype Reference Consortium panel version 1.1.[18] Imputation for autosomal chromosomes was done using Minimac3 and was facilitated by the Michigan Imputation Server.[19] QC-ed, imputed data of nonrelated European-ancestry participants were available for 590 participants genotyped with Axiom-NL and 1,689 participants genotyped with GSA (cohort 1: N = 491, cohort 2: N = 631, cohort 3: N = 567).

Polygenic Risk Scores

PRS-D were constructed as the sum of risk alleles weighted by their effect size based on the results from a large meta-analysis from the PGC[7] excluding 23 and Me samples (in total, 135 458 cases and 344 901 controls). Strand ambiguous SNPs and insertion/deletion mutations from the discovery GWAS were removed. SNPs with imputation INFO score greater than 0.9 and minor allele frequency greater than 0.01 were retained. Overlapping SNPs between the discovery GWAS and two LASA arrays were clumped (r^2 <0.1 within 3,000kb window) using PLINK 1.9 software[20] to remove SNPs in linkage disequilibrium. Two risk scores were created using SNPs associated with depression at p value below 0.05 (23,032 SNPs) (main analysis) and 0.2 (57,077 SNPs) (sensitivity check) since PRS-D applying these thresholds explained the higher proportion of depression variance in the replication sample of the discovery GWAS. Risk scores were obtained using PLINK 1.9 software[20] according to the method described by Purcell et al.[21] The PRS-D were standardized (mean = 0, SD = 1) in order to aid interpretability.

Social Factors

The current literature is inconclusive on whether the qualitative or quantitative aspects of social contacts are more important in depression. Therefore, here we take into account partner status and network size as quantitative aspect of social contacts and received and given emotional support as qualitative aspect of social contacts. Data on social factors was collected at baseline and each follow-up visit (Supplemental Digital Content, Supplemental Fig. 1).

Participants were asked if they had someone of the same sex or opposite sex whom they considered their partner. A partner is either a spouse, a person of the opposite sex sharing living quarters considered by the respondent to be a partner, a person of the same sex sharing living quarters considered by the respondent to be a partner, or someone who is considered to be a partner, but with whom the respondent does not share living quarters (referred as Living-Apart-Together).

Social network size was defined as the total number of network members with whom the respondents had important and regular contact and was measured based on the procedure described by Cochran et al.[22] Network members of 18 years and older in seven domains (household members, children, other family members, and neighbors, contacts through work and school, members of organizations, and others) were identified by name (range 0−75).

Received emotional support was collected for nine network members with whom the respondent had most frequent contact and participants were asked how often had it occurred in the previous year that the respondent told his or her network member about personal experiences and feelings (range 0−36).

Given emotional support was collected for nine network members with whom the respondent had most frequent contact and participants were asked

how often had it occurred in the previous year that his or her network member told the respondent about personal experiences and feelings (range 0–36).

To ensure comparable values of support of respondents with and without a partner, only the support within the nine relationships other than with the partner were included.

Outcome

Depressive symptoms were assessed using the Center for Epidemiological Studies – Depression Scale (CES-D).[23] The total score ranges from 0 to 60, with higher scores indicating more depressive symptoms. A score of 16 or more is considered as clinically relevant depression. To better fit normal distribution, depressive symptoms score were transformed into log(1+CES-D score). CES-D was measured at baseline and each follow-up visit (Supplemental Digital Content, Supplemental Fig. 1). Analysis were performed for both depressive symptoms and depression.

Covariates

The following covariates measured at baseline were taken into account: age, sex, 10 ancestry-informative principal components (PC), education, cognitive function, and functional limitations. PCs (10 in total) were calculated from the genotype data and included in the model in order to take into account potential population stratification. To assess educational attainment participants were asked how many years of education they had completed. Then, they were categorized in three categories: less than 9 years of education, 9–12 years, and more than 12 years. Cognitive function was assessed using Mini-Mental State Examination[24] and was dichotomized using a cut-off score of 24. Functional limitations were measured with a validated self-reported scale on difficulty with several activities of daily living and dichotomized in no difficulty and difficulty in one or more activities.[25,26] An overview of all the variables and their measurement moment is presented in Supplemental Digital Content, Supplemental Fig. 1.

Statistical Analysis

Descriptive statistics of the baseline characteristics of the participants were assessed per cohort and per genotyping array (for the first cohort). The proportion of variance explained by the PRS-D was estimated per genotyping array based on the difference in R^2 between a linear model including only covariates (age, sex, and PCs) and a model additionally including PRS-D. Even though the social variables were selected as such to present different aspects of social functioning the correlation between them could not be excluded and was therefore checked by calculating Pearson correlation coefficients. The association of PRS-D with baseline partner status was tested using logistic regression and the association between PRS-D with baseline social network and social support was tested using linear regression to test for the independence assumption: no GxE correlation (rGE), which could lead to spurious results in GxE studies.[27]

Since CES-D and social factors were measured at multiple time points, linear Generalized Estimating Equations (GEE) was used to test the association of PRS-D, partner status, social network, received and given emotional support and their GxE interaction term with depressive symptoms over time. GEE is a population average approach that takes into account the correlation between repeated measurements. The model was initially adjusted for age (continuous), sex (dichotomous), 10 PCs (continuous), and follow-up time (continuous) (Model 1). We additionally adjusted for education (categorical), Mini-Mental State Examination (dichotomous), and activities of daily living (dichotomous) in Model 2. Furthermore, the main and interaction effect of PRS-D and social factors in depression was checked using logistic GEE. The analyses were performed per cohort and per genotyping array separately and the results were pooled using inverse-variance weighting, random effect meta-analysis using Review Manager 5.3[28] or meta package in R.[29]

Analyses were performed using SPSS Statistics for Windows, version 22.0 (Armonk, NY: IBM Corp.), R software version 3.5.3 (Vienna, Austria) and Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Baseline characteristics of the participants can be found in Table 1. Participants in the first cohort were on average older (70.51 and 68.76 years in the first cohort versus 59.97 and 60.47 years in the second and

TABLE 1. Baseline Characteristics of Participants Per Cohort

	LASA 1	LASA 1	LASA 2	LASA 3
Genotyping array	Axiom-NL	GSA	GSA	GSA
Number of participants	590	491	631	567
Follow-up (years)	23	23	13	3
Age (years)	70.51 (7.61)	68.76 (8.2)	59.97 (2.99)	60.47 (2.86)
Sex, female (%)	299 (50.7%)	276 (56.2%)	333 (52.8%)	292 (51.5%)
Partner status, Yes (%)	407 (69%)	353 (71.9%)	538 (85.3%)	476 (84%)
Network size	13.36 (7.65)	15.78 (9.51)	16.07 (9.67)	22.68 (13.08)
Emotional support received	21.28 (7.91)	22.59 (7.95)	22.77 (7.52)	23.51 (6.89)
Emotional support given	20.15 (8.26)	21.63 (8.25)	24.23 (7.14)	24.82 (6.58)
Depressive symptoms*	6 (3−11)	4 (2−9)	6 (2−11)	5 (2−10)
Clinically relevant depression, CES-D ≥16 (%)	90 (11.9%)	44 (9%)	77 (12.2%)	63 (11.1%)
Education:				
<9 years completed, N (%)	327 (55.4%)	315 (64.2%)	266 (42.2%)	148 (26.1%)
9−12 years completed, N (%)	182 (30.8%)	117 (23.8%)	220 (34.9%)	241 (42.5%)
>12 years completed, N (%)	81 (13.7%	58 (11.8%)	145 (23.0%)	178 (31.4%)
MMSE <24, N (%)	50 (8.5%)	52 (10.6%)	34 (5.4%)	17 (3%)
Functional limitations in ≥ 1 activities, N (%)	198 (33.6%)	163 (33.2%)	167 (26.5%)	154 (27.2%)

Notes: CES-D: Center for Epidemiologic Studies − Depression scale; MMSE: Mini-Mental State Examination. Mean (SD) or N (%).
* Median (interquartile range).

third cohort respectively), had longer follow-up and worse cognitive function as expected due to the cohort structure. There were also differences in the percentage of participants who had a partner and the network size with participants from the first cohort having less often a partner (69% and 71.7 % versus 85.3% and 84%) and smaller network sizes (13.36 and 15.78 versus 16.07 and 22.68) (Table 1).

PRS-D explained between 0.5% and 1.8% of the variation in baseline depressive symptoms across different cohorts and genotyping arrays in line with the out-of-sample prediction reported in the discovery GWAS.

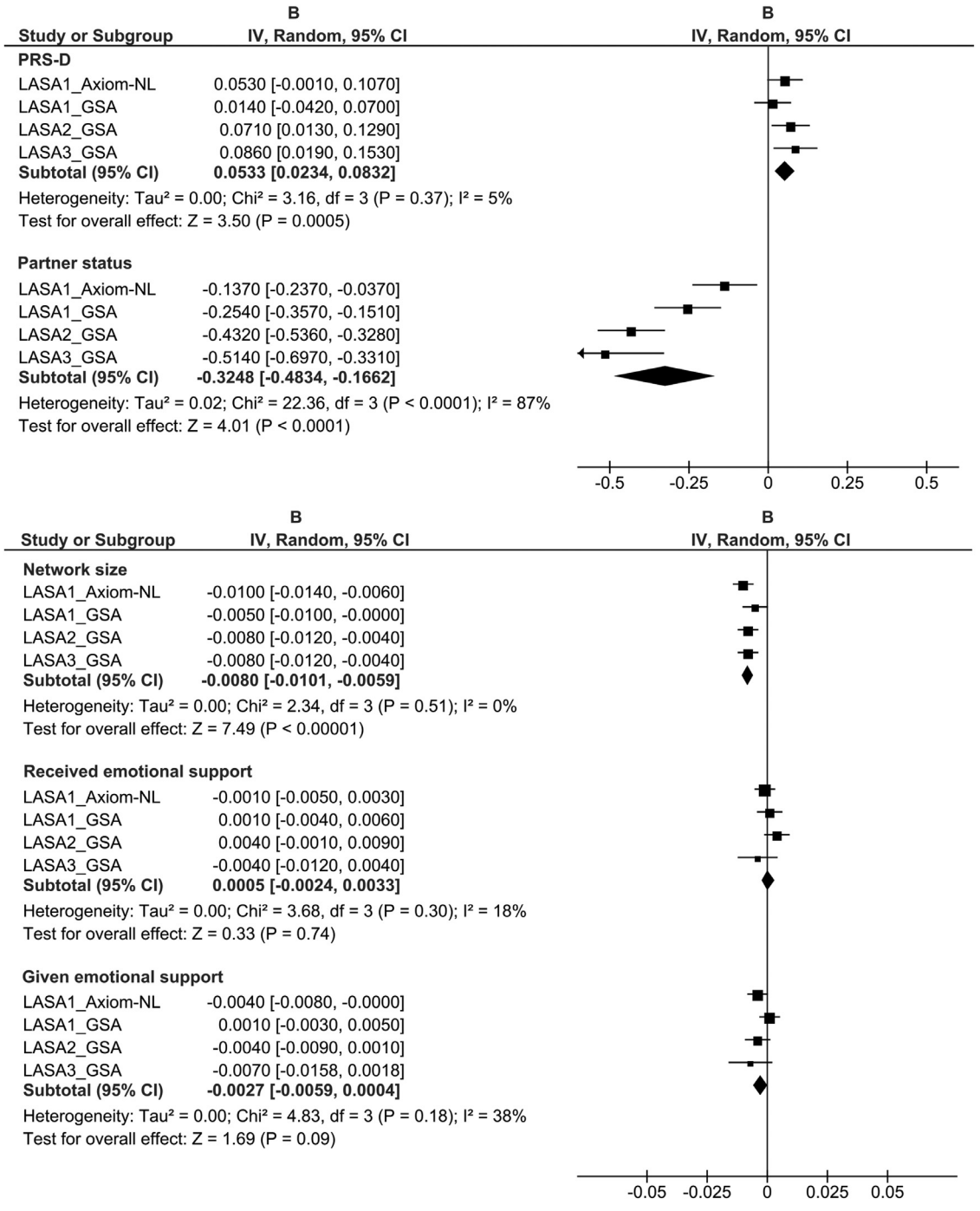
Between social variables network size was correlated with partner status, received and given emotional support and received emotional support was correlated with given emotional support. There was no correlation between partner status and received or given emotional support. (Supplemental Digital Content, Supplemental Table 1). The PRS-D was not associated with the social factors, excluding the possibility of a gene-environment correlation and its potential bias on interaction effects (Supplemental Digital Content, Supplemental Table 2).

Overall, higher PRS-D was associated with higher depressive symptoms (B = 0.053, 95%CI (0.023,0.083), Z = 3.5, p = 0.0005). Furthermore, having a partner (B = −0.325, 95%CI (−0.483, −0.166), Z = 4.01, p <0.0001) and having a bigger network size (B = −0.008, 95%CI (−0.010, −0.005), Z = 7.49, p <0.0001) were associated with less depressive symptoms but no association was found for received emotional support (B = 0.001, 95%CI (−0.002,0.003), Z = 0.33, p = 0.74) and borderline significance was found for given emotional support (B = −0.003, 95%CI (−0.006, 0.000), Z = 1.69, p = 0.09) (Fig. 1). However no indication for gene-environment interaction was found in our sample (PRS-D*Partner status: B = −0.014, 95%CI (−0.077, 0.049), Z = 0.43, p = 0.67; PRS-D*Network size: B = −0.001, 95%CI (−0.003, 0.002), Z = 0.49, p = 0.62; PRS-D*Received emotional support: B = 0.001, 95%CI (−0.002, 0.003), Z = 0.58, p = 0.56; PRS-D*Given emotional support: B = 0.001, 95%CI (−0.002, 0.004), Z = 0.52, p = 0.60) (Fig. 2). Similar results were found when assessing depression (Figs. 3 and 4). After further adjustment for education level, cognitive function and functional limitations participants who gave more emotional support had less depressive symptoms. (Supplemental Digital Content, Supplemental Fig. 2). Yet no gene-environment interaction was found after further adjustment (Supplemental Digital Content, Supplemental Fig. 3).

Extra analysis using PRS-D that included SNPs with p value ≤0.2 in the discovery GWAS were in line with the main analysis excluding the possibility of spurious results due to the SNP threshold selection (Supplemental Digital Content, Supplemental table 3).

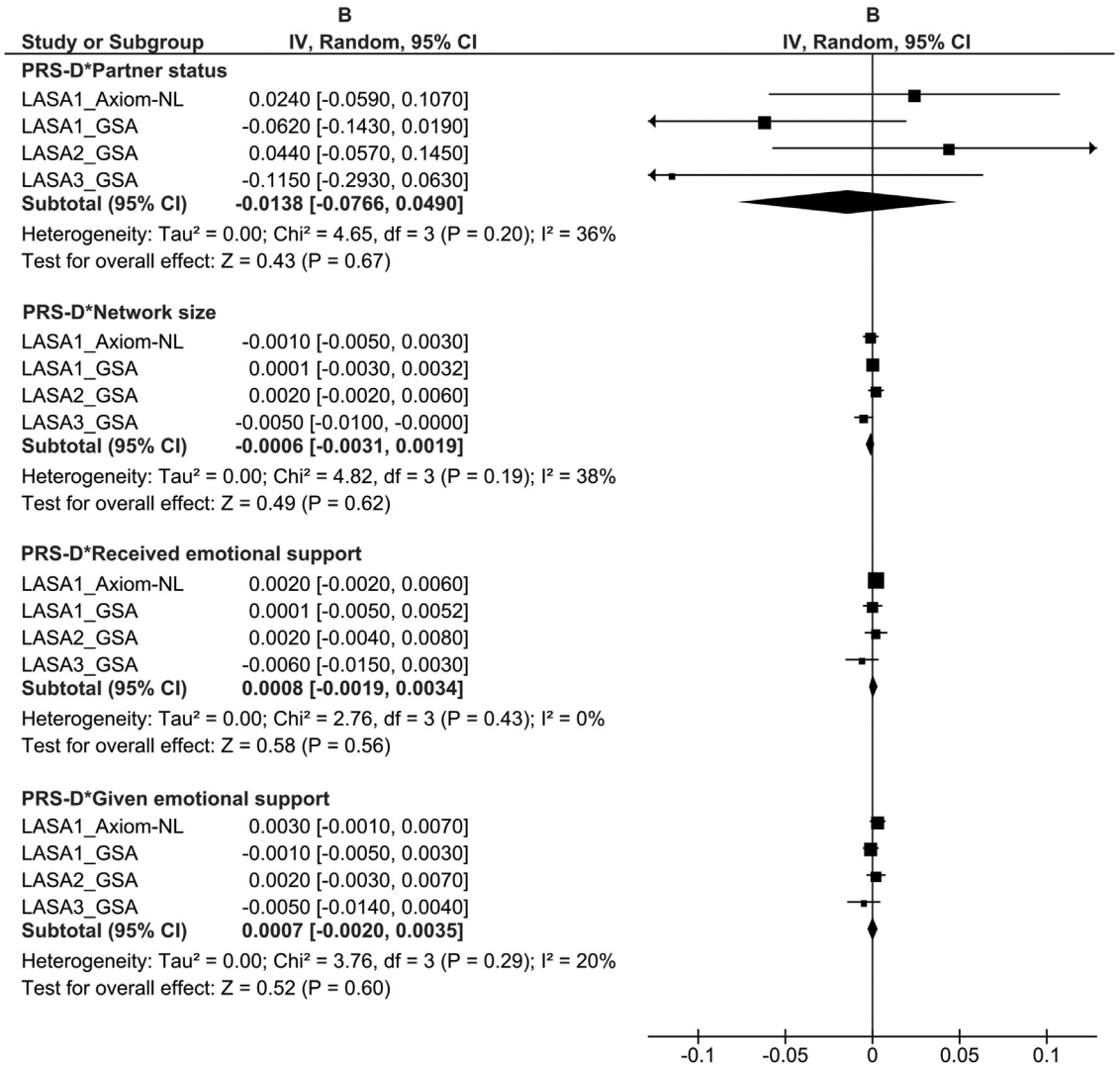
The findings were homogenous across cohorts except for the main effect of partner status on

FIGURE 1. The main association between PRS-D and social factors with depressive symptoms (Model 1).



Adjusted for age, sex, 10 ancestry-informative principal components and follow-up time.

FIGURE 2. The interaction effect between PRS-D and social factors with depressive symptoms (Model 1).



Adjusted for age, sex, 10 ancestry-informative principal components and follow-up time.

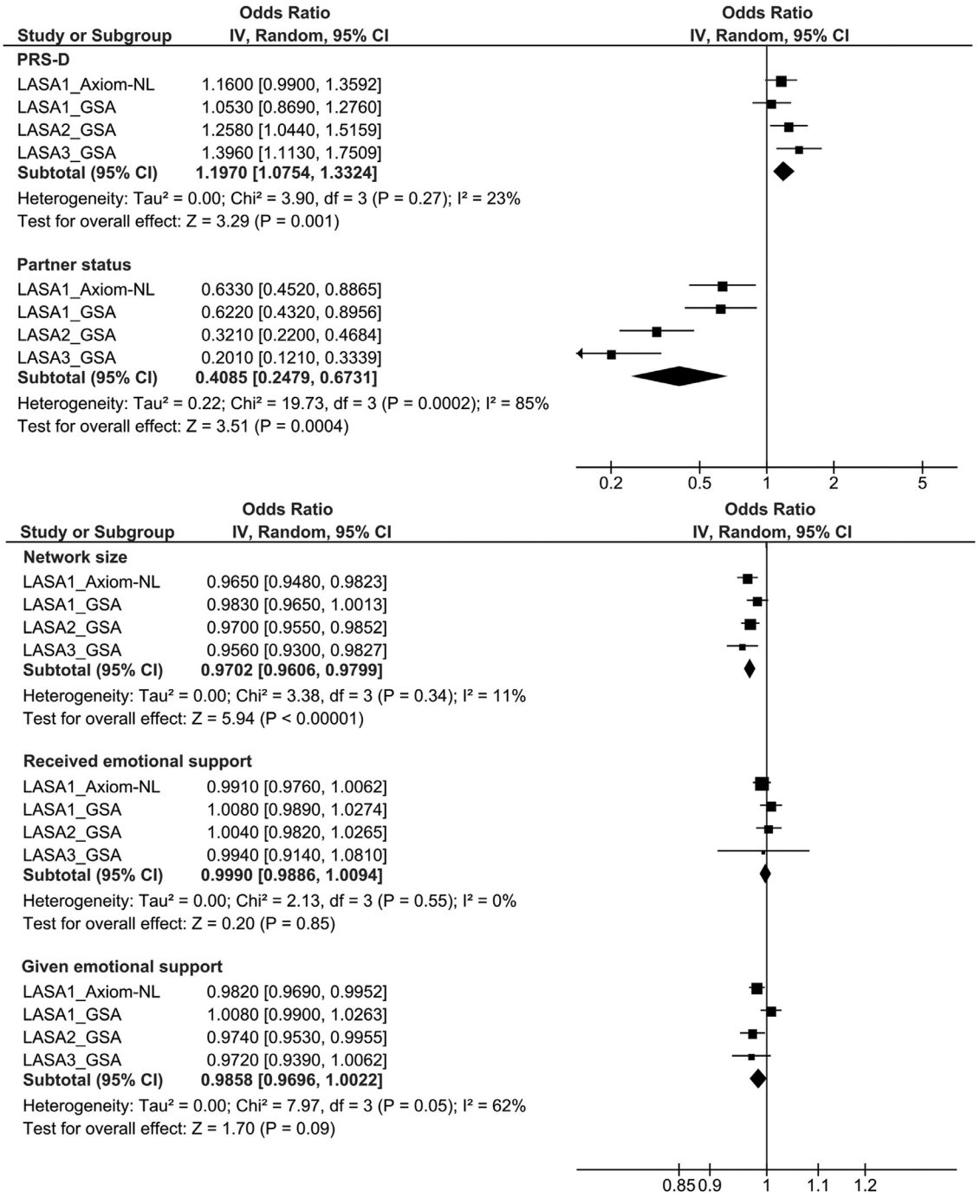
depressive symptoms and depression with higher effect estimates in the newer cohorts (Figs. 1 and 3).

DISCUSSION

In this study we found that participants with higher genetic predisposition for major depression had more depressive symptoms and depression in old age. Participants who had a partner and larger network size had less depressive symptoms and depression in old age. After additional adjustment for education, cognitive function and functional limitations, higher given emotional support was also associated with less depressive symptoms. Received emotional support was not associated with depressive symptoms or depression and no gene-environment interaction could be concluded from our results.

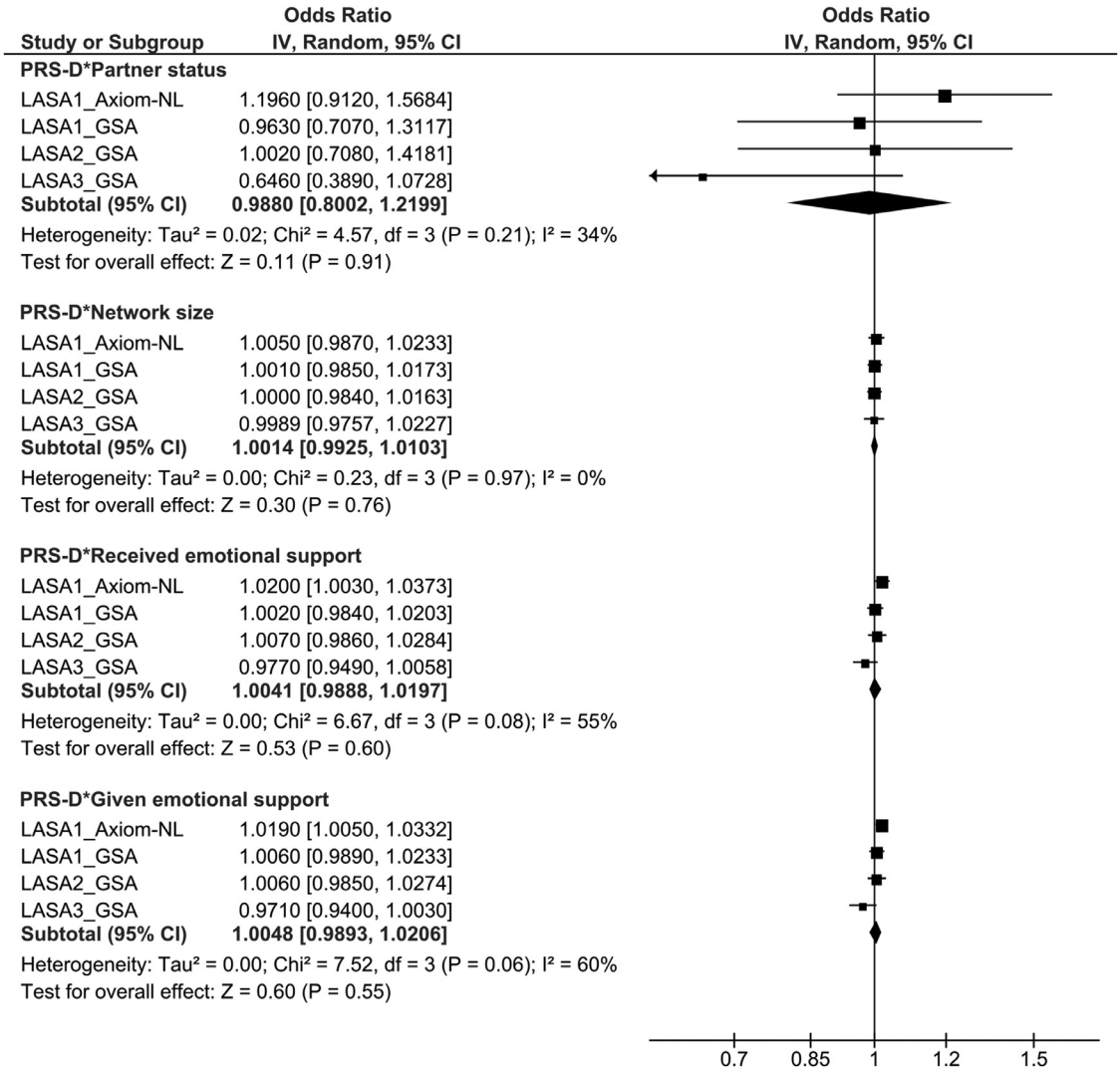
Depression is a complex trait with multifactorial etiology that results from the combination of genetic and environmental factors. Twin studies estimate that 37% of major depression is attributable to additive genetic

FIGURE 3. The main association between PRS-D and social factors with depression (Model 1).



Adjusted for age, sex, 10 ancestry-informative principal components and follow-up time.

FIGURE 4. The interaction effect between PRS-D and social factors with depression (Model 1).



Adjusted for age, sex, 10 ancestry-informative principal components and follow-up time.

effect while a substantial proportion, 67%, is due to individual-specific environment.[30] This was also reflected in our results with social factors (i.e., partner status) having higher effects compared to genetic liability.

PRS-D were built from summary statistics derived from patient cohorts with major depression. However they were associated with depressive symptoms in our study reinforcing the idea that depressive symptoms and major depression are part of the same genetic continuum with major depression being the high end of the spectrum.[6] Also the age of the participants in the discovery GWAS was younger than in our sample. It has been postulated that early-onset and late-onset depression might be influenced by different SNPs but to date no SNPs specific for late-onset depression have been identified. Moreover, a family-based study[31] found a genetic correlation of 0.85 between early-onset and late-onset depression. In our study, PRS-D were associated with depressive symptoms and depression in later life supporting the high genetic overlap previously reported.

Based on our results, structural network characteristics play a bigger role than the functional network characteristics in depression. This might be partially due to how the functional network

characteristics were assessed in our study. To ensure comparable values of support of respondents with and without a partner, the support given/ received by/from the partner was not measured in the total given/received emotional support variable even though partner support is an important source of support in later life.[32] Current literature on the importance of structural versus functional network characteristics in depression is heterogeneous probably due to the different instruments used to asses these characteristics.

Research in genetic-social interaction in depression is limited. The study of Woods et al.[33] found no moderation effect of one single polymorphisms in BDNF gene in the relation between social support and depression among 945 students. Still gene-environment interactions with candidate genes in depression are criticized as results can rarely be replicated.[34] Also the study of Dunn et al.[35] did not identify genome wide interactions with social support in depressive symptoms in African-American and Hispanic/Latina women even though the sample size was an important issue in that study.

Previous research in LASA including only participants aged 55−64 years has reported that social factors such as partner status and network size could explain the differences in depression prevalence over the last 20 years.[12] Here we found differences between cohorts only for partner status; having a partner was more protective against depressive symptoms and depression in the more recent cohorts.

Strength and Limitations

Strength of this study include its prospective design, long follow-up period and the ample number of observations. PRS-D were based on a large and independent discovery sample.

To our knowledge, this is the first study to assess gene-environment interaction between PRS-D and social factors in depressive symptoms and depression among older adults. Moreover, this is also one of the few studies to assess the main effect of social factors on depressive symptoms and depression during a follow-up period of more than 15 years.

Nevertheless, the current study has some limitations. First, not all cohorts had the same follow-up length. This limitation was taken into account by the statistical methods used but still no direct comparison between cohorts can be made. Second, reverse causality bias between depressive symptoms and network size cannot be ruled out as previous research has shown that people with depression have smaller network size.[36] Third, the study population is of European ancestry and the generalizability of the results in other ancestries should be taken with caution.

The utility of PRS in complex traits like depression is still far from clinical use or individual risk prediction. The limited out-of-sample predictive power of PRS-D is a function of the genetic architecture of depression − highly polygenic with several small effect variants scattered across the genome − and the sample size of the discovery GWAS used to derive the PRS-D. At this stage PRS-D can be used to index the underlying liability to depression and stratify subjects across the risk spectrum. Our results showed that having a partner and having a bigger network size were consistently protective for depression across the entire underlying genetic liability.

CONCLUSION

Genetic and social factors are independently associated with depressive symptoms and depression. Based on the individual genetic liability, no subgroups that would benefit more from interventions that boost social functioning could be identified and therefore such interventions should be encouraged in the general population of older adults regardless of the genetic liability for depression.

The field of genetics is evolving fast and future GWAS based on larger samples might improve the performance of PRS-D. Future studies should replicate these results when the performance of PRS-D improves and when specific late-life depression SNPs are identified.

AUTHOR'S CONTRIBUTION

NS, YM and NvS designed the study, analyzed the data and drafted the manuscript. BS contributed to the data collection, interpretation and drafting the manuscript. SvdL, HH, MJTR contributed to the data analysis and interpretation and provided computing facilities for the genotyping data. AB and MH helped with the data acquisition, interpretation of the results

and drafting the manuscript. All authors revised and approved the final version of the manuscript.

DISCLOSURE

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The funding agencies had no role in the study design, data collection and analysis, interpretation of results, writing or publishing of the manuscript.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2020.02.011.

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