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1 **Examining the association between genetic liability for schizophrenia and**

2 **psychotic symptoms in Alzheimer's disease**

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55

56 **Abstract**

57

58 Psychosis (delusions or hallucinations) in Alzheimer's disease (AD+P) occurs in up to 50% of

59 individuals and is associated with significantly worse clinical outcomes. Atypical

60 antipsychotics, first developed for schizophrenia, are commonly used in AD+P, suggesting

61 shared mechanisms. Despite this implication, little empirical research has been conducted to

62 examine whether there are mechanistic similarities between AD+P and schizophrenia. In this

63 study, we tested whether polygenic risk score (PRS) for schizophrenia was associated with

64 AD+P. Schizophrenia PRS was calculated using Psychiatric Genomics Consortium data at

65 10 GWAS p-value thresholds (P_T) in 3,111 AD cases characterized for psychosis using

66 validated, standardized tools. Association between PRS and AD+P status was tested by

67 logistic regression in each cohort individually and the results meta-analyzed. The

68 schizophrenia PRS was associated with AD+P at an optimum P_T of 0.01. The strongest

69 association was for delusions where a one standard deviation increase in PRS was associated

70 with a 1.18-fold increased risk (95% CI: 1.06-1.3; p=0.001). These new findings point towards

71 psychosis in AD – and particularly delusions – sharing some genetic liability with schizophrenia

72 and support a transdiagnostic view of psychotic symptoms across the lifespan.

73

74

75 Key words: psychosis, Alzheimer's disease, genetics, delusions, hallucinations.

1. Introduction

Psychosis in Alzheimer's disease (AD+P) - broadly comprising delusions and hallucinations - is experienced by up to 50% of people over the course of the illness, with prevalence peaking in the later stages [1]. AD+P is associated with accelerated cognitive decline (independent of disease duration), higher mortality rates and distress to both people with the disease and their carers [2-4]. Moreover, there are wider societal implications with long-term follow up studies indicating that AD+P is associated with a shorter time to nursing home care [5]. Despite these compelling reasons for effective management, there is a critical treatment gap, with no licensed treatments available in many jurisdictions. Atypical antipsychotics – developed first for schizophrenia – are frequently used to treat AD+P (in many countries off label) and, while they have some modest benefits, are associated with considerable harms, including a 1.5- to 1.8-fold increase in mortality and a 3- fold increase in stroke [6].

Clinically useful alternatives to antipsychotics are scarce. There are only two new antipsychotic compounds in phase II or later stages of development (pimavanserin and MP-101) but both are refinements of existing mechanisms of action of atypical antipsychotics targeting mechanisms relevant to schizophrenia (e.g. 5HT2A, mGluR2/3) and side effects remain a concern[7]. The limited understanding of the biological mechanisms underpinning AD+P represents a major challenge to the effective targeting of existing treatments and the identification of novel treatment targets.

One key question is whether some or all of the psychotic symptoms experienced by people with AD have a similar basis to schizophrenia. Phenomenologically the psychotic symptoms in each are different; in AD visual hallucinations are more common than auditory hallucinations, delusions are usually simple, and the so-called first rank symptoms of

102 schizophrenia are very rare. In addition, schizophrenia is characterized by both positive and

103 negative symptoms. While negative symptoms can also accompany psychosis in AD

104 consensus is yet to be reached on whether these other neuropsychiatric symptoms form part

105 of the AD+P clinical syndrome. Despite the different phenomenology, atypical antipsychotics

106 confer some treatment benefits in some cases of AD+P [8], and similar neuropsychological

107 deficits in processing speed and executive function have been observed in individuals with

108 very-late-onset schizophrenia-like psychosis and AD+P[9], suggesting some overlap.

109

110 A transdiagnostic hypothesis, proposing a mechanistic overlap between AD+P and

111 schizophrenia, is gaining some traction [10] and is supported by genetic studies of psychosis in

112 adolescence, the general adult population and Huntington's disease all showing overlap with

113 schizophrenia [11-13]. In view of these findings and the high heritability of schizophrenia [14] and

114 of AD+P (estimated at 81% and 61% respectively) [15], it is logical to look for common genetic

115 underpinnings of the two disorders. Comparative studies examining common mechanisms

116 between AD and schizophrenia point towards synaptic elimination and disruption, and

117 telomere length [16-18], but studies examining AD+P specifically and schizophrenia are less

118 common. It is of note that a recent major GWAS reported a nominally significant genetic

119 correlation between schizophrenia and AD [19]. It is possible that the presence of psychosis in

120 the AD sample (which was unknown in this study) was contributing to part of the association,

121 underscoring the need for dissection of the AD phenotype by psychosis status. In a small

122 study, a copy number variant (CNV) with significant overlap of a duplicated region implicated

123 in schizophrenia and autism (16p11.2) was found in two of 440 AD+P cases but not in AD

124 without psychosis, or in those with more occasional symptoms [20]. Linkage studies have also

125 implicated regions of the genome in AD+P that have been identified in schizophrenia [21, 22].

126 Another approach is to examine whether polygenic risk for schizophrenia, summarized in a

127 score (the weighted sum of risk associated alleles) with better discrimination properties than

128 single markers [23], is associated with AD+P. Work in this area is limited to only one recent

129   study which, surprisingly, reported that a genetic risk score comprising 94 SNPs reaching

130   genome wide significance for association with schizophrenia was lower in AD+P compared

131   with AD without psychosis [24]. While this study represents an important preliminary step in

132   AD+P research, a full genome-wide polygenic risk score (PRS) approach is imperative to

133   address this key question[25, 26].

134

135   Another largely unexplored avenue in AD+P genetic research relates to the split of delusions

136   and hallucinations. Although the two symptoms frequently co-occur in AD, there is evidence

137   from longitudinal cohort studies indicating that 10-20% of people experience hallucinations

138   without delusions and that the two symptoms are associated with different clinical outcomes [2,

139   27], suggesting the presence of two distinct clinical phenotypes. While it is commonplace to

140   separate out composite psychotic symptoms in neuroimaging studies of AD+P [28, 29], their

141   separate genetic associations have not yet been examined in any large-scale AD studies

142   leveraging GWAS data [30]. This is a particularly relevant issue when assessing genetic overlap

143   with schizophrenia where the emerging evidence from neuroimaging and the clinical similarity

144   supports the hypothesis that shared etiology would be specific to delusions.

145

146   We conducted an analysis of the relationship between genetic liability for schizophrenia and

147   AD+P with two principal objectives; firstly, we tested whether a PRS for schizophrenia was

148   associated with AD+P and secondly, we examined the association of the PRS with AD+P

149   stratified to focus on delusions.

150

151   **2. Methods**

152

Ethical approval for this analysis protocol was obtained from University of Exeter Medical School Research Ethics Committee (Nov17/D/143).

2.1 Cohorts

AD+P target data consisted of 3,111 AD cases from 11 cohort studies in Europe and the USA: AddNeuroMed [31] (Europe, longitudinal: assessment every three months for maximum 1 year), Alzheimer's Disease Neuroimaging Initiative [32] (ADNI; USA, longitudinal: assessment baseline, 6, 12, 24 and 36 months for maximum 3 years), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS 1; Italy, cross sectional), Health and Memory Study in Nord-Trøndelag [33] (HMS; Norway, cross sectional), Resource Use and Disease Couse in Dementia [34] (REDIC; Norway, longitudinal: assessment every 6 months for maximum 2.5 years), Norwegian registry of persons assessed for cognitive symptoms [35] (NorCog; Norway, cross sectional), Samhandling mellom avdeling for alderspsykiatri og kommunale sykehjem (SAM-AKS; Norway, cross sectional), The Dementia Study in Northern Norway [36] (NordNorge, Norway, longitudinal: assessment baseline and 1 year), Progression of Alzheimer's Disease and Resource Use [37] (PADR; Norway, longitudinal: assessment baseline and 1 year), The Dementia Study in Western Norway [38] (DemVest; Norway, longitudinal: assessment every 12 months maximum 6 years); and data from the National Alzheimer's Coordinating Center (NACC; USA, longitudinal: assessment approximately every 12 months) and the National Institute on Aging Genetics Data Storage Site (NIAGADS), Table 1). Full cohort details are contained in the supplementary material and the Norwegian cohorts are also described in the latest GWAS of Alzheimer's disease [39]. Informed consent was obtained by each study for all participants.

Some data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

2.2 AD clinical assessments

Diagnosis of AD was performed according to ICD-10 etiological diagnosis, NINCDS-ADRDA criteria or clinical diagnosis by psychiatrist or geriatrician. Longitudinal data was available for 7 cohorts (ADNI, AddNeuroMed, DemVest, NordNorge, PADR, REDIC, NACC) and psychotic symptom classification was on the maximum amount of follow up data available. Any cases with a history of bipolar disorder or schizophrenia were excluded. For NorCog, PADR, REDIC, SAM-AKS, NACC and ADNI the necessary information on psychiatric history was extracted from source study data resulting in 3, 1, 2, 1, 31 and 1 exclusions respectively. For AddNeuroMed, DemVest, IRCCS 1 and NordNorge this was an exclusion criterion applied at entry to those individual studies. No information about psychiatric history was available for the HMS study. Dementia severity was assessed in all cohorts by Mini Mental State Examination (MMSE) and psychotic symptoms were assessed by the Neuropsychiatric Inventory (NPI) or its short version, the Neuropsychiatric Inventory Questionnaire (NPI-Q), they are among the most widely used validated instruments to assess psychosis[40]. Psychotic symptoms are rated on the basis of items A (delusions) and B (hallucinations) of the NPI and NPI-Q. These are two different versions of the same scale, which are strongly correlated and

203   have good between-rater and test-retest reliability, particularly for the psychosis items [31, 43].

204   Ratings were carried about by trained research staff in all cases. In the full NPI,

205   neuropsychiatric symptoms are coded as present or absent first. If rated present they are

206   further scored according to their frequency (1-4) and severity (1-3) with the resulting scores

207   multiplied to give an overall rating (i.e. possible scores are 1,2,3,4,6,8,9 and 12 with 0

208   indicating no symptoms). The NPI-Q is rated only on a scale of 0 to 3 according to the severity

209   of the symptom. Both scales have been designed to be completed by verbal interview with a

210   proxy informant who knows the person with AD well. Several diagnostic criteria for AD+P

211   have been proposed but none have been adopted clinically, meaning that where in other

212   psychiatric disorders medical records can be screened, in AD+P this would be unreliable and

213   ratings on specific validated assessment scales must be used. Using such scales, we thus

214   undertook examination of three related but progressively more homogenous psychotic

215   phenotypes:

216

217   *1. Psychosis wide:* Psychosis present: the presence of delusions or hallucinations (>0)

218   at any point; No psychosis: no evidence of delusions or hallucinations at any point in

219   follow up.

220

221   *2. Psychosis narrow:* Psychosis present: the presence of delusions or hallucinations (>0)

222   at any point; No psychosis: here, an additional level of screening was applied to those

223   rated as having no delusions or hallucinations. In these cases, if an individual was

224   psychosis-free based on criteria for psychosis wide but had not yet reached a

225   moderately-severe dementia stage based on available data (defined as MMSE<20)

226   they were excluded from the analysis. This is a similar approach to that used in most

227   previous AD+P genetic research [24, 41].

228

229   *3. Delusions narrow:* Delusions present: the presence of delusions (>0) at any point

230   during follow up. Thus, the delusion group was the psychosis group above with any

231   individuals rated as having hallucinations only removed. No delusions: as per

232   psychosis narrow.

233

234   2.3 Genotyping and QC

235

236   The genotyping chips used are detailed in Table 1. Raw genotype data for individual cohorts

237   underwent appropriate QC steps (implemented in PLINK). SNPs with a minor allele frequency

238   ≤5% and a Hardy Weinberg equilibrium $p < 10^{-5}$ were excluded. The SNP and individual

239   genotype failure threshold was set at 5% and individuals with mean heterozygosity ±3

240   standard deviations were excluded. The analysis was restricted to individuals of European

241   ancestry using genetic principal components computed by EIGENSTRAT. Related (pi-hat

242   >0.2) or duplicate individuals both within and between cohorts were excluded. Phasing

243   (EAGLE2) and imputation (PBWT) was done via the Sanger Imputation Service using the

244   Haplotype Reference Consortium (r1.1) reference panel on all cohorts. After imputation only

245   SNPs with an imputation quality (INFO) score >0.4 and MAF >0.05 were retained. This

246   resulted in 4,895,913 SNPs common across all eleven cohorts available to compute polygenic

247   risk scores.

248

249   The most recently published schizophrenia GWAS data from the Psychiatric Genomics

250   Consortium (PGC) was used as base data to generate PRS in the target AD sample [26]. SNPs

251   with MAF<0.1, INFO<0.9 and indels were excluded from the base dataset to leave only the

252   most informative SNPs and only one SNP from the extended MHC region was included [42]. As

253   a positive control and to evaluate the specificity of the association we then generated PRS of

254   height and depression using the latest GIANT consortium and PGC GWAS results [43, 44].

255

256   2.4 Analysis

257

258   PRS for schizophrenia were generated in PRSice [45] at the following 10 GWAS p-value

259   thresholds (P_T): 5×10^{-8}, 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 0.01, 0.05, 0.1, 0.2, 0.5 and 1. Clumping was

260   performed (250kb, r2>0.1) to retain only the SNP with the strongest association in each

261   window. The resulting PRS were standardized (centering by mean, scaling by standard

262   deviation) for the analysis.

263

264   Power was calculated using AVENGEME[46], with schizophrenia parameters as set out in Palla

265   and Dudbridge[46], number of markers genotyped in both datasets was 76,213 (see section

266   3.1), a prevalence of 40%[1] and of 36%[1] was used for psychosis and delusions, and case

267   control sample fractions as per Table 2. There is no data available for estimated covariance

268   between AD+P and schizophrenia but if this value is assumed to be 0.08 (less than the 0.13

269   and 0.17 for schizophrenia and major depressive disorder and bipolar disorder estimated by

270   AVENGEME[46]), this study has >=80% power for each P_T>=0.01 for psychosis and delusions

271   respectively but <80% power below this value. All statistical analysis was implemented in R.

272   For each cohort 10 logistic regression models (one per P_T) were run with each of the previously

273   defined psychosis phenotypes as the binary outcome and the first 10 ancestry principal

274   components included as covariates. Disease severity is accounted for in our 'narrow'

275   phenotype definitions and as there is no strong evidence that age and gender are associated

276   with AD+P[1] so these were not included as covariates. Logistic regression assumptions were

277   confirmed using the R 'car' package. Proportion of variance explained (R^2) by PRS, on the

278   observed scale, was determined by subtracting the Nagelkerke's pseudo-R^2 of the null model

279   from that of the full model. Regression coefficients for each P_T across all cohorts were then

280   included in random effects meta-analyses to account for between-study variation in data

281 collection protocols, frequency of psychosis and dementia severity [47-49]. Meta-analysis was

282 undertaken using the 'rma' function in the 'metafor' package using the REML method [50].

283 Because the PRS calculated were correlated a Bonferroni correction for multiple testing was

284 considered too stringent. Using a correlation matrix of the 10 PRS and the matSpD tool

285 https://gump.qimr.edu.au/general/daleN/matSpD/), the effective number of independent tests

286 was determined to be 5 and the experiment-wide significance threshold for type I error rate of

287 5% determined to be p=0.01. All tests reported are two-sided.

288

3. Results

290

291 On average across all eleven cohorts, individuals were in the mild-moderate stages of

292 dementia at first assessment (mean MMSE of 19). Mean MMSE by cohort ranged from an

293 MMSE of 12 (IRCCS 1) to 24 (ADNI) and this was a correlate of the prevalence of psychosis

294 in each cohort (note the denominator would be the overall cohort N in Table 1), with cohorts

295 that contained individuals with more severe dementia typically having a higher proportion of

296 people with psychosis. Between cohorts, mean age at baseline ranged from 75 to 87 years

297 and the proportion of male participants ranged from 26% to 59%. There was little difference

298 in age between the psychosis and no psychosis groups across all studies but gender

299 distributions did differ.

300

301 Frequency of the three phenotypes investigated by cohort is shown in Table 2. Of the 3,111

302 individuals screened, 1,116 (36%) had psychosis (wide definition group). Of the 1,995 who

303 were rated as having no psychosis based on their assessment scale result alone, 879 had not

304 yet reached the moderate stages of disease and so were excluded; 1,116 AD+P cases and

305 1,116 AD no psychosis 'controls' were included in the analysis of the narrow phenotype of

306 psychosis. 936 cases met the criteria for having delusions narrow.

307

3.1 Schizophrenia PRS is associated with AD psychosis status

309

310 After clumping, 76,213 independent variants were available for computing PRS. Random

311 effects meta-analysis across the 11 cohorts showed the largest OR for the schizophrenia PRS

312 was at P_T=0.01 and this was significantly associated with symptom status across the

313 psychosis wide, psychosis narrow and delusions narrow phenotypes despite the progressively

314 smaller sample size in each of these groups (OR: 1.14 95% CI:1.05-1.23, p=0.003; OR: 1.16

315 95% CI:1.06-1.28 p=0.004; OR: 1.18 95% CI:1.06-1.30, p=0.001 respectively), see Figure 1

316 and Table 3. PRS was also significantly associated with both the psychosis narrow and

317 delusions narrow phenotypes at every P_T >0.01. The largest effect size was observed in the

318 delusions narrow group. Overall, there was no evidence of significant heterogeneity; I^2

319 statistics were close to 0% for P_T =0.01 across the three phenotypes.

320

321 In the individual cohort analysis, we observed that the effect estimates of association between

322 schizophrenia PRS and AD+P in nine of the 11 studies were in the same direction (OR>1);

323 albeit not statistically significantly (Supplementary Table 1). A forest plot of individual study

324 estimates for delusions narrow at P_T=0.01, the strongest association found in the above meta-

325 analysis, is shown in Figure 2. A similar plot at P_T=1 for comparison is shown in the

326 Supplementary material along with plots for psychosis wide and psychosis narrow

327 phenotypes. The highest Nagelkerke's R^2 estimate was 2.9% (AddNeuroMed) and the lowest

328 was <0.1% (IRCCS 1). An overall variance explained (Nagelkerke's R^2) in AD+P by

329 schizophrenia PRS of 0.08% was estimated by calculating the weighted average R^2 across

330 the 11 studies. To determine the specificity of the signal, PRS for major depression (using the

331 PGC GWAS[44]) and height (GIANT consortium GWAS[43]) were generated post-hoc at P_T=1 and

332 tested for association with delusions using the same procedure as described in Section 2.4.

333   Neither PRS showed any evidence of association (major depression: OR: 1.03, 95% CI: 0.91-

334   1.18, p=0.61; height: OR: 0.99, 95% CI: 0.85-1.17, p=0.99).

335

336   **4. Discussion**

337

338   We set out to examine whether genetic risk for psychotic symptoms in AD (AD+P) is

339   attributable to common schizophrenia variants. Using polygenic scoring, we found that

340   schizophrenia PRS was associated with AD+P in a collection of over 3,000 well characterized

341   cases and the association persisted as the AD+P phenotype was more precisely defined

342   resulting in a smaller N. The largest effect size was observed at P_T=0.01 which was

343   associated with a 1.14, 1.16 and 1.18-fold (per standard deviation increase in PRS) increased

344   risk of psychosis (wide), psychosis (narrow) and delusions (narrow) respectively. In the

345   individual cohort analysis, the odds ratios of nine of the eleven studies were in the same

346   direction (OR>1). In all, these new findings suggest that AD+P is part of a spectrum of

347   neuropsychiatric conditions characterized by psychosis across the lifespan but in common

348   with other PRS studies in psychiatric genomics are yet not appropriate for symptom or disease

349   course prediction. Although the variance explained by schizophrenia PRS in AD+P is only

350   modest, with the R^2 estimates being less than 1%, this should be seen in the context of the

351   same PRS explaining around 2.5% of the variance in bipolar disorder and 1% in MDD in a

352   cross-disorder analysis of the Psychiatric Genomics Consortium with significantly larger target

353   sample sizes [51].

354

355   In line with our findings, a recent study in UK Biobank, found psychotic experiences in the

356   general population to be associated with PRS for schizophrenia, with the strongest association

357   observed for delusions [12]. Several possible conclusions can be drawn from the finding that

358   the association was still observed in the delusions phenotype in this study, despite a

359 considerably smaller N compared with the psychosis phenotypes. This finding may point

360 towards a subset of AD+P patients that have a more schizophrenia-like phenotype. More

361 work is needed to investigate whether further diagnostic refinements to AD+P syndrome

362 definitions are necessary, which may provide a more robust approach for pharmacological

363 intervention trials. Related to this, from a methodological point of view, we show that there is

364 a need for future studies in AD to consider delusions and hallucinations separately. We cannot

365 rule out a genetic association between hallucinations in AD and schizophrenia in these cohorts

366 but the evidence at present suggests a weaker association than for delusions. One might

367 speculate that this is due to visual hallucinations in AD being more often the result of a broader

368 range of causes (e.g. visual hallucinations due to medication or delirium) than delusions, thus

369 introducing more noise into the phenotype. The final wider implication is related to the

370 schizophrenia PRS being associated with a broad spectrum of psychotic disorders and

371 personality traits [11-13, 51-53]. Our findings support a transdiagnostic explanation of delusions,

372 which reaches into neurodegenerative disease and is underpinned by a degree of common

373 genetic liability.

374

375 A key strength of our study is the detailed phenotyping with longitudinal data being available

376 in seven of the eleven cohorts. Rather than relying on medical record screens, which would

377 be highly unreliable for AD+P given the lack of universally accepted and used diagnostic

378 criteria, every individual in our analysis was assessed using specific, reliable assessment

379 tools. We then used this data to dissect AD+P phenotype genetics for the first time by focusing

380 on delusions as well as the broader syndrome. We also followed previous research by taking

381 extra measures to screen the 'control' groups. This removed any cases in the mild stages of

382 disease who had not yet developed symptoms (i.e. those still at risk [1]). This approach has

383 been used in most previous genetic research but our extension to focus on delusions in AD+P

384 is novel. Our finding that this more precision definition the phenotype strengthened the

385 association is consistent with genetic studies of other polygenic traits, like depression [44].

386

387　For one study (HMS) data on history of major psychiatric conditions were not available. It is

388　possible that some individuals with schizophrenia were present in this cohort however HMS is

389　a cohort with a mean age of 87 so it is highly unlikely that the number would be more than one

390　or two out of 178 people in the HMS cohort (this is also supported by the very small numbers

391　we found among the other studies we screened). With over 3,000 samples, this is, to our

392　knowledge, the largest analysis of AD+P to exploit GWAS data [41]. We acknowledge that using

393　different cohorts has led to some variability due to sampling but it is important to acknowledge

394　that there are no single cohorts which are large enough to conduct an analysis of this kind and

395　because of potential sampling and protocol variations across the individual studies we ensured

396　an appropriate analysis was implemented to account for this variability; the same approach as

397　used in other studies examining PRS in complex phenotypes [47-49]. We had access to raw

398　individual-level clinical and genotype data, allowing us to run the same regression models in

399　each study. This included undertaking the same QC across cohorts, imputing all chip data to

400　the same reference panel and analyzing only SNPs present across all cohorts. After ensuring

401　this standardized process was followed for each cohort we ran a random effects meta-

402　analysis, allowing for the effect of the PRS on AD+P to vary across studies. In all, and in the

403　absence of a single large enough study, these measures provide the most robust estimates,

404　as reflected in the low heterogeneity statistics of the meta-analysis and the narrow range of

405　effect estimates and overlapping confidence intervals across the eleven studies included

406　(Figure 2 and Supplementary figures 1-3). Finally, as with all similar studies, these results are

407　not generalizable to individuals with non-European ancestry; there is an equal imperative to

408　extend the genomics of AD+P to other populations as in AD itself.

409

410　A previous study which examined a genetic risk score at a more conservative P_T comprised of

411　only 94 genome-wide significant schizophrenia SNPs found it to be lower in AD+P cases[24].

412 Our study is a similar size to this previous study, and the NACC data was used in both. Given

413 that a PRS with only 94 SNPs will be a less powerful predictor than a full genome-wide score

414 it is possible larger studies will be needed to confirm associations at this more conservative

415 P_T. Nevertheless, schizophrenia is highly polygenic; tens of thousands of markers explain

416 only 7% of the variance on the liability scale, while for optimum cross-trait case-control (e.g.

417 schizophrenia and bipolar) prediction many thousands more SNPs are required[51]. In addition,

418 cases of schizophrenia in the PGC study (used as base sample to estimate PRS), include

419 patients with both a positive and negative syndrome. There is evidence that negative and

420 disorganized symptoms are more heritable than positive, which – although we report a positive

421 association – may reduce the power of schizophrenia PRS at more conservative P_T to

422 discriminate AD cases with or without psychotic symptoms [54, 55]. Accordingly, a full account

423 of association between schizophrenia and AD+P should exploit the full polygenic nature of

424 schizophrenia; our study is the first to do this and the findings represent an important further

425 step towards a complete account of the relationship between common schizophrenia variants

426 and AD+P. Another important milestone will be an appropriately powered discovery GWAS

427 of AD+P and all of these points underscore the need for increasing samples sizes in this field.

428

429 In summary, these findings support shared genetic liability between schizophrenia and

430 delusions in AD. This provides a strong rationale for further work to build a clearer clinical and

431 biological understanding of the psychosis syndrome in AD, an urgently needed step for better

432 management and treatment development.

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508 **Conflict of Interest**

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REFERENCES

1. Ropacki SA, Jeste DV. Epidemiology of and Risk Factors for Psychosis of Alzheimer's Disease: A Review of 55 Studies Published From 1990 to 2003. *American Journal of Psychiatry* 2005; **162**(11)**:** 2022-2030.

2. Connors MH, Ames D, Woodward M, Brodaty H. Psychosis and Clinical Outcomes in Alzheimer Disease: A Longitudinal Study. *The American Journal of Geriatric Psychiatry* 2017.

3. Weamer EA *et al.* The Relationship of Excess Cognitive Impairment in MCI and Early Alzheimer Disease to the Subsequent Emergence of Psychosis. *International psychogeriatrics / IPA* 2009; **21**(1)**:** 78-85.

4. Savva GM *et al.* Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *The British Journal of Psychiatry* 2009; **194**(3)**:** 212.

5. Wergeland JN, Selbæk G, Bergh S, Soederhamn U, Kirkevold Ø. Predictors for Nursing Home Admission and Death among Community-Dwelling People 70 Years and Older Who Receive Domiciliary Care. *Dementia and Geriatric Cognitive Disorders Extra* 2015; **5**(3)**:** 320-329.

6. Corbett A, Smith J, Creese B, Ballard C. Treatment of behavioral and psychological symptoms of Alzheimer's disease. *Current treatment options in neurology* 2012; **14**(2)**:** 113-125.

7. Creese B, Da Silva MV, Johar I, Ballard C. The modern role of antipsychotics for the treatment of agitation and psychosis in Alzheimer's disease. *Expert Review of Neurotherapeutics* 2018; **18**(6)**:** 461-467.

8. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci* 2006; **7**(6)**:** 492-500.

9. Van Assche L *et al.* The Neuropsychological Profile and Phenomenology of Late Onset Psychosis: A Cross-sectional Study on the Differential Diagnosis of Very-Late-Onset Schizophrenia-Like Psychosis, Dementia with Lewy Bodies and Alzheimer's Type Dementia with Psychosis. *Arch Clin Neuropsychol* 2019; **34**(2)**:** 183-199.

10. Bebbington P, Freeman D. Transdiagnostic Extension of Delusions: Schizophrenia and Beyond. *Schizophrenia Bulletin* 2017; **43**(2)**:** 273-282.

11. Pain O *et al.* Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2018; **177**(4)**:** 416-425.

559 12. Legge SE *et al.* Genetic association study of psychotic experiences in UK Biobank. *bioRxiv* 2019**:**
560   583468.

561
562 13. Ellis N *et al.* Genetic risk underlying psychiatric and cognitive symptoms in Huntington's
563   Disease. *bioRxiv* 2019**:** 639658.

564
565 14. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-
566   analysis of twin studies. *Arch Gen Psychiatry* 2003; **60**(12)**:** 1187-1192.

567
568 15. Bacanu SA *et al.* Heritability of psychosis in Alzheimer disease. *The American journal of*
569   *geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2005;
570   **13**(7)**:** 624-627.

571
572 16. Alexandrov PN, Zhao Y, Jaber V, Cong L, Lukiw WJ. Deficits in the Proline-Rich Synapse-
573   Associated Shank3 Protein in Multiple Neuropsychiatric Disorders. *Frontiers in Neurology*
574   2017; **8**(670).

575
576 17. Cardozo PL *et al.* Synaptic Elimination in Neurological Disorders. *Curr Neuropharmacol* 2019.

577
578 18. Anitha A, Thanseem I, Vasu MM, Viswambharan V, Poovathinal SA. Telomeres in neurological
579   disorders. *Adv Clin Chem* 2019; **90:** 81-132.

580
581 19. Jansen IE *et al.* Genome-wide meta-analysis identifies new loci and functional pathways
582   influencing Alzheimer's disease risk. *Nature Genetics* 2019.

583
584 20. Zheng X *et al.* A Rare Duplication on Chromosome 16p11.2 Is Identified in Patients with
585   Psychosis in Alzheimer's Disease. *PLoS ONE* 2014; **9**(11)**:** e111462.

586
587 21. Hollingworth P *et al.* Increased familial risk and genomewide significant linkage for Alzheimer's
588   disease with psychosis. *American journal of medical genetics Part B, Neuropsychiatric genetics*
589   *: the official publication of the International Society of Psychiatric Genetics* 2007; **144b**(7)**:** 841-
590   848.

591
592 22. Shah C, DeMichele-Sweet MAA, Sweet RA. Genetics of psychosis of Alzheimer disease.
593   *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2017; **174**(1)**:** 27-35.

594
595 23. Dudbridge F. Power and Predictive Accuracy of Polygenic Risk Scores. *PLoS Genetics* 2013;
596   **9**(3)**:** e1003348.

597
598 24. DeMichele-Sweet MAA *et al.* Genetic risk for schizophrenia and psychosis in Alzheimer
599   disease. *Mol Psychiatry* 2017.

600
601 25. International Schizophrenia C. Common polygenic variation contributes to risk of
602   schizophrenia that overlaps with bipolar disorder. *Nature* 2009; **460**(7256)**:** 748-752.

26. Ripke S *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**.

27. Qian W, Fischer CE, Schweizer TA, Munoz DG. Association Between Psychosis Phenotype and APOE Genotype on the Clinical Profiles of Alzheimer's Disease. *Current Alzheimer Research* 2018; **15**(2)**:** 187-194.

28. McLachlan E, Bousfield J, Howard R, Reeves S. Reduced parahippocampal volume and psychosis symptoms in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 2018; **33**(2)**:** 389-395.

29. Darby RR, Laganiere S, Pascual-Leone A, Prasad S, Fox MD. Finding the imposter: brain connectivity of lesions causing delusional misidentifications. *Brain : a journal of neurology* 2017; **140**(2)**:** 497-507.

30. Fischer CE, Sweet RA. Psychosis in Alzheimer's Disease: a Review of Recent Research Findings. *Current Behavioral Neuroscience Reports* 2016; **3**(4)**:** 308-317.

31. Lovestone S *et al.* AddNeuroMed--the European collaboration for the discovery of novel biomarkers for Alzheimer's disease. *Annals of the New York Academy of Sciences* 2009; **1180:** 36-46.

32. Mueller SG *et al.* Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimer's & Dementia* 2005; **1**(1)**:** 55-66.

33. Bergh S *et al.* Cohort Profile: The Health and Memory Study (HMS): a dementia cohort linked to the HUNT study in Norway. *International Journal of Epidemiology* 2014; **43**(6)**:** 1759-1768.

34. Roen I *et al.* Resourse use and disease couse in dementia - nursing home (REDIC-NH), a longitudinal cohort study; design and patient characteristics at admission to norwegian nursing homes. *BMC Health Services Research* 2017; **17**.

35. Helvik AS, Engedal K, Šaltytė Benth J, Selbæk G. Time from Symptom Debut to Dementia Assessment by the Specialist Healthcare Service in Norway. *Dementia and Geriatric Cognitive Disorders Extra* 2018; **8**(1)**:** 117-127.

36. Andersen F *et al.* Recruitment methods in Alzheimer's disease research: general practice versus population based screening by mail. *BMC Medical Research Methodology* 2010; **10**(1)**:** 35.

37. Eldholm RS *et al.* Progression of Alzheimer's Disease: A Longitudinal Study in Norwegian Memory Clinics. *J Alzheimers Dis* 2018; **61**(3)**:** 1221-1232.

647   38.   Vik-Mo AO, Bencze J, Ballard C, Hortobágyi T, Aarsland D. Advanced cerebral amyloid
648   angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease.
649   *Journal of Neurology, Neurosurgery &amp; Psychiatry* 2018: jnnp-2018-318445.

650
651   39.   Jansen IE *et al.* Genome-wide meta-analysis identifies new loci and functional pathways
652   influencing Alzheimer's disease risk. *Nature Genetics* 2019; **51**(3)**:** 404-413.

653
654   40.   Kaufer DI *et al.* Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory.
655   *J Neuropsychiatry Clin Neurosci* 2000; **12**(2)**:** 233-239.

656
657   41.   Hollingworth P *et al.* Genome-wide association study of Alzheimer's disease with psychotic
658   symptoms. *Mol Psychiatry* 2012; **17**(12)**:** 1316-1327.

659
660   42.   Vassos E *et al.* An Examination of Polygenic Score Risk Prediction in Individuals With First-
661   Episode Psychosis. *Biol Psychiatry* 2017; **81**(6)**:** 470-477.

662
663   43.   Yengo L *et al.* Meta-analysis of genome-wide association studies for height and body mass
664   index in ∼700000 individuals of European ancestry. *Human Molecular Genetics* 2018; **27**(20)**:**
665   3641-3649.

666
667   44.   Wray NR *et al.* Genome-wide association analyses identify 44 risk variants and refine the
668   genetic architecture of major depression. *Nature genetics* 2018; **50**(5)**:** 668-681.

669
670   45.   Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics* 2015;
671   **31**(9)**:** 1466-1468.

672
673   46.   Palla L, Dudbridge F. A Fast Method that Uses Polygenic Scores to Estimate the Variance
674   Explained by Genome-wide Marker Panels and the Proportion of Variants Affecting a Trait.
675   *The American Journal of Human Genetics* 2015; **97**(2)**:** 250-259.

676
677   47.   Peyrot WJ *et al.* Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-
678   analysis of 5765 Subjects From the Psychiatric Genomics Consortium. *Biol Psychiatry* 2018;
679   **84**(2)**:** 138-147.

680
681   48.   Ward J *et al.* Polygenic risk scores for major depressive disorder and neuroticism as predictors
682   of antidepressant response: Meta-analysis of three treatment cohorts. *PLOS ONE* 2018; **13**(9)**:**
683   e0203896.

684
685   49.   Zhang J-P *et al.* Schizophrenia Polygenic Risk Score as a Predictor of Antipsychotic Efficacy in
686   First-Episode Psychosis. *American Journal of Psychiatry* 2018; **176**(1)**:** 21-28.

687
688   50.   Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *2010* 2010; **36**(3)**:**
689   48.

690

691   51.   Consortium C-DGotPG. Identification of risk loci with shared effects on five major psychiatric
692   disorders: a genome-wide analysis. *Lancet (London, England)* 2013; **381**(9875)**:** 1371-1379.

693

694   52.   Smeland OB *et al.* Identification of genetic loci shared between schizophrenia and the Big Five
695   personality traits. *Scientific Reports* 2017; **7:** 2222.

696

697   53.   Power RA *et al.* Polygenic risk scores for schizophrenia and bipolar disorder predict creativity.
698   *Nature Neuroscience* 2015; **18:** 953.

699

700   54.   Fanous AH *et al.* Genome-wide association study of clinical dimensions of schizophrenia:
701   polygenic effect on disorganized symptoms. *Am J Psychiatry* 2012; **169**(12)**:** 1309-1317.

702

703   55.   Cardno AG, Sham PC, Murray RM, McGuffin P. Twin study of symptom dimensions in
704   psychoses. *Br J Psychiatry* 2001; **179:** 39-45.

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Table 1: Baseline characteristics by cohort

	N	Age				Gender		MMSE				Scale	Follow up (years)*+	Number of assessments done+	Array
		AD-P		AD+P		AD-P	AD+P	AD-P		AD+P					
		Mean	SD	Mean	SD	% male	% male	Mean	SD	Mean	SD				
AddNeuroMed	225	76	7	78	5.6	42	24	21	4.6	20	4.8	NPI	1	5	Illumina 610
ADNI	248	76	7.2	74	7.4	63	43	24	2.5	23	2.5	NPI-Q	3	4	Illumina OmniExpress
DemVest	80	77	8.3	76	5.5	23	38	24	2.4	23	2.4	NPI	5	6	Illumina OmniExpress
IRCCS 1	326	78	7.4	79	6.4	44	36	14	6.1	10	6.3	NPI	0	1	Illumina GSA
HMS	178	86	6.2	86	7.6	24	28	14	6.8	12	6.0	NPI	0	1	Illumina OmniExpress
NorCog	563	74	9.1	77	8.2	43	39	22	4.2	21	4.6	NPI-Q	0	1	Illumina OmniExpress
NordNorge	133	80	6.7	83	6.2	42	36	24	4.3	22	4.5	NPI	1	2	Illumina OmniExpress
PADR	106	76	6.6	77	6.6	35	30	21	4.3	21	4.4	NPI-Q	1	2	Illumina OmniExpress
REDIC	323	86	6.9	84	7.4	35	32	17	6.4	16	6.5	NPI	2	5	Illumina OmniExpress
SAM-AKS	93	86	6.8	86	5	29	38	16	5.0	15	5.2	NPI	0	1	Illumina OmniExpress
NACC	836	79	7.8	78	9	54	44	20	7.1	19	7.0	NPI-Q	2	3	Illumina 660/Omni Express
TOTAL	**3111**	**79**	**8.7**	**80**	**8.2**	**44**	**37**	**20**	**6**	**18**	**6.8**	**-**	**-**	**-**	**-**

709   NPI: Neuropsychiatric Inventory (full version); NPI-Q: Neuropsychiatric Inventory- Questionnaire; MMSE: Mini Mental State Examination

710   *'0' denotes that the study was cross sectional (i.e. one assessment available)

711   +figures are median

712

713

714 **Table 2: Frequencies of symptoms by cohort for the three psychosis phenotypes**

	Psychosis wide					Psychosis narrow					Delusions narrow				
	N	**Absent**		**Present**		**N**	**Absent**		**Present**		**N**	**Absent**		**Present**	
		n	%	n	%		n	%	n	%		n	%	n	%
AddNeuroMed	225	133	59	92	41	157	65	41	92	59	142	65	46	77	54
ADNI	248	183	74	65	26	117	52	44	65	56	99	52	53	47	47
DemVest	80	30	38	50	63	75	25	33	50	67	69	25	36	44	64
IRCCS 1	326	222	68	104	32	293	189	65	104	35	271	189	70	82	30
HMS	178	107	60	71	40	162	91	56	71	44	152	91	60	61	40
NorCog	563	402	71	161	29	288	127	44	161	56	260	127	49	133	51
NordNorge	133	105	79	28	21	45	17	38	28	62	38	17	45	21	55
PADR	106	62	58	44	42	83	39	47	44	53	80	39	49	41	51
REDIC	323	158	49	165	51	276	111	40	165	60	265	111	42	154	58
SAM-AKS	93	73	78	20	22	80	60	75	20	25	75	60	80	15	20
NACC	836	520	62	316	38	656	340	52	316	48	601	340	57	261	43
TOTAL	**3111**	**1995**	**64**	**1116**	**36**	**2232**	**1116**	**50**	**1116**	**50**	**2052**	**1116**	**54**	**936**	**46**

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716 Percentages may not sum to 100 due to rounding.

717

Table 3: Random effects meta-analysis results for association between schizophrenia PRS across 10 GWAS thresholds (P_T) and AD+P.

P_T	nSNPs	Psychosis wide OR	95% CI			P	Psychosis narrow OR	95% CI			P	Delusions narrow OR	95% CI			P
5×10^{-08}	125	1.04	0.96	-	1.13	0.32	1.01	0.92	-	1.10	0.89	1.03	0.94	-	1.14	0.48
1×10^{-05}	511	1.07	0.98	-	1.16	0.15	1.06	0.97	-	1.16	0.20	1.06	0.97	-	1.17	0.20
1×10^{-04}	1147	1.07	0.96	-	1.18	0.21	1.07	0.96	-	1.19	0.21	1.07	0.96	-	1.18	0.21
1×10^{-03}	2,922	1.09	0.98	-	1.21	0.11	1.10	0.98	-	1.22	0.10	1.09	0.98	-	1.21	0.10
0.01	8,709	1.14	1.05	-	1.23	0.003	1.16	1.06	-	1.28	0.002	1.18	1.06	-	1.30	0.001
0.05	19,656	1.12	1.03	-	1.22	0.01	1.13	1.02	-	1.24	0.02	1.14	1.03	-	1.26	0.01
0.1	28,143	1.11	1.01	-	1.21	0.02	1.12	1.02	-	1.24	0.02	1.15	1.04	-	1.28	0.01
0.2	40,253	1.10	1.01	-	1.20	0.04	1.12	1.01	-	1.24	0.03	1.14	1.02	-	1.26	0.02
0.5	61,727	1.10	1.00	-	1.22	0.04	1.13	1.02	-	1.25	0.02	1.15	1.03	-	1.28	0.01
1	76,213	1.10	0.99	-	1.23	0.08	1.13	1.02	-	1.25	0.02	1.14	1.03	-	1.27	0.02

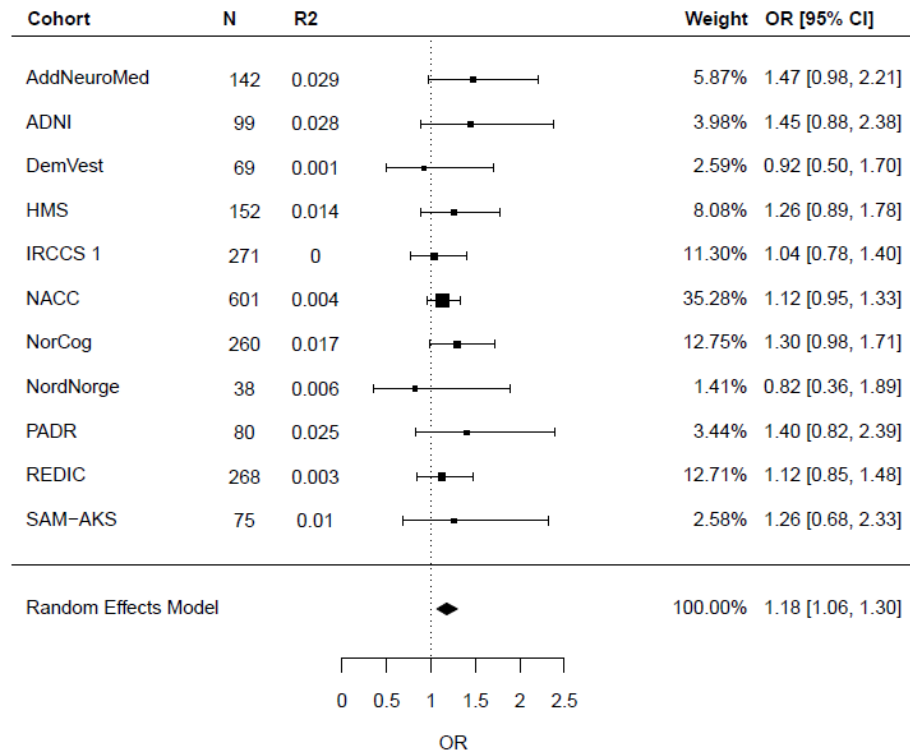OR: Odds ratio; odds ratio estimates may differ slightly from those represented in Figure 1 due to rounding

Figure 1: Odds ratios from random effects meta-analysis of AD psychosis wide, narrow and delusions narrow association with
schizophrenia PRS. Each bar represents PRS composed of markers at 10 different schizophrenia GWAS p-value thresholds (P_T). P-
values shown above each bar
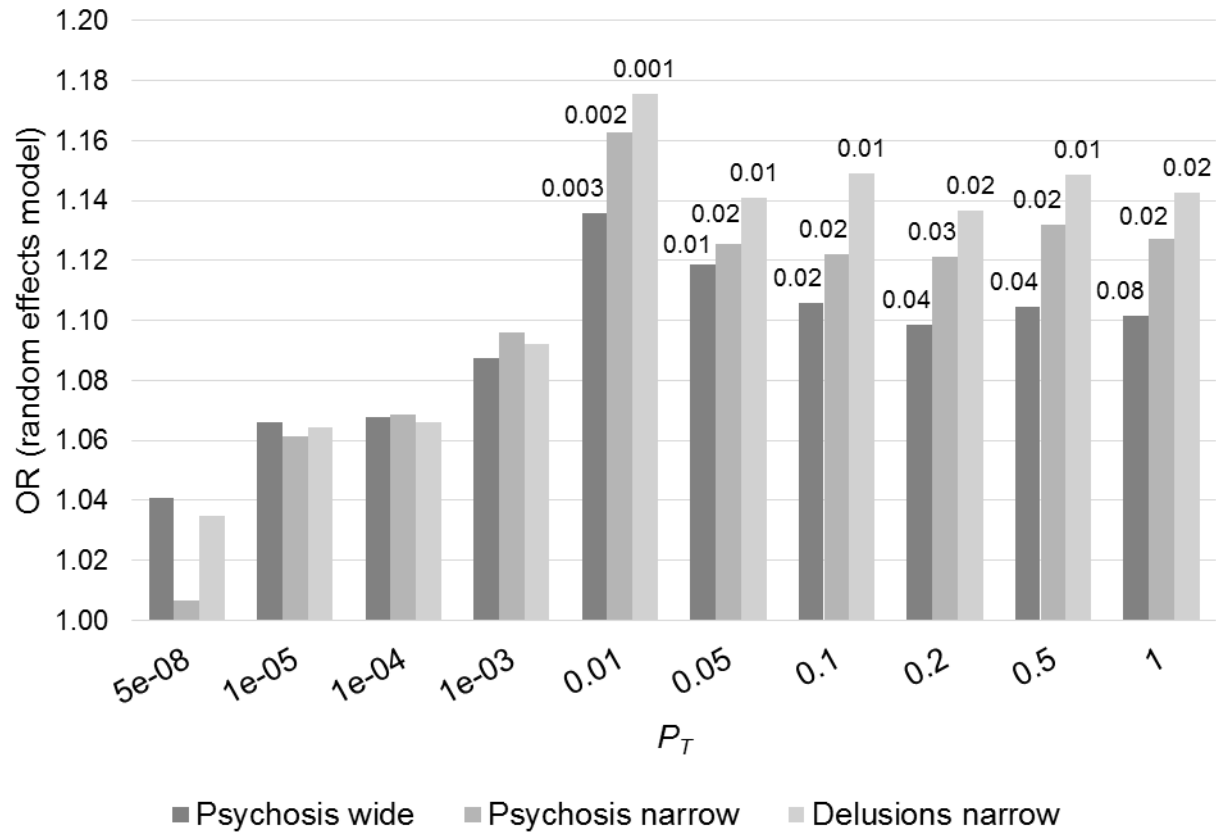
Figure 2: Forest plot of meta-analysis of delusions narrow for PRS calculated at P_T=0.01 (i.e. 8,709 SNPs). Overall estimate from random effects model is represented by the diamond below the individual study estimates.