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Late-life depression and its association with polygenic risk scores for Alzheimer´s disease and cognition in a population-based sample from Gothenburg

Degree Project in Medicine

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Abstract

Introduction: Late-life depression and dementia are two common diseases in later life, and it is not unusual for them to co-occur. Previous research has suggested that they might share genes. The results, however, have been contradictive. Since the relationship between Alzheimer´s disease (AD) and late-life depression is unresolved, genes for general cognitive ability might be a clue to resolve the cognitive connection to depression.

Aim: The primary aim of this study is to investigate if a polygenic risk score for Alzheimer´s disease is associated with depression among individuals aged 70-109 years in a population-based sample in Gothenburg. The secondary aim is to investigate if a polygenic risk score for cognitive performance (based on genetic variants associated with cognition in individuals at 30 years of age) is associated with depression in the same population.

Method: The study sample was comprised of 3054 participants, from four cohorts from the Gothenburg Cohort Studies. For the statistical analysis participants data was included based on genotype data and data of depression and was excluded based on data of dementia. Six PRS were analyzed with general estimating equation to see if they were associated with late-life depression.

Results: Statistical analysis with generalized estimating equation, did not show any association with polygenic risk score for AD and depression. However, for major depressive disorder and PRS for cognition, there was a significant association.

Conclusions: In this study there was no evidence that depression has an association with a PRS for AD. However, a significant association was found between major depression and PRS for cognitive performance. Due to the relatively small study sample future research is required to strengthen this association.

Key words: Late-life depression, Alzheimer´s disease, SNP, polygenic risk score, GWAS

1. Introduction

1.1. Depression and late-life depression

Depression is a common disease in the general population, and more so, it is a common disease in older individuals (1). Late-life depression classifies as a depressive syndrome in people older than 65 years of age (2). It has a prevalence of about 6 to 13 % depending on included age and type of depression (major or/and minor depression) (3-5). Symptoms common for depression are those described in DSM-V (6). It includes: depressed mood or decreased interest, change in weight or in appetite, sleep disturbance (the patient can have trouble sleeping or problems with tiredness despite sufficient or even more than enough sleep), psychomotor agitation or inhibition, fatigue, sense of worthlessness/ decreased self-esteem, lack of concentration, repeated thoughts about death/ hopelessness/meaninglessness (6, 7). Which symptoms that appear in an individual can vary based on age and it is not uncommon that the prominent symptoms differ when comparing older and younger people diagnosed with depression (7, 8). Regarding the symptom of sleep disturbance, studies have shown that it is more common for people with late-life depression to suffer from difficulties such as maintaining sleep during the night and waking up too early. This in comparison to younger individuals with depression, which instead face problems of not feeling well-rested, despite a sufficient amount of sleep (9). Other symptoms that more frequently appear in individuals which are diagnosed with late-life depression are somatic symptoms such as pain and abdominal problems, for example constipation or diarrhoea, but also cognitive complications involving, for example, trouble concentrating (8, 9).

Furthermore, depression has a great impact on society. Partly because it is an expensive disease (10), but also because the impact is so abundant on the affected individual. Depression can lead to loss of function, decreased quality of life, long recovery time, conversion to a more chronic condition and premature death (3, 11). In addition to these consequences it is also a disease which frequently occur in individuals of high age, that often already suffers from chronic diseases or other health issues, and therefore already are vulnerable (4).

1.2. Dementia

Another frequently occurring disease among older individuals is dementia (12) and the prevalence varies between 2-5 % (13). Dementia is a severe condition, with consequences such as loss of function and a decreased life-quality (14). Furthermore, individuals with dementia have a much higher mortality rate compared to healthy individuals of the same age (14). There are many subtypes of dementia, such as, Alzheimer´s disease, vascular dementia, Lewy body dementia, and Frontotemporal dementia (15). The most common of these subtypes are Alzheimer´s disease (16) which accounts for more than 50 % of all cases of dementia (17).

1.3. The connection between depression and cognitive functions

It is not unusual for Alzheimer´s disease (AD) and depression to occur together (1). Individuals with AD are often also diagnosed with major depressive disorder, and how often the two diagnoses coincide differs in different studies, with numbers from 17 % to over 20 % of all cases (4, 12). More so, people who suffers from dementia can show symptoms of depression, like trouble with sleep disturbance and apathy (18, 19). Older individuals that suffer from depression can also have cognitive impairments, like loss of memory function and trouble concentrating, but they can also have trouble with their speech and solving simpler tasks (12, 20-22). Mild cognitive impairment is also common in people suffering from late-life depression (23).

Though we know that these two conditions frequently appear together, their relation to one another is not fully understood. Previous research has shown that depression can be a risk factor for developing dementia but that it also can be a prodromal phase (12, 24). However, there are studies saying that late-life depression might be one or the other (25), but there is also results showing the opposite (2).

Several studies have been made on possible shared pathological mechanisms for depression and Alzheimer´s. One of the suggested mechanisms is the HPA-axis-theory, where increased glucocorticoid levels, induced by stress, might lead to decreased hippocampus-volume, which is evident in individuals both of Alzheimer´s and depression (26). Another mechanism Alzheimer´s and depression might have in common is neuroinflammation (27-29). One explanation for the shared pathological mechanisms is that the two illnesses share genes (12).

1.4. The genetics of a disease

Most of human diseases are a result of both the many different genes we have in our genome and the surrounding environment (30), but there are also diseases that mainly occur only due to mutations in one or a few genes, however they are more rare (30). From one person to another, the genome varies extremely little, and there are only small variations in our genome (30). If such a variation occurs in more than 1% of the population it is called a polymorphism, where the most common are SNPs (single nucleotide polymorphisms) (31, 32). These variations can increase or decrease the risk of developing a disease, though most of them only contribute very little to the absolute risk of, or protection against, a disease (33). It is a combination of these different variants, together with the environment, that increases or decreases the risk of developing a disease (34). Predicting the risk of developing a disease, which is derived from a combination of different genes, is not as easy as doing so for a disease caused from a single gene (35). However, researchers have shown that calculating a polygenetic risk score (PRS) can help predict the risk of developing a polygenetic disease (35, 36). A PRS is a score that is an estimate of the risk an individual has of developing a specific disease and is calculated by first multiplying an individual's risk alleles with weighted effect measures and then all off these are summarized (37, 38). The risk allele effect size derives from GWAS (genome-wide association studies), studies where the aim is to use information from genetic variations, SNPs, distributed over the genome, and finding variations, that are connected with a specific disorder/trait (39, 40).

1.4.1. Genetics and depression - single genes

Depression is hereditary and previous research has shown a heritability of 35 – 37 % (41, 42). Various genes have been associated with a higher risk of developing depression, such as *LACC1*, *OLFM4*, *TIAF1*, and *NR4A2,* which are all connected to inflammation (43). Genes that are also suggested to increase the risk for developing major depression are *TMEM161B-AS1, VRK2, L3MBTL2, NEGR1, MEF2C, RERE* (44, 45) which all might have a role in development functions in CNS (45). In total 44 risk variants have been established by several different GWASs (36).

As mentioned earlier, AD and late-life depression might share risk genes. One established risk gene for Alzheimer´s is *APOE*, where carriership of the E4-allele gives an increased risk of developing the disease (46-48). Studies have shown that this allele might also have a role in increasing the risk of developing late-life depression (49, 50). As already mentioned, genes that are important for inflammation may play a part in the development of depression, and for both depression and dementia neuroinflammation is a part of the pathogeneses of the diseases (27, 28, 43). Studies have shown that the genes encoding IL-1β and TNF-α, which both modulate inflammation, have an association with both AD as well as late-life depression (51-54).

1.4.2. Genetics and depression - Polygenic risk score

Previous studies have shown that depression has an association with PRS for bipolar disorder (55, 56). Furthermore, major depressive disorder has been shown to have a relation with other polygenic risk scores such as PRS for schizophrenia (57). A study from Translational Psychiatry showed that the scores for the case-group, representing individuals with major depressive disorder, were significantly higher than the control group, but the results could not all be significantly replicated in another study population (57). Though Alzheimer´s and late-life depression, both share symptoms and underlying mechanisms, the study made by Gibson et al. has not shown that polygenic risk score for Alzheimer´s increases the risk of developing major depression (58). However, there are other studies indicating that Alzheimer´s and late-

life depression have a polygenic overlap and that the *APOE*-gene can hide a significant genetic association between the two diseases (59).

1.5. Finding a genetic link

In this paper the focus will be on late-life depression and whether there is an association between the disease and a polygenic risk score for Alzheimer´s disease, both with and without the *APOE*E*-allele, by using an epidemiologic study sample from Gothenburg. In previous research of the connection between the two diseases the results have been contradictory and while some research has been able to establish a connection, other has not (49-54, 58, 59). Few studies have been done on the correlation between AD-PRS and late-life depression. The previously mentioned paper investigating if AD-PRS and major depression are connected, and were no genetic relationship was found, is one of the few. That study compares depression with AD-PRSs calculated with the *APOE*-gene, but it does not compare depression with AD-PRSs calculated without the *APOE*-gene (58). Since there are studies that suggest that this allele might hide a significant association between late-life depression and risk genes for AD it is important to see if this is the case with a PRS for AD (59). This study also focuses only on major depression, and in our study, we aim to investigate the relationship between both major and minor depression with AD-PRS (58). Depression is a heterogenic disease (60) and studies have shown that there might be different subtypes that may have different underlying mechanisms and genetic backgrounds (43, 61), and thus might have more or less of a genetic connection to dementia. This emphasises the importance of continued research on the genetic link between dementia and late-life depression. Finding a genetic connection between the two diseases could help us understand disease pathogeneses, which could also be of importance for early prevention, early diagnosis, and work with identifying potential drug targets.

Furthermore, it will be investigated if late-life depression and a polygenic risk score for cognitive performance are associated. Since the relation between depression and genetic risk for dementia is not elucidated, and findings are contradictive, investigating if there is a

relation between a genetic score based on genetic variants associated with general cognition in younger individuals and late-life depression could provide additional clues.

1.6. Aim

1.6.1. Primary aim

The aim of this study is to investigate if a polygenic risk score for Alzheimer´s disease is associated with depression among individuals aged 70-109 years in a population-based sample in Gothenburg, Sweden.

1.6.2. Secondary aim

The secondary aim of this study is to investigate if a polygenic risk score for general cognition (based on genetic variants associated with cognitive performance in individuals at least age 30) is associated with depression among individuals aged 70-109 years in a population-based sample in Gothenburg, Sweden.

2. Material and Methods

2.1. Description of the study sample

2.1.1. Gothenburg Cohort Studies

This study was performed by using a population-based sample, which was derived from The Gothenburg H70 Birth Cohort Studies (62, 63). The Gothenburg H70 Birth Cohort Studies include several different cohorts which are: H70, PPSW (Prospective Population Study of Women), H85 and the H95+ (62). These cohorts, and how the election process was performed, as well as exact study procedures, have been described elsewhere (62-71). Overall, the participants from the cohorts were selected, firstly, based on the year they were born, and secondly on date of birth, with different dates for the different cohorts (62-72). This yielded a systematic collection representative for the ages studied. The individuals included in this specific project were born in the years 1901–1911, 1914, 1918, 1922–1924, 1930, or 1944. The data from the cohorts used for this study is derived from examinations made on participants 70 to 109 years of age (i.e., baseline age 70 years).

The participants selected for this specific study had to have genotype data, which involved those who went through an examination from year of 2000 to 2015, described in Figure 1. Most of the individuals have had follow-up examinations during the years, hence, most of the participants have had more than one examination and data on dementia and depression has been gathered several times.

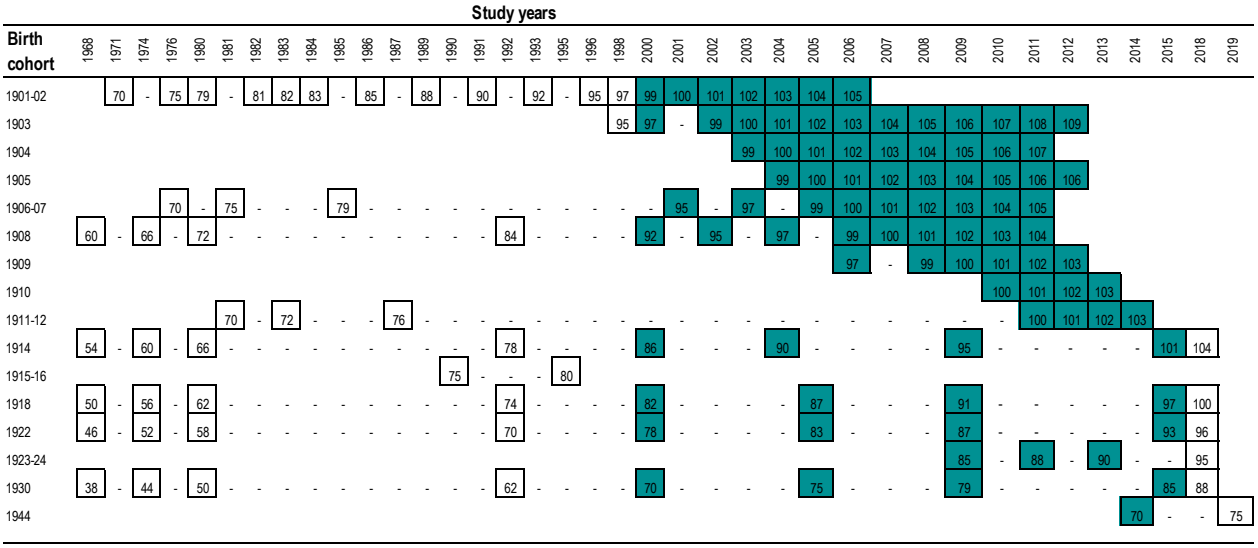

Figure 1: summary over cohorts and examination year, with age within square, and blue colour representing examination years for gathering of genetic data included in this specific study

The total amount of participants with genetic data, was 3612. After that, the genetic data underwent quality control which left 3467 participants. To be eligible for this paper it was a criterion that data of depression had been gathered from the participant. Those who did not fit this criterion were excluded and this left a total of 3414 participants. Those with a diagnosis of dementia at baseline were excluded, which was 360 participants. The data of a participant who developed a diagnose of dementia was excluded from that examination and onwards, but the data before the diagnose was used. Participants with data excluded from one/several or all examinations, due to dementia, were 713.

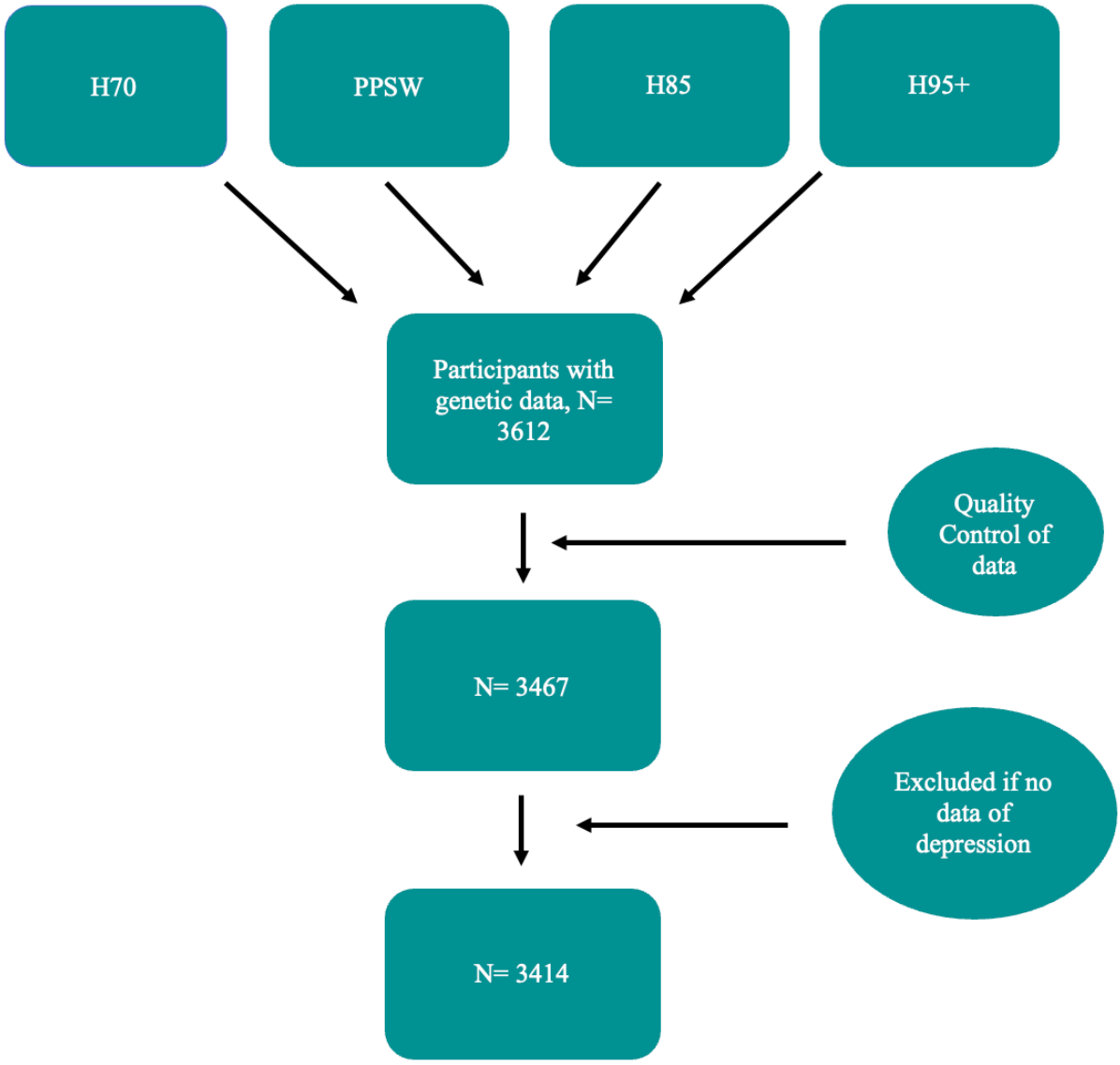

Figure 2: flow chart of the election process of the study participants

2.2. Study procedures

2.2.1. Examinations

The participants were examined at Sahlgrenska University Hospital at the Neuropsychiatric Clinic. The examinations that the participants had to went through, to be included in this

study, were a semi-structured psychiatric interview, a comprehensive cognitive examination and blood sampling for genetic data (64). The individuals also participated in examinations of somatic health, functional ability/disability and physical fitness/activity, and interviews regarding their general health and social factors (64). As mentioned, when describing the cohorts, most of the participants have participated in one or several follow-up-examinations.

2.2.2. Diagnostics of depression and dementia

CPRS (Comprehensive Psychopathological Rating Scale) (73) and MADRS (Montgomery-Åsberg Depression Rating Scale) (74) were the base of the psychiatric examination, which was performed by either a psychiatrist, a medical doctor or a trained nurse. The last two were trained on these semi-structed interviews by a psychiatrist. CPRS and MADRS are both considered to be good evaluation tools when assessing older individuals (75, 76).

The base of the depression diagnose was the CPRS (73), which provided the representing symptoms of depression. Depression was diagnosed as either major or minor depression through the DMS-IV or DSM-IV-TR (6, 77). The nine criteria for diagnosing depression with this tool are: depressed mood and/or markedly diminished interest or pleasure (which are the main criteria), significant weight loss or weight gain or decreased or increased appetite, insomnia or hypersomnia almost daily, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, or indecisiveness and recurrent thoughts of death or suicidal ideation (6). For a major depression diagnose the participants need to exhibit the main criteria and four or more of the other symptoms also need to be present (6). The symptoms described above must also have been present during the last month (6). For minor depression DSM-IV-TR was used and for this diagnose 2-4 of the mentioned criteria had to be fulfilled (77). For the statistical analysis the major and minor depression diagnoses were categorized as both one category which was labelled as “Any depression”, and also separated as minor and major depression.

The Diagnostic and Statistical Manual of Mental Disorders Third Edition-Revised DSM III-R was used to diagnose dementia (78) with the obtained information from a clinical examination

and close informant interviews (79). The examination was comprised of a series of neuropsychological tests (80), where assessments were made of memory ability, language difficulties (such as presence of apraxia and word finding difficulty), language comprehension and the ability to concentrate (64, 70).

2.3. Genetic procedures

Extraction of DNA from whole blood was executed at the LGC Genomics in Berlin (Germany) by standardised methods (LGC Genomics, Hoddesdon, Herts, UK, http://www.lgcgroup.com/. Genotyping was performed using the Neurochip array from Illumina (81). The base of the Neurochip array is a genome-wide genotyping array, which contains 486,137 SNP-variants (81).

2.3.1. Quality control (QC) of the genetic data

Participants were removed based on quality control of the genetic raw data. Quality control of the genetic data is necessary for the data to be as accurate as possible. In short, DNA-samples and SNPs that do not fulfil the standards for the analysis are excluded and some additional checks/removals are performed to further increase the data quality. The quality control in this study included removal of individuals with the following: gender mismatch, per sample rate < 98 % and immoderate heterozygosity (which was established with FHET outward ± 0.2, where F is a coefficient estimate for measuring heterozygosity). Immoderate heterozygosity is an indication that the genotyping of an individual has not been successful. The mean value of the European sample in the 1000 Genomes Project global reference population was used to define if samples were of non-European descent, which they were defined as if their two first main components surpassed six standard deviations from the mean value. If so, they were removed. First and second-degree relatives were also removed, based on pairwise PI_HAT ≥ 0.2 (i.e., proportion of the genome that are in identity-by-descent: calculated using- genome option in PLINK). Identity-by-descent is an indication that the samples are too genetically alike, because the individuals are related. If these genes are included in the final analysis, they

have a larger contribution to the genetic material than they should. If the markers had Hardy-Weinberg disequilibrium ($P < 1\times 10^{-6}$) and minor allele frequency (MAF) under 0.01 as well as a per-SNP call rate under 98% they were removed. The reference panel of Haplotype Reference Consortium data (HRC1.1) was used for post-QC with the use of the Sanger imputation service. Exclusion of further SNPs was due to low imputation quality, which was set at ≤ 0.3.

2.3.2. Polygenic risk score

The data used for calculating a polygenic risk score (PRS) needs to come from two independent data- sets (82): the base data, which comes from a GWAS (genome wide association studies), consisting of summary statistics (including effect sizes) for genotype-phenotype (AD and cognition in our case) associations, and the target data, which contains genotypes (to be transformed into PRSs) and the phenotype (depression in our case) of interest (37). The selection of SNPs for the PRSs was completed using linkage disequilibrium (LD) clumping. To enable removal of variants in LD, the reference panel used was The European ancestry samples (from the Genomes Project), ($R^2 < 0.001$). Calculation of the polygenetic risk score for Alzheimer´s disease and cognitive performance was then computed by multiplying the number of effect-alleles for a specific SNP with the B-coefficient (the effect size) for that specific SNP. This procedure was then performed for all the SNPs. All these values, calculated on each SNP, was then summarized to create the PRS. The B-coefficients were derived from summary statistics from one of the most recent GWASs on Alzheimer´s disease (83) and summary statistics from one of the most recent educational attainment GWASs (84), both which had used genetic data from people of European ancestry.

For this study four PRSs for AD and two PRSs for cognitive performance were calculated. One of the PRSs was calculated based on SNPs with a genome wide significance level of 1×10^{-5} (AD-all-$1e^{-5}$, AD-APOfree-$1e^{-5}$, Cognition-$1e^{-5}$) and the other based on SNPs with a genome wide significance level of 1×10^{-8} (AD-all-$5e^{-8}$, AD-APOfree-$5e^{-8}$,

Cognition-$5e^{-8}$). The AD-PRSs were made with and without *APOE* (AD-APOfree-$1e^{-5}$, AD-APOfree-$5e^{-8}$).

2.4. Statistics

SPSS, version 27 (IBM: www.ibm.com) was used to perform the statistical analyses. A significance level of 0.05 was used.

Sample characteristics were calculated using chi-square and Fischer's exact test, where sex, diagnosis of dementia and no dementia were compared between the groups of participants with or without a diagnose of depression. Mean values of age at first examination among individuals with depression and no depression were compared using independent sample-t-test (student´s t-test). The mean values, of the PRS, among depressed and not depressed individuals were also compared with an independent t-test.

For comparisons of mean value of age over all exams and mean value of number of examinations a non-parametric test, independent samples Mann-Whitney U Test, was used, since this data was not evenly distributed.

Statistical analyses of the relation between PRSs for Alzheimer's disease/cognitive performance and depression were performed using general estimation equation models, taking the various number of examination times at different ages for each individual, into account. At the first stage, "Any depression" (all the participants with a depression diagnose) was used as the outcome (dependent variable), but the "any depression" group was also divided into two groups where those with major and minor depression were compared separately. PRS, age, and sex, were the independent variables in the analyses (separate analyses for each PRS).

2.5. Ethics

The study was approved by the Regional Ethical Review Board in Gothenburg (reference number: S096-01), and written informed consent was obtained from all participants and/ or their relatives in cases of dementia. All the participants from the different cohorts have an individual serial number and they are therefore not identifiable.

3. Results

3.1. Sample characteristics

Sample characteristics are presented in table 1. The percentage of females in the depression group was significantly different from the no depression group. In the depression group the percentage of demented was also significantly higher in comparison to the no depression group. The mean age also differed significantly between the two groups ($p < 0.001$), where the depression group had a higher mean age then the no depression group. A significant difference in age could also be seen when comparing the groups ages at first exam. Mean number of surveys also differed significantly with 2.34 for the depression group and 1.72 for the no depression group. Considering the mean difference of the polygenic risk scores, the differences observed were not significant, p-values were between 0.463 and 0.927 (table 1).

Table 1: Characteristics of the study sample

	Any Depression (*n*= 836)[d]	**No depression (*n*=2578)**	**p-value**
Gender (female), ***n* (%)**	631 (75.5)	1606 (62.3)	< 0.001[a]
Demented, ***n* (%)**	265 (31.8)	448 (17.4)	< 0.001[a]
Mean age over all exams, ***mean* (SD)**	81.49 (8.7)	78.4 (9.4)	< 0.001[c]
Age at first exam, ***mean* (SD)**	79.4 (9.6)	77.1 (9.5)	< 0.001[b]
Average number of surveys, ***m* (SD)**	2.3 (1.3)	1.7 (1.0)	< 0.001[c]
PRS: AD-all-1e^{-5}, ***mean* (SD)**	–0.13 (0.89)	–0.13 (0.92)	0.93[b]
PRS: AD-APOfree-1e^{-5}, ***mean* (SD)**	–0.06 (1.01)	–0.04 (0.99)	0.74[b]
PRS: AD-all-5e^{-8}, ***mean* (SD)**	–0.13 (0.90)	–0.13 (0.91)	0.87[b]
PRS: AD-APOfree-5e^{-8}, ***mean* (SD)**	–0.06 (1.02)	–0.03 (0.99)	0.48[b]
PRS: Cognition-1e^{-5}, ***mean* (SD)**	0.01 (0.98)	0.02 (1.00)	0.90[b]
PRS: Cognition-5e^{-8}, ***mean* (SD)**	–0.01 (1.01)	0.02 (1.00)	0.46[b]

a: Fischer´s exact test

b: Independent samples t-test

c: Independent samples Mann-Whitney U-test

d: 258 with major depression (participants who have had at least one major depressive episode at any examination, 88 of these also have had a minor depressive episode at any examination) and 578 with minor depression.

3.2. Polygenic risk score for Alzheimer´s disease and cognition versus any depression

None of the polygenic risk scores for Alzheimer´s (AD-all-$1e^{-5}$, AD-APOfree-$1e^{-5}$, AD-all-$5e^{-8}$, AD-APOfree-$5e^{-8}$) had an association with "Any depression" outcome (major and minor depression in the same group). Furthermore, there was no association found for the cognition-PRS (Cognition-$1e^{-5}$, Cognition-$5e^{-8}$) (see Table 2).

Table 2: Association between "Any depression" and polygenic risk score for Alzheimer´s disease and cognition

Polygenic risk score	B	Std. Error	P-value
AD-all-$1e^{-5}$	0.007	0.046	0.879
AD-APOfree-$1e^{-5}$	–0.023	0.043	0.592
AD-all-$5e^{-8}$	0.015	0.047	0.748
AD-APOfree-$5e^{-8}$	–0.009	0.045	0.848
Cognition-$1e^{-5}$	–0.064	0.043	0.137
Cognition-$5e^{-8}$	–0.066	0.043	0.127

Results based on Generalized Estimating Equations adjusted for sex and age.

3.3. Polygenic risk score for Alzheimer´s disease and cognition versus major and minor depression

The results for the major depression sub-group are presented in table 3. No significant association between major depression and PRS for AD could be found. However, for the cognition-PRS there was a significant association with major depression.

For the minor depression group (results presented in table 4), no associations were found. This was true for both the AD- PRS and the cognitionPRS, and also irrespective of the PRSs significance level (i.e., $5e^{-8}$ and $1e^{-5}$).

Table 3: Association between major depression and polygenic risk score for Alzheimer´s disease and cognition

Polygenic risk score:	**B**	**Std. Error**	**P-value**
AD-all-$1e^{-5}$	–0.052	0.076	0.491
AD-APOfree-$1e^{-5}$	–0.061	0.070	0.384
AD-all-$5e^{-8}$	–0.033	0.077	0.668
AD-APOfree-$5e^{-8}$	–0.022	0.072	0.764
Cognition-$1e^{-5}$	–0.141	0.069	0.040
Cognition-$5e^{-8}$	–0.131	0.064	0.041

Results based on Generalized Estimating Equations adjusted for sex and age.

Table 4: Association between minor depression and polygenic risk score for Alzheimer´s disease and cognition

Polygenic risk score:	**B**	**Std. Error**	**P-value**
AD-all-$1e^{-5}$	0.021	0.051	0.673
AD-APOfree-$1e^{-5}$	–0.006	0.049	0.908
AD-all-$5e^{-8}$	0.025	0.051	0.621
AD-APOfree-$5e^{-8}$	0.001	0.049	0.993
Cognition-$1e^{-5}$	–0.034	0.046	0.463
Cognition-$5e^{-8}$	–0.038	0.048	0.435

Results based on Generalized Estimating Equations adjusted for sex and age.

4. Discussion

In this study of possible associations between polygenic scores for cognitive traits and late-life depression, no associations were found between AD-PRS and PRS for general cognitive performance and any depression. However, when analysing the PRSs in relation to major and minor depressive disorder separately, there was a significant association between the PRS for general cognitive performance and the major depressive disorder group.

Previous research on polygenic risk scores for Alzheimer´s disease and its association with depression is in line with the results from our study (58). One of the few prior studies showed no association with a polygenic risk score for AD and neither for late- or early-life depression (58). However, even though the results are similar there are differences between the studies. The previous study had five different PRSs (58). They were based only on different significance levels and the *APOE*-gene was not excluded (58). This could have been of importance since there are studies suggesting that the *APOE*-gene can interfere with the results and hide a significant association with other genes (59). However, in our study that seems to not be the case, since excluding the *APOE*-gene did not change the result (i.e., no association between a PRS for AD and late-life depression). Another difference is that they only analysed the relation between the AD-PRS and major depressive disorder (58). As already mentioned, depression is a heterogenous disease (43, 60) and different subtypes can have different genetic backgrounds (43). However, in our study we could not find a difference in results based on major and minor depression, when analysing in relation to AD-PRS, which might suggest that in late-life these two subtypes do not have a different genetic background regarding genes of importance for AD.

Comparing to early-onset depression, late-onset depression is suggested, in prior research, to be more connected to AD (85, 86). Early onset is when the first depression episode occurs before the age of 50 and is then reoccurring in later life, while late-onset depression is when first episode occurs after the age of 50 (85). In our study we did not take age at onset into account, since that data was not possible to obtain. However, the study made by Gibson, J.

et.al. (58) has taken age at onset into account in the analysis, and age onset did not affect the results, suggesting that late onset depressive disorder do not have more connection to AD than early onset, which contradicts previous research. This result might suggest that even if age at onset had been taken into account in our study, it would not have made a difference on the outcomes.

One study does point in a direction of a conjoint polygenic risk between AD and late-onset depression (59). However, in this study they did not investigate PRSs, but instead SNPs of importance for AD, in relation to major depression disorder, using a comprehensive pleiotropy analysis (investigating the overlap of significant SNPs between AD and major depressive disorder (MDD), using data from AD and MDD-GWAS) (59). Their results showed that late-onset MDD and AD might have a genetic overlap. Furthermore, they both excluded and included variants in the *APOE*-region in their analysis. When doing so they got a result which showed a stronger polygenic overlap between AD and major depressive disorder when excluding the *APOE*-region, indicating that the *APOE*-gene may hide a significant association between the two conditions (59). However, even if we in our study used PRSs both with and without the *APOE*-gene, the *APOE*-gene did not seem to hide significant associations.

Even though previous research does not provide any distinct support that late-life depression and AD share a polygenic overlap, research has indicated that they could share specific genetic factors (i.e., single genes) (49, 87, 88). *APOE*E*, which has a high impact on AD-development (46-48), may increase the risk of developing depression in late-life, independent of AD development (49). This contradicts our result that the *APOE*-gene did not influence the results, both when included and excluded in the PRS. However, the design for the study made by Skoog et. al., differed from ours considering that they followed the participants for incident depression for five years, unlike our study, where data on depression from all examination times (from age 70 and onwards) was included (49). Based on the study made by Skoog. et.al. it is possible to say that having the allele might increase the risk of a future development of depression (49). Another study also indicates that the *APOE*-gene has an association with late-onset major depressive disorder, however the study sample was small

and they only compared the prevalence of the *APOE*-gene and late-onset depression and not the risk of developing late-life depression (50). However, a prior study has contradicting results that show no association with the *APOE*-gene and the risk of developing late-life depression (87). This study measured if the participants have had symptoms of depression during four follow-up examinations, however, they did not use DSM to set a depression diagnose, instead they used the Hospital Anxiety and Depression Scale (HADS) (87).

Based on the discussed studies and the result from our study it seems difficult to conclude if AD and late-life depression share genes or not, since the results are contradictive. As mentioned in the introduction, depression is a heterogenic disease with more than one subtype (43, 60). Subtypes, which can be based on specific symptoms and not diagnoses (major and minor depression), may have different genetic background (43), and in order to investigate that one would have to divide persons with different specific symptoms into smaller groups. Even though the depression group in our study was divided into two subgroups, the division could have been made based on specific symptoms instead of diagnoses. Then it might have been possible to see if AD is poly-genetically linked to one symptomatic subtype and not late-life depression in general.

As previously mentioned, dementia is an illness which includes different subtypes, two of which are vascular dementia and Alzheimer´s disease. Although they are two different subtypes, previous research has shown that vascular dysfunction plays a part in the development of Alzheimer´s disease (89-92). This is also accurate for depression, where vascular disease can increase the risk of developing depression and vascular changes in the brain triggers the development (93, 94). The prevalence of vascular disease increases with age, and possibly the genetic connection between AD and late-life depression occurs in genes connected to vascular pathology. However, this might not be evident in our study considering that the genes/SNPs included in our AD-PRS possibly are more connected to pure AD-pathology than to vascular pathology.

When it comes to cognition, no prior study has investigated PRS for cognitive performance and its potential association with late-life depression. However, there are prior studies (i.e.,

Yuan, S. et al 2021) that do not support that genetically predicted intelligence is associated with depression (95). In our study we did find an association between PRS for cognitive performance and late-life major depression. This suggests that genes of importance for general cognition can have a correlation with late-life depression, which contradicts the study by Yuan, S. et al (95). However, the study by Yuan. S. et al did not separate late-life depression and depression in younger age (95), and as already stated, different subtypes of depression can be genetically different from one another, which could be a possible explanation for the different results. A previous study has suggested that poorer cognitive ability has an association with mood disorders (96), which could support our finding that genes for general cognition are related with depression. However, this study, made by Gale, C.R., is only done on men and the outcome is mood disorders and not depression only (96). Further, the outcome was measured when the participants were in their middle-ages (96). Still, in the study: "Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age" the authors could show a connection between poorer cognitive ability and the risk of developing depression (97). However, this study was also solely made on men and measured depression in midlife, not late life (97). In the study "Intelligence in childhood and risk of psychological distress in adulthood" the results also showed that lower cognitive ability was related to a higher risk of developing depression (98). The study population was comprised of both men and women, but the examinations were made in early adulthood rather than later in life (98), and the outcome was measured as psychological distress (a state that includes depression, but also other conditions) (98). This, as well as the differences in the other studies, makes the results somewhat difficult to use for comparison with the results found in our study. Nonetheless the overall result of these studies is that a poorer cognitive ability increases the risk of developing depression, which might support the idea that genes for general cognitive ability may impact the risk of developing depression. Even though the studies discussed are not based on genetic risk, it suggests a connection similar to the one in our study.

In this study we used six versions of PRSs. Two of them were cognitionPRSs and four AD-PRSs (two including, and two excluding, the APOE-region). The AD-PRSs comprise SNPs that involve genes that mainly control functions involving cell development, signalling and

functions in the immune system (99, 100). When comparing if there were SNPs that were the same between the cognitionPRS and the AD-PRSs, there were none (84, 99). There are SNPs in the cognition PRS that are in close proximity to AD-PRS, however they are only a few (84, 99-101). Furthermore, there seems to be only one shared gene between the AD-PRS and the cognitionPRS which is the gene *SPPL2A* (84, 99-101). This means, in our study, when late-life depression is analysed in relation to the AD-PRSs and the cognitionPRSs different genes (apart from one gene) are investigated.

4.1. Strengths and weaknesses

There are several strengths with our study. The work with the diagnoses of depression and dementia was performed, or supervised, by psychiatrists which guarantee a high standard of the variables for depression and dementia used in this study. Additionally, the participants of this study were a homogenous group, in this case Caucasians with European ancestry. This is important in a study based on GWAS-data and when calculating PRS, since a large genomic difference between individuals decreases the chances of finding correct associations. The population-based design is also a strength, together with a high response rate for all the cohorts-studies, both for the first exams and for the follow-ups.

The study also has limitations. Since the study is based on a Caucasian population, the results are difficult to generalize to other ethnical groups. A limitation to the field of genetics in general is that the GWASs performed so far are mostly made on genetic material from individuals with European ancestry, and studies on individuals of Asian, African, and Hispanic descent are limited (102, 103). This makes it difficult to conduct PRS-studies on other ethnical groups than Europeans, and therefore to get results applicable on the entire population. Furthermore, the number of study participants was also quite small for a genetic study and this can lead to spurious findings due to limited power, and it was not possible for us to divide the depression group based on their symptoms. Another limitation to this study is that it is difficult to know whether the study participants have had a depression episode before baseline or if they have had an episode between follow-up examinations, which means some

of the participants may not have had late onset depression and some might have been included as “individuals without depression” due to episodes that were not registered. Since there was a limited amount of time for this study we did not have the opportunity to take education and socioeconomic status into account. These two covariates are important factors for development of mental health problems and they could possibly have had an impact on our results. Our study is made on older people and there is a lot of things that could happen later in life that can lead to a depressive episode. As an example, somatic diseases, as mentioned in the introduction, can lead to depression. Another example is loss of family and friends. Since our study only found a small significant association, it is possible that these discussed factors could have had an impact on our result.

4.2. Conclusion and future implications

In this study there was no evidence that depression has an association with a PRS for AD, neither when comparing with “any” depression (major and minor depression combined) or when subdividing the group into major and minor depression. However, prior research has shown that the connection between the diseases might be the reverse, that major depression-PRSs, have a relation with the development of AD (58), but these results were not significant after multiple testing correction (58). Even though the association was not significant this might be where we find a connection between the two diseases. Because of the heterogenic nature of depression, it has been hard to establish genome-significant SNPs in GWAS studies (45, 104) and maybe many of the genes important for depression is yet to be found, which makes future research on this connection desirable. Furthermore, because of the heterogenic nature of depression it would be interesting to investigate if a symptomatic subdividing of the depression group could change the results. However, in order to do that, the number of participants needs to be extremely large, and therefore such a study faces considerable challenges. An alternative to this design is to study depression as a continuous scale, which can be done if the MADRS scale is used as independent variable. Then the relationship between a participant´s MADRS score and AD-PRS could be evaluated, which also could be done on the cognitionPRS.

Even though our study did not show a connection between AD-PRS and late-life depression, a significant association was found between major depression and PRS for general cognitive performance. The effect size of the association was relatively small, but result might still suggest that late-life depression and general cognition are genetically linked, and this link might be one explanation to why these two illnesses are interconnected. However, future research is required to verify this association, partly due to the relatively small study sample. Moreover, the research on general cognition and late-life depression is not only unexplored when it comes to PRS, but also in general, and more research is necessary to establish if and what kind of connection late-life depression has with general cognitive ability. Furthermore, as previously stated, polygenic risk scores have to be calculated on genetic material that have the same ancestry. Therefore, future GWAS-studies may also concentrate on populations with another descent to enable risk prediction for the entire population, and not just a specific ethnical group (i.e., Europeans).

To summarize, even though our study did not support a connection between AD-PRS and depression it might give an insight to how late-life depression and cognition may be connected. The genetics behind depression and late-life depression are still not fully understood. Trying to increase the understanding of late-life depression could help us prevent and more efficiently treat the disease. However, even if this study might have given one more clue, more research is needed to understand the genetics behind late-life depression.

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Populärvetenskaplig sammanfattning

Depression sent i livet och sambandet med riskgener för Alzheimers sjukdom och gener för generell intellektuell förmåga

Depression sent i livet är ett ganska utbrett samhällsproblem och drabbar många. En annan vanlig diagnos i denna åldersgrupp är demens, där den vanligaste typen är Alzheimers sjukdom. Det är inte helt ovanligt att dessa två sjukdomar sammanfaller med varandra, det vill säga att en och samma person drabbas av båda sjukdomarna. Förutom detta så delar de även symptom. Personer som drabbas av depression sent i livet drabbas ganska ofta av minnessvårigheter, språkliga svårigheter samt nedsatt förmåga att utföra vardagliga sysslor (symptom som är vanliga för personer med en demenssjukdom) och patienter som drabbas av demens kan få symptom så som apati, minskad aptit och sömnsvårigheter (symptom som är vanliga för personer med en depressionsdiagnos).

Trots att dessa två sjukdomar har ganska många saker gemensamt så är sambandet mellan dem inte helt klarlagt. Ett samband som har utforskats är möjligheten att de delar riskgener, det vill säga att vissa gener ger ökad risk att drabbas av båda sjukdomarna, men resultaten har varit motstridiga. De flesta av våra vanliga sjukdomar är dock inte ett resultat av enskilda gener utan de är ett resultat av ett samspel mellan väldigt många olika gener och många små variationer i de olika generna. Variationer i olika gener, tillsammans med miljön, kan då ge en viss riskökning (eller riskminskning) för olika sjukdomar. Det går idag att kartlägga väldigt många genetiska variationer hos människor, och lägga ihop dem till en sammanlagd poäng. Denna poäng ger ett mått på en individs genetiska risk för en viss sjukdom. Beroende på vilka sjukdom/drag som studeras, kan olika riskpoäng för just dessa sjukdomar/drag räknas ut.

Forskning har visat på att en viss gen, kallad *APOE*, skulle kunna vara kopplad till båda sjukdomar, men huruvida det finns ett större genetiskt överlapp behöver utredas vidare.

Eftersom en av de få studier som analyserat depression i förhållande till en genetisk riskpoäng inte jämfört ett sådant här poäng både med och utan APOEgenen inräknad, ville vi se om det fanns en skillnad i resultat om detta gjordes. Därför ville vi undersöka om genetisk riskpoäng för Alzheimers, både med och utan *APOE*-genen, skulle kunna vara kopplat till depression senare i livet.

I vår studie, på en population med 3054 äldre personer, kunde vi dock inte se ett genetiskt samband mellan genetisk risk för Alzheimers och depression sent i livet. Dock hade vår studie även ett annat mål, vilket var att undersöka om depression sent i livet skulle kunna ha en association med ett genetiskt poäng för generell intellektuell förmåga. Detta för att se om det kunde ge ytterligare information om hur depression kan vara kopplat till intellektuella funktioner. I vår studie fick vi fram ett samband med en av undergrupperna av depression, men med tanke på vår relativt lilla studiepopulation måste detta resultat replikeras i en större studie för säkrare resultat.

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