

1 **Hearing difficulty is linked to Alzheimer’s disease by common**
2 **genetic vulnerability, not shared genetic architecture**

3 Fatin N. Zainul Abidin^{a,b}, Helena R. R. Wells^{a,c}, Andre Altmann^{b*}, Sally J. Dawson^{a*}

4
5 a UCL Ear Institute, University College London, London, UK.

6 b Centre for Medical Image Computing, Department of Medical Physics and Biomedical
7 Engineering, University College London, London, UK.

8 c Department of Twin Research and Genetic Epidemiology, King’s College London,
9 London, UK.

10 * Joint senior authors

11
12 Corresponding author at:

13 UCL Ear Institute, University College London, 332 Gray’s Inn Road, WC1X 8EE, London,
14 UK.

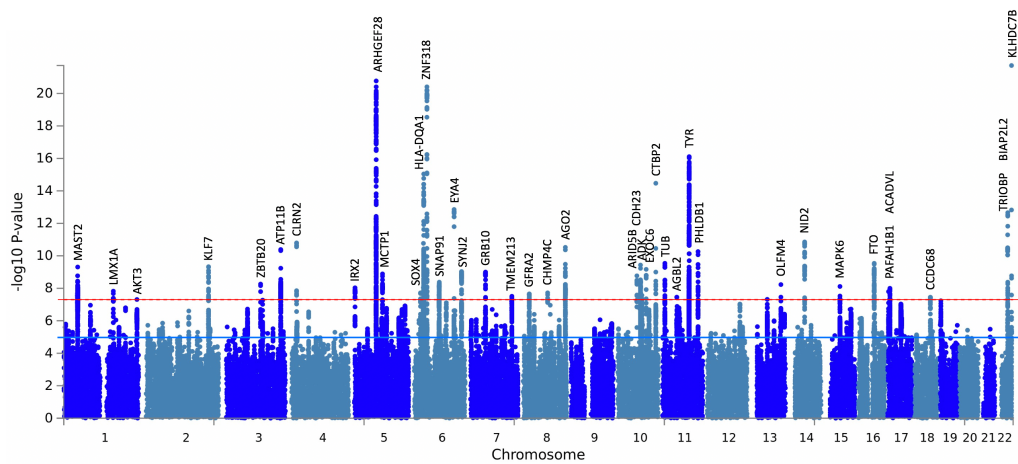
15 Tel: +44 (0)20 7679 8935

16 E-mail address: sally.dawson@ucl.ac.uk (Sally Dawson)

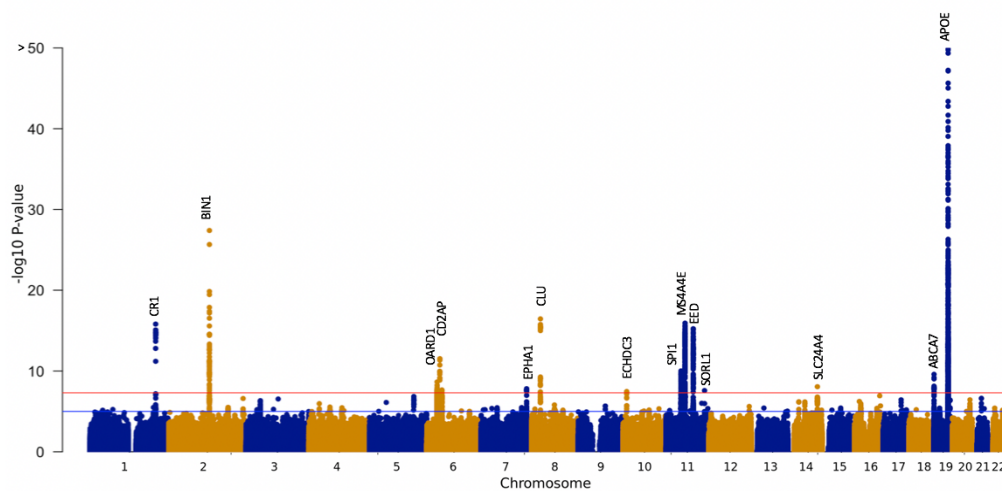
17
18 **Supplementary Tables and Data**

19	Supplementary Figure 1	Manhattan plots displaying GWAS results for HDiff and AD	
20			
21			2
22	Supplementary Table 1	Two-sample bidirectional Mendelian randomization	
23		of HDiff and AD	3
24	Supplementary Table 2	Shared causal traits for HDiff and AD	4
25	Supplementary Table 3	Characteristics of genetic variants as instruments	
26		from glutamine, gamma-glutamylglutamine, and citrate	5
27	Supplementary Data 1	34 instruments (HDiff SNPs) for Mendelian randomisation	
28		analysis of HDiff as exposure	.xls
29	Supplementary Data 2	11 instruments (AD SNPs) for Mendelian randomisation	
30		analysis of AD as exposure and HDiff as outcome	.xls
31	Supplementary Data 3	379 MR-base instruments association with HDiff and AD	.xls

32 (a)



33 (b)
34



35
36 **Supplementary Figure 1| Manhattan plots displaying GWAS results for (a) UKBB**
37 **Hearing difficulty (*HDiff*), and (b) Stage 1 IGAP late-onset Alzheimer's disease (*AD*)**
38 **phenotypes.** The Manhattan plots display the P-values of all SNPs tested in discovery
39 analysis from (Kunkle et al., 2019; Wells et al., 2019). The threshold for genome-wide
40 significance (P-value <5e-08) is indicated by a red solid horizontal line and the genome-wide
41 suggestive threshold (P-value <1e-05) is indicated by a blue horizontal solid line. Loci that
42 reached genome-wide significance are annotated with gene symbol. The inflation factors, λ
43 for *HDiff* and *AD* are 1.31 and 1.09 respectively.

44
45
46
47
48
49
50
51

52 **Supplementary Table 1|**

53 Two-sample bidirectional Mendelian randomization of Hearing difficulty and Alzheimer's
 54 disease.

55

56	Exposure	Outcome	MR method	nSNP	Beta	SE	P-value
57	<i>HDiff</i>	<i>AD</i>	IVW	34	-0.261	0.304	0.390
58			MR Egger	34	0.042	1.362	0.975
59			Simple Mode	34	-0.479	0.816	0.561
60			Weighted Median	34	-0.464	0.424	0.274
61			Weighted mode	34	-0.455	0.707	0.524
62	<i>AD</i>	<i>HDiff</i>	IVW	11	0.004	0.002	0.061
63			MR Egger	11	0.003	0.003	0.382
64			Simple Mode	11	0.016	0.008	0.071
65			Weighted median	11	0.003	0.002	0.044
66			Weighted mode	11	0.003	0.002	0.080

67

68 Key: *AD*, Alzheimer's disease; *HDiff*, Hearing difficulty; IVW, Inverse variance weighted;
 69 MR, Mendelian randomization; SE, Standard error.

70

71 **Supplementary Table 2|**

72 Shared causal traits for Hearing difficulty and Alzheimer's disease. Two-sample Mendelian
 73 randomization of glutamine, gamma-glutamyl glutamine, and citrate as exposure and Hearing
 74 difficulty and Alzheimer's disease as outcome.

75

76

77 Exposure	MR method	78 <i>HDiff</i>				79 <i>AD</i>			
		nSNPs	Beta	SE	Pval	nSNPs	Beta	SE	Pval
78 GGG	IVW**	3	-0.202	0.054	0.000	3	-1.948	0.578	0.001
79 GGG	MR Egger	3	-0.197	0.186	0.482	3	-2.996	1.993	0.374
80 GGG	Simple mode	3	-0.177	0.077	0.148	3	-2.224	0.746	0.096
81 GGG	Weighted median**	3	-0.185	0.063	0.003	3	-2.060	0.673	0.002
82 GGG	Weighted mode	3	-0.181	0.072	0.129	3	-2.160	0.782	0.110
83 Gln	IVW**	5	-0.017	0.006	0.006	5	-0.222	0.069	0.001
84 Gln	MR Egger	5	-0.022	0.012	0.172	5	-0.235	0.132	0.175
85 Gln	Simple mode	5	-0.017	0.012	0.237	5	-0.235	0.120	0.122
86 Gln	Weighted median**	5	-0.019	0.007	0.007	5	-0.227	0.072	0.002
87 Gln	Weighted mode	5	-0.020	0.008	0.058	5	-0.228	0.084	0.052
88 Citrate	IVW**	4	-0.020	0.008	0.012	4	-0.207	0.088	0.018
89 Citrate	MR Egger	4	-0.034	0.062	0.639	4	-0.137	0.684	0.860
90 Citrate	Simple mode	4	-0.016	0.014	0.319	4	-0.204	0.111	0.165
91 Citrate	Weighted median**	4	-0.018	0.009	0.047	4	-0.207	0.103	0.045
92 Citrate	Weighted mode	4	-0.015	0.011	0.275	4	-0.206	0.114	0.170

93

94 Key: *AD*, Alzheimer's disease; *HDiff*, Hearing difficulty; IVW, Inverse variance weighted;
 95 Gln, glutamine; GGG, gamma-glutamyl glutamine; SE, Standard error. Beta < 0 means
 96 negative effect/protective on the outcome (decreased glutamine, gamma-glutamylglutamine,
 97 and citrate) and Beta > 0 means positive effect on the outcome (increased glutamine, gamma-
 98 glutamylglutamine and citrate). ** MR methods that are significant for both *HDiff* and *AD* at
 99 uncorrected P-value of 0.05

100 **Supplementary Table 3|**

101 Characteristics of genetic variants as instruments from glutamine, gamma-glutamylglutamine, and citrate GWAS with corresponding Hearing
 102 difficulty and Alzheimer's disease GWAS data sets. The effect of assessed allele at each locus is indicated by beta.

103

104	SNP	Chr	Nearby gene	EA	NEA	EAF	<u>Glutamine GWAS</u>			<u>HDiff GWAS</u>			<u>AD GWAS</u>		
105	N=24,462						Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
106	rs1260326	2	GCKR*	C	T	0.638	0.062	0.010	9.87E-10	0.002	0.001	0.13	8.0E-04	0.016	0.96
107	rs6729711	2	GLS	A	G	0.181	-0.069	0.012	2.23E-08	0.000	0.002	0.84	0.011	0.018	0.54
108	rs12306007	12	SLC38A4	T	C	0.140	0.079	0.013	3.63E-09	0.000	0.002	0.94	-0.017	0.025	0.49
109	rs2657879	12	GLS2*	G	A	0.176	-0.221	0.012	3.30E-70	-0.004	0.002	9.6E-03	0.047	0.021	0.024
110	rs7078003	10	HOGA1	T	C	0.195	0.074	0.011	2.96E-10	0.001	0.002	0.48	-0.022	0.023	0.035
111							<u>GGG GWAS</u>			<u>HDiff GWAS</u>			<u>AD GWAS</u>		
112	N=7,662						Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
113	rs1260326	2	GCKR*	T	C	0.412	-0.012	0.002	5.61E-09	0.002	0.001	0.13	0.001	0.016	0.96
114	rs1751956	10	LYZL1	T	G	0.864	0.016	0.002	2.35E-08	0.000	0.002	0.94	-0.017	0.025	0.49
115	rs2657879	12	GLS2*	A	G	0.826	0.024	0.002	5.85E-09	-0.004	0.002	9.6E-03	0.047	0.021	0.024
116															
117							<u>Citrate GWAS</u>			<u>HDiff GWAS</u>			<u>AD GWAS</u>		
118	N=24,770						Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value
119	rs1468269	22	GSC2	A	G	0.2613	-0.065	0.011	5.04E-09	0.001	0.001	0.71	0.017	0.018	0.353
120	rs172642	17	SLC13A5	C	A	0.481	-0.080	0.009	4.80E-18	0.001	0.001	0.34	0.015	0.014	0.304
121	rs2040771	22	SLC25A1	T	C	0.476	-0.091	0.009	1.28E-22	-0.001	0.001	0.36	0.019	0.014	0.192
122	rs2921604	5	ANKH	C	T	0.444	0.097	0.094	3.65E-25	0.003	0.001	0.035	0.020	0.014	0.161

123

124 Key: *AD*, Alzheimer's disease; *HDiff*, Hearing difficulty; EA, effect allele; NEA, non-effect allele; GGG, gamma-glutamylglutamine; SE,
125 Standard error; SNPs in bold are single SNP that driving the association and influencing the causal relationship using leave one out test * Exonic
126 SN

