

1 **Variation at the Klotho gene locus does not affect**
2 **cognitive function in up to 335,074 British Caucasians**
3 **in the UK Biobank**

4

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23

24 **Abstract**

25

26 The proportion of older adults in Western populations is increasing and there is,
27 therefore, a need to define factors affecting maintenance of physical and
28 cognitive health in old age. Variations in the Klotho (*KL*) gene, and specifically
29 the *KL-VS* haplotype, have been identified by several authors as potentially
30 influencing cognitive function and decline. We have attempted to verify the
31 reported associations between *KL* variants, including the *KL-VS* haplotype, and
32 cognitive function in up to 335,074 British Caucasian participants aged 40-79
33 years from the UK Biobank. We do not find evidence that *KL-VS* affects
34 cognitive function or its decline with increasing age. We examined a further 244
35 *KL* variants and found that rs117650866 was associated with Prospective
36 Memory, but could not replicate this in follow-up samples. In conclusion, there is
37 insufficient evidence in the UK Biobank to support the concept that *KL* variants
38 affect cognitive function or its rate of decline.

39

40 **Introduction**

41

42 The demographics of Western populations are changing, with an increase in the
43 proportion of older adults. There is, thus, a need to define the factors affecting
44 maintenance of physical and cognitive health in old age. Cognition can be
45 defined as any process that is required for an individual to be aware of their
46 situation and to use that information to respond to it (1). As individuals get older,
47 memory, learning and processing speed decline (2); often leading to reduced
48 independence and increased reliance on families and social care. As life
49 expectancy increases, it becomes ever more necessary to explore some of the
50 factors that might explain variation in cognitive function and cognitive decline in
51 adults.

52

53 Several authors have highlighted variants in the Klotho (*KL*) gene as associated
54 with ageing. *KL* is located on chromosome 13 in humans, and encodes a single-
55 pass transmembrane protein that acts as an FGF23 co-receptor (3-5). It was
56 first identified in mice by Kuro-o *et al.* (6) who showed that decreased *kl*
57 expression resulted in a condition resembling premature ageing. In humans, *KL*
58 variants have been reported to be associated with longevity, cardiovascular risk
59 factors and cancer (7-10).

60

61 In addition, multiple studies have been carried out exploring the relationship
62 between *KL* variants and cognitive function and decline, mostly focusing on the
63 *KL-VS* haplotype, which refers to a pair of functional variants that result in
64 F352V (rs9536314) and C370S (rs9527025) substitutions. Previous evidence

65 has been varied: some authors have suggested that among adults aged 70
66 years or more, people homozygous for V (valine) at position 352 have poorer
67 cognitive function (11,12), but also suggests that V352 heterozygotes have
68 better cognitive function than those who are homozygous for (F) phenylalanine
69 at position 352 (11,13). On the other hand, Mengel-From *et al.* (14) showed
70 that, in Danish populations aged between 92-100 years, V352 heterozygotes
71 had poorer cognition and Almeida *et al.* (15) showed that among men aged 71-
72 87 years, V352 carriers were more likely to get dementia. De Vries *et al.* (16)
73 showed that V352 heterozygotes have a slower rate of cognitive decline, but
74 Porter *et al.* (17) did not find any such relationship in their data.

75

76 In addition to the *KL-VS* haplotype, there are reports of associations between
77 variants in the *KL* promoter region and cognition. Mengel-From *et al.* (14)
78 reported that carriers of the rs398655 C allele had better cognitive function than
79 non-carriers and Hao *et al.* (18) reported that those with who are homozygous
80 for the G (guanine) allele at G-395A (rs1207568) have an increased risk of
81 cognitive impairment.

82

83 At present, conflicting reports indicate that, at a population level, the relationship
84 between the *KL-VS* haplotype and cognitive function or cognitive decline is not
85 particularly clear: there is, therefore, a need to explore this area further using
86 significantly bigger sample sizes. Here, we aim to verify the reported
87 associations between *KL* variants, including the *KL-VS* haplotype, and cognitive
88 function in up to 335,074 UK Biobank (UKB) participants aged between 40 and
89 79 years, by carrying out a phenome scan of cognitive measures, including

90 reaction time and various memory tests. We also aim to search for novel
91 associations between the *KL* genetic variants and cognitive function using the
92 same approach.

93

94 **Subjects and Methods**

95

96 Population and study design

97

98 This study was carried out using data from the UK Biobank (UKB). UKB is a
99 large prospective cohort study that recruited ~502,600 UK residents aged
100 between 40 and 69 years of age between 2006 and 2010. The participants
101 provided blood, urine and saliva samples, and underwent various physical
102 assessments, as well as touchscreen questionnaires and verbal interviews (19).

103

104 Phenotypes

105

106 Table 1 summarises the phenotypes relating to cognitive function (referred to as
107 cognitive measures) that were used for our analyses. For some cognitive
108 measures, a baseline measurement was carried out (referred to as 'Baseline')
109 at one of 22 assessment centres as well as 2 follow-up measurements (referred
110 to as 'Follow-Up 1' and 'Follow-Up 2') for a subset of participants. For Fluid
111 Intelligence, Pairs Matching and Numeric Memory, an online assessment was
112 performed in addition to the measurements undertaken at the assessment
113 centres. For Pairs Matching, there were 3 rounds; the first round had 3 pairs
114 that the participants needed to match and the second and third rounds had 6.
115 For Trail Making, only data from the online measurement was available to us.
116 We did not include participants in the analysis for a given cognitive function test
117 if they abandoned the test and/or if they completed the test with a pause. Each

118 round/follow-up of each measure was treated as a separate phenotype unless
119 otherwise stated.

120

121 Genotyping and quality control

122

123 488,377 individuals were genotyped for up to 812,428 variants using DNA
124 extracted from blood samples on either the UK Biobank Axiom array (438,427
125 participants) and the UK BiLEVE Axiom array (49,950 participants). Variant
126 quality control metrics were provided by UKB as described previously (20). For
127 genotyped variants, all variants that did not pass standard quality control checks
128 carried out by Affymetrix and the Wellcome Trust Centre for Human Genetics
129 were excluded. Specifically, hypothesis testing was carried out to check for
130 differences in genotyping due to batch effects, plate effects, sex effects and
131 array effects as well as any departures from Hardy-Weinberg Equilibrium using
132 a p-value threshold of 10^{-12} . In addition, variants with a missingness of >1%
133 and/or a minor allele frequency of <0.01 were also excluded. For imputed
134 variants, all variants with an INFO score of <0.8 were excluded. The *KL* gene is
135 located at 13:33590571-33640282 (GRCh37.p13) and 246 variants passed QC
136 within ± 5 Kb of *KL*. These were selected for the association analyses.

137

138 Sample quality control metrics were provided by UKB and were generated as
139 described by Bycroft *et al.* (20). Samples were excluded from the analysis if
140 they were determined to be outliers for missingness and/or heterozygosity
141 and/or if they had any sex chromosome aneuploidies as well as if the
142 genetically inferred sex differed from the reported sex. Samples which did not

143 have a genetically-determined White British ancestry were also excluded. A list
144 of related individuals was also provided by UK Biobank and one individual from
145 each related pair was excluded at random.

146

147 Statistical Analyses

148

149 PLINK 2.0 was used to fit an additive linear model between the cognitive
150 measures and the genotypes in all individuals. This was then repeated for a
151 subset of individuals who were aged 69 years or more at the time of performing
152 the cognitive test. Unless otherwise specified, all association analyses (i.e.
153 additive linear models) were adjusted for the first 4 genetic principal
154 components (PCs) (UKB Field 22009) and the genotyping chip on which the
155 participant was genotyped on. The cognitive measures and any quantitative
156 covariates were standardised to a mean of 0 and a variance of 1 before any
157 linear modelling was performed.

158

159 Since multiple testing was undertaken, we applied statistical correction for this.
160 A principal component (PC) analysis showed that 24 PCs represented >90% of
161 variation in the 28 cognitive measures. To determine the number of
162 independent variants, all pairs of variants within the locus with $R^2 > 0.1$ were
163 listed, one variant from each pair was removed and this process was repeated
164 until there were no pairs of variants remaining. When this is implemented using
165 --indep-pairwise 60 kb 1 0.1 in PLINK 2.0, 15 independent variants remain. A p-
166 value threshold of 0.05 is used and Bonferroni-corrected when necessary for
167 the appropriate number of independent tests in each case (up to 360

168 independent tests: 15 independent variants and 24 PCs). Supplementary Figure

169 1 summarises the analyses and the threshold used for each of them.

170

171 **Results**

172

173 After QC, there were 335,074 individuals remaining for analysis. A summary of
174 the sample by phenotype is provided in Table 2.

175

176 Since the 2 variants making up the *KL-VS* haplotype are well-characterised
177 functional *KL* variants in humans, we investigated whether either of them was
178 associated with any of the cognitive function measures available. Neither
179 rs9536314 nor rs9527025 were significantly associated at a p-value threshold of
180 0.05/24 with any of the cognitive measures when unadjusted (Supplementary
181 Table 1) and when adjusted for age, age² and sex (Figure 1).

182

183 Previous studies have largely concentrated on older individuals: to test whether
184 these variants exerted their effects only in later life, we repeated the analyses,
185 but only included individuals who were aged ≥ 69 years at the time that they
186 performed the cognitive test. However, we again found that neither rs9536314
187 nor rs9527025 were significantly associated at a p-value threshold of 0.05/24
188 with any of the cognitive measures available (Figure 1 & Supplementary Table
189 1). It was not possible to increase this age threshold beyond 69 years because
190 all participants were aged between 40 and 69 years at the time of recruitment.

191

192 Although the associations were not statistically significant, the effect size
193 appeared to increase when excluding individuals under the age of 69 years. We
194 therefore repeated the analyses but included a genotype*age interaction term to
195 test whether the effect of *KL-VS* variants on the cognitive function measures

196 available changed with age. We found that age does not have a statistically
197 significant effect on the relationship between *KL-VS* and any of the cognitive
198 function measures available at a p-value threshold of 0.05/24 adjusting for age,
199 age^2 and sex (Supplementary Table 2).

200

201 We next sought to test whether rs9536314 or rs9527025 were associated with
202 change in any of the cognitive measures over age. For all measures for which
203 more than one data point was available per participant (i.e. participants had
204 performed a given cognitive test on more than one occasion), a rate of change
205 was calculated for each participant (where the rate of change is the change in
206 the cognitive measure, $M2-M1$, divided by the age difference, $T2-T1$, in years:
207 on average, the difference between two measurements is 8.3 years). We found
208 that neither rs9536314 nor rs9527025 was significantly associated at a p-value
209 threshold of 0.05 with a change in any of the available cognitive measures over
210 age, either when unadjusted or when adjusted for age_{T1} , age_{T1}^2 and sex
211 (Supplementary Table 3).

212

213 We next tested to see if any other *KL* variants were statistically associated at a
214 p-value threshold of 0.05/360 with any of the available cognitive measures. We
215 found that rs117650866 was associated with Prospective Memory (UKB Field
216 4291) adjusting for age, age^2 and sex (referred to as Discovery in Table 3).

217 There were no other significant associations, with or without adjustment for age,
218 age^2 and sex (Supplementary Table 4 & 5); there were also no significant
219 associations when excluding individuals under the age of 69 years
220 (Supplementary Table 4 & 5).

221

222 We then attempted to internally replicate the rs117650866 association. To do
223 this, we repeated the association analysis in participants who performed the
224 Prospective Memory test only on one occasion (i.e. those participants who
225 performed the test at either Baseline only, or at Follow Up 1 only, or at Follow
226 Up 2 only). The rs117650866 association was present in those tested at
227 Baseline only (beta = 0.112, s.e. = 0.0229, power = 0.92, $v = 99054$), but was
228 absent ($p > 0.05$) in those tested only at either Follow Up 1 only (beta = -0.059,
229 s.e. = 0.0794, power = 0.12, $v = 8179$) or at Follow Up 2 only (beta = -0.117,
230 s.e. = 0.101, power = 0.09, $v = 5656$) (Table 3). Despite the lack of power to
231 detect the association observed at Baseline, the inconsistent direction of the
232 effect between Baseline and Follow Up 1 and 2 suggest that the association
233 observed at Baseline was likely to be a false positive. The power calculations
234 were carried out using the `pwr.f2.test` function from the `pwr` package in R with `u`
235 set to 9, `f2` set to 0.000216 and `sig.level` set to 0.05.

236

237 We next sought to test whether any *KL* variants were significantly associated at
238 a p-value threshold of 0.05/15 with a change in any of the cognitive measures
239 (for which there are repeat measurements) over age, in the same way that *KL*-
240 VS was tested. We did not find any significant associations (Supplementary
241 Table 6).

242

243 Discussion

244

245 Previous evidence suggested that *KL-VS* and other *KL* variants are associated
246 with cognitive function during the later stages of life. Our aim was to explore
247 these findings in a younger and much larger cohort, namely the UK Biobank.
248 We did not find evidence of a relationship between *KL-VS* and cognitive
249 function, nor did we find any evidence that the age of an individual had a
250 significant effect on this relationship. The association we found between
251 Prospective Memory and rs117650866 did not replicate consistently, nor is
252 there any evidence of it in previously published studies, so it is likely to be a
253 false positive. We also did not find evidence of any other *KL* variants being
254 associated with cognitive function nor with cognitive decline.

255

256 An important point is that previous studies which have identified relationships
257 between *KL* variants and cognition use populations that are much older (usually
258 aged 70 years or more), whereas the population we examined is relatively
259 young (the larger Baseline samples had a mean age of 57 years). We
260 attempted to address this limitation by repeating our analyses, but only
261 including individuals over the age of 69 years; we still did not find associations
262 probably because only about 1% of this subset in the Online tests are over 75
263 years of age and no individuals are over 79 years of age. Indeed, whenever
264 authors report an absence of statistically significant associations between *KL*
265 variants and cognition, the mean age of the cohorts that they analyse are closer
266 to the one we analysed. For example, Deary *et al.* (12) examined 2 cohorts and
267 the cohort who undertook cognitive testing at age of 64 years did not show

268 statistically significant associations between *KL*-VS and cognition. Dubal *et al.*
269 (13) also did not find an association in one of the 3 cohorts that they analysed,
270 and the mean age of this cohort was 63 years.

271

272 Deary *et al.* (12) provided evidence suggesting that *KL*-VS may influence
273 cognitive decline. We did not find any evidence to support this. This may be
274 because the difference between the repeated measurements available to us
275 was about 8 years whereas Deary *et al.* compared the cognitive abilities of
276 individuals first tested when aged 11 years and then at the age of 79 years. It is
277 also important to note that whilst some authors do report relationships between
278 *KL*-VS and cognitive decline (12,16), other authors do not find any such
279 relationship (14,17).

280

281 The UKB dataset, despite the advantage of its size, does have biases. In
282 particular, the participants are generally healthier than average (21). There is
283 evidence to suggest that the effect of *KL* variants on cognitive function/decline
284 may be as a result of affecting the severity of a pre-existing psychopathology
285 (22,23) and individuals suffering from early dementia, etc. would be either
286 unlikely or even unable to volunteer to participate.

287

288 In conclusion, there is insufficient evidence in the UK Biobank to support the
289 concept that *KL* variants affect cognitive function or its rate of decline in British
290 Caucasian individuals aged between 40 and 79 years. Further follow-up testing
291 would be required to verify the reported effects of *KL* on cognitive function and
292 decline that are reported in very elderly individuals.

293

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295

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298 paid for by Calico LLC (South San Francisco, California, United States). Hasnat
299 Amin is the recipient of a PhD studentship from the College of Health and Life
300 Sciences, Brunel University London.

301

302 **Conflicts of interest**

303

304 This study was carried out under UK Biobank application 19968. The
305 application was paid for by Calico LLC (South San Francisco, California, United
306 States), who had no role in the interpretation of the data. Hasnat Amin is the
307 recipient of a PhD studentship from the College of Health and Life Sciences,
308 Brunel University London. The authors have no other conflicts of interest to
309 declare.

310

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383

384

385 **Figures**

386

387 Figure 1

388 Standardised beta coefficients with 95% Confidence Intervals when regressing
389 cognitive measures on rs9536314 and on rs9527025 in the UK Biobank with (All
390 Participants) and without (≥ 69) including participants less than 69 years old and
391 adjusted for age, age² and sex.

392

393 Supplementary Figure 1

394 A breakdown of the analyses carried out in this study. LD = linkage
395 disequilibrium. PCs = principal components.

396

397 **Tables**

398

399 Table 1

400 A description of the cognitive measures from the UK Biobank used in this study.

401

402 Table 2

403 Demographics of the cohort by phenotype. The distribution of the phenotype is
404 presented in the original units.

405

406 Table 3

407 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
408 values (p) when regressing cognitive measures on rs117650866 in the UK
409 Biobank adjusted for age, age² and sex in the full baseline sample (Discovery),
410 and in 3 independent samples (i.e. in participants who were present at baseline
411 only (Baseline) and in participants who were present at the first follow up only
412 (Follow Up 1) and in participants who were present at the second follow up only
413 (Follow Up 2)).

414

415 Supplementary Table 1

416 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
417 values (p) when regressing cognitive measures on rs9536314 and on
418 rs9527025 in the UK Biobank with (All Participants) and without (≥ 69 years old)
419 including participants less than 69 years old and not adjusted.

420

421 Supplementary Table 2

422 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
423 values (p) when regressing cognitive measures on rs9536314 and on
424 rs9527025 in the UK Biobank with a genotype*age interaction term and
425 adjusted for age, age² and sex.

426

427 Supplementary Table 3

428 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
429 values (p) when regressing the rate of decline of cognitive measures on
430 rs9536314 and on rs9527025 in the UK Biobank with (Adjusted) and without
431 (Unadjusted) adjusting for age_{T1}, age_{T1}² and sex.

432

433 Supplementary Table 4

434 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
435 values (p) when regressing cognitive measures on 246 *KL* variants in the UK
436 Biobank with (All Participants) and without (≥69 years old) including participants
437 less than 69 years old and not adjusted.

438

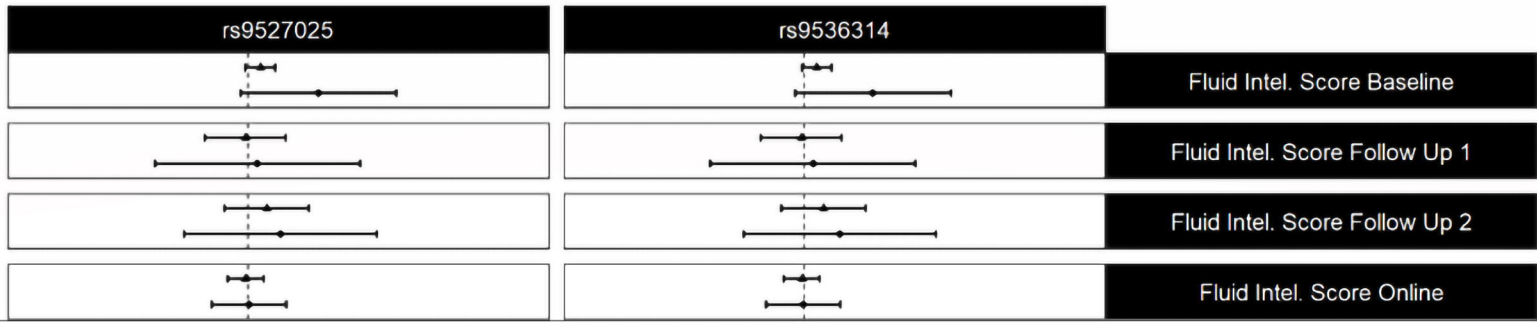
439 Supplementary Table 5

440 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
441 values (p) when regressing cognitive measures on 246 *KL* variants in the UK
442 Biobank with (All Participants) and without (≥69 years old) including participants
443 less than 69 years old and adjusted for age, age² and sex.

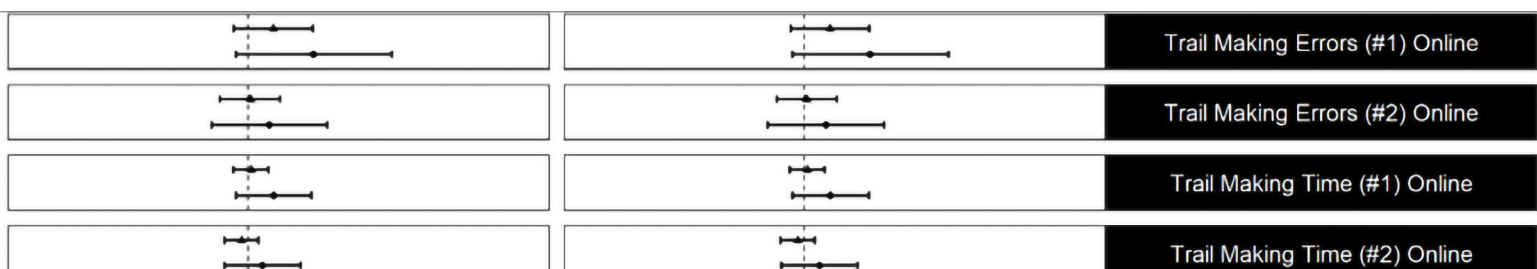
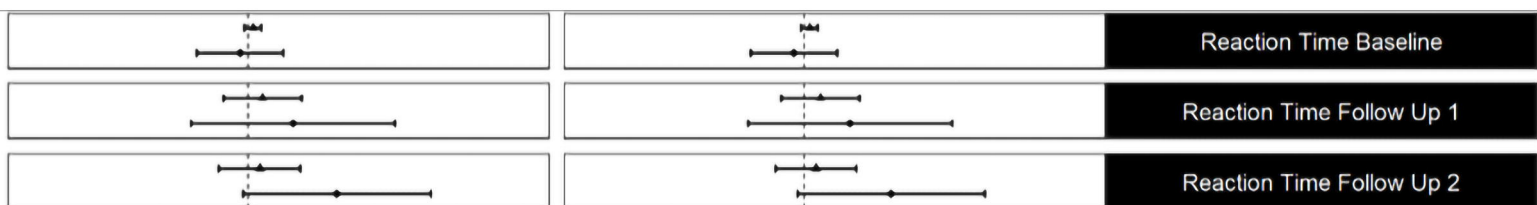
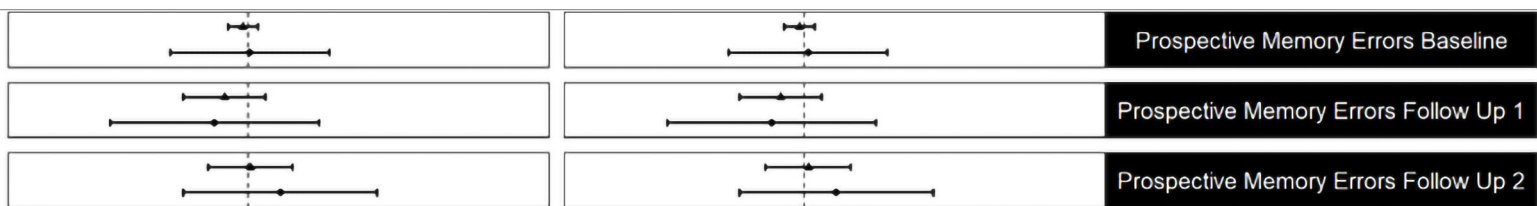
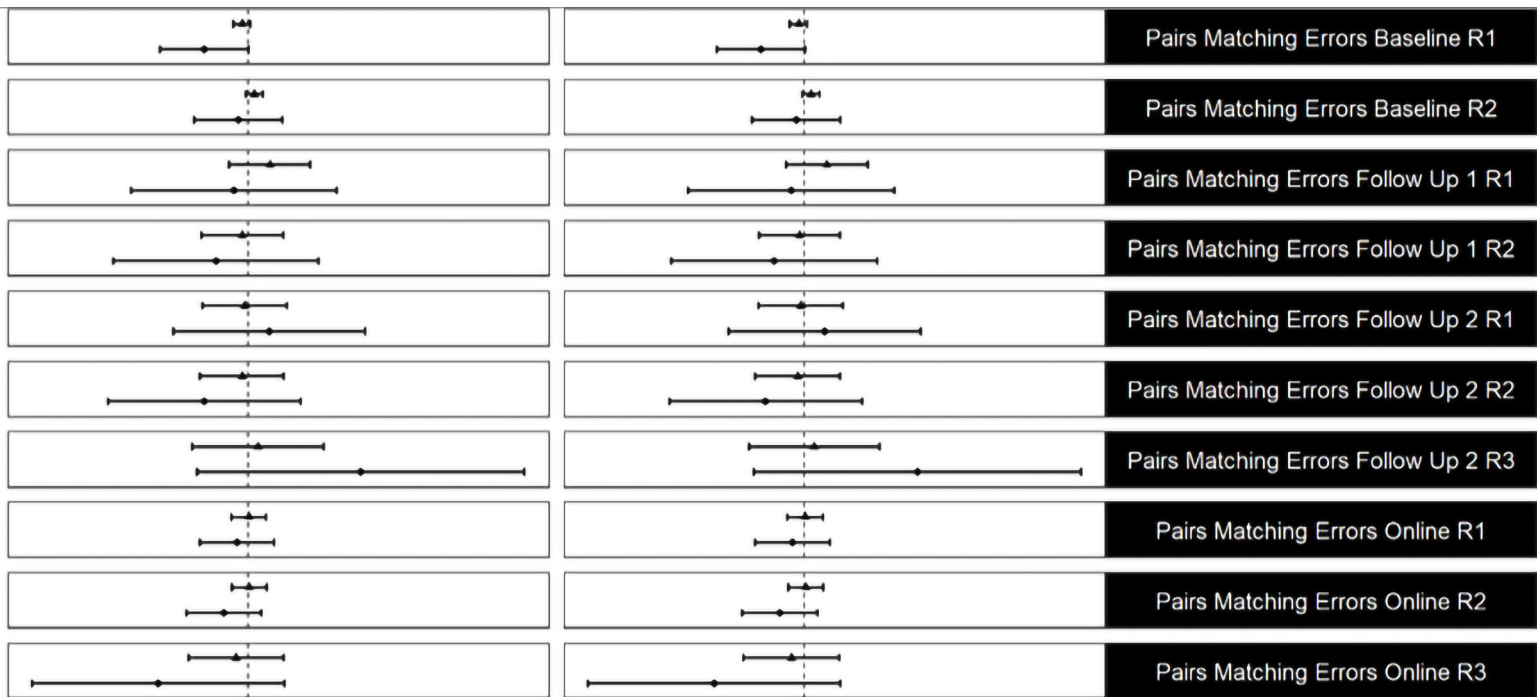
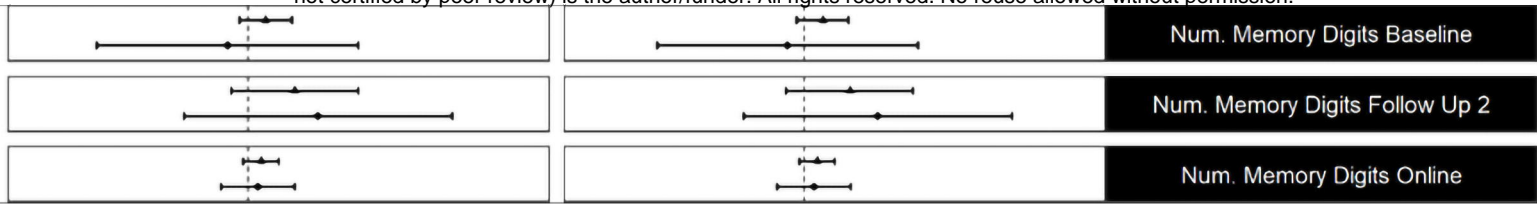
444

445 Supplementary Table 6

446 Standardised coefficients (beta), standard errors (s.e.), sample sizes (n) and p-
447 values (p) when regressing the rate of decline of cognitive measures on 246 *KL*
448 in the UK Biobank with (Adjusted) and without (Unadjusted) adjusting for age_{T1},
449 age_{T1}² and sex.



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-0.1 0.0 0.1 0.2 beta -0.1 0.0 0.1 0.2