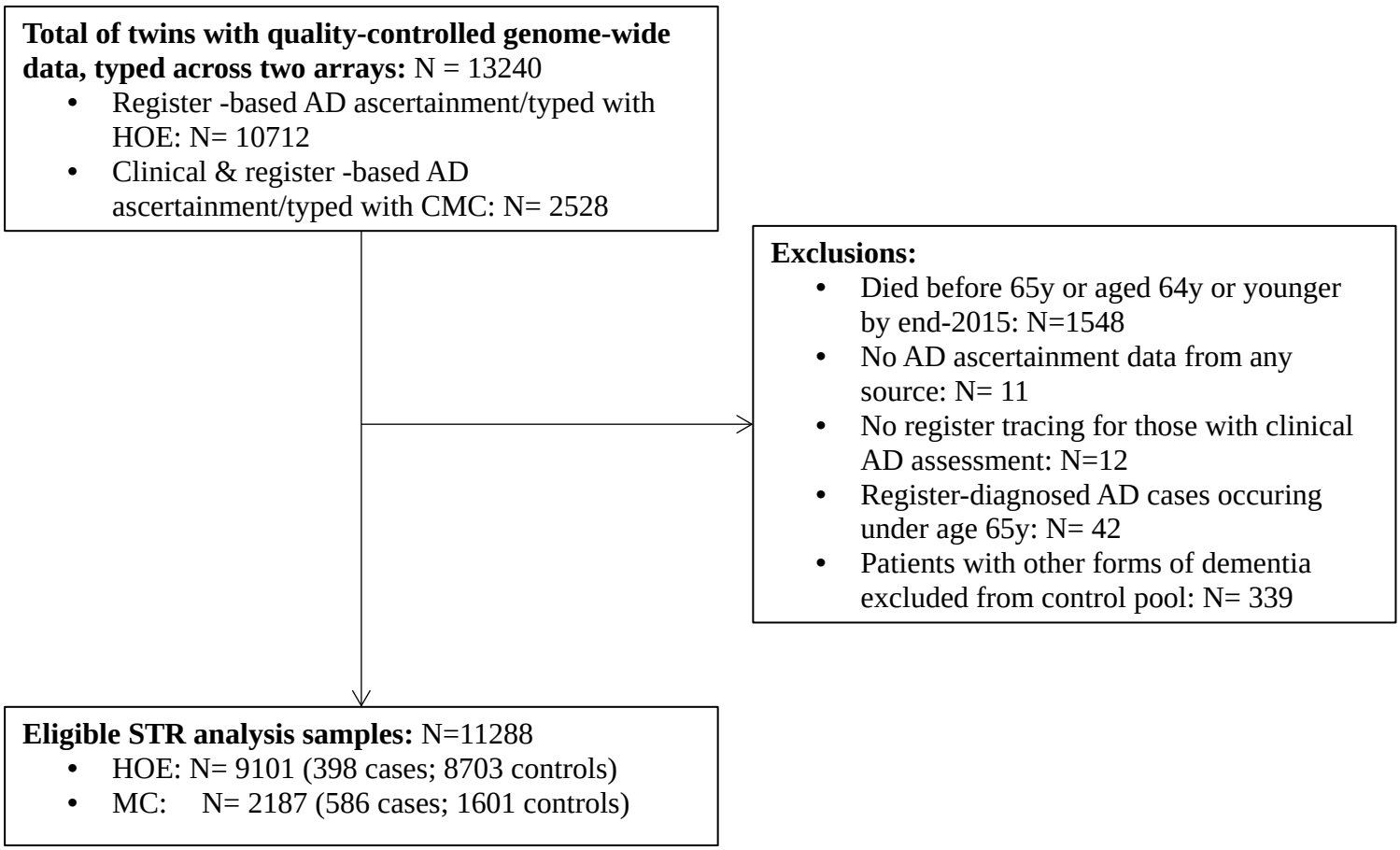
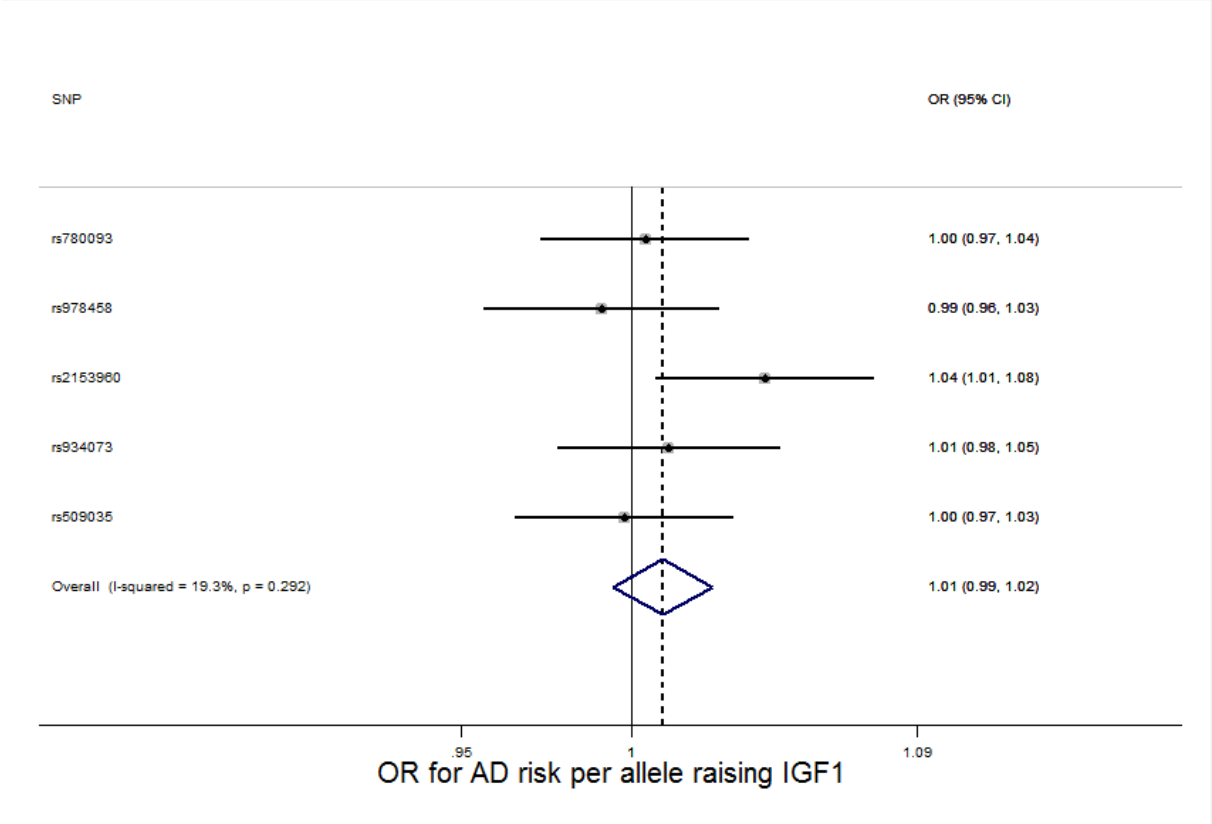
Figure e-1. Derivation of the two analysis samples with genotype data from the Swedish Twin Register participants.



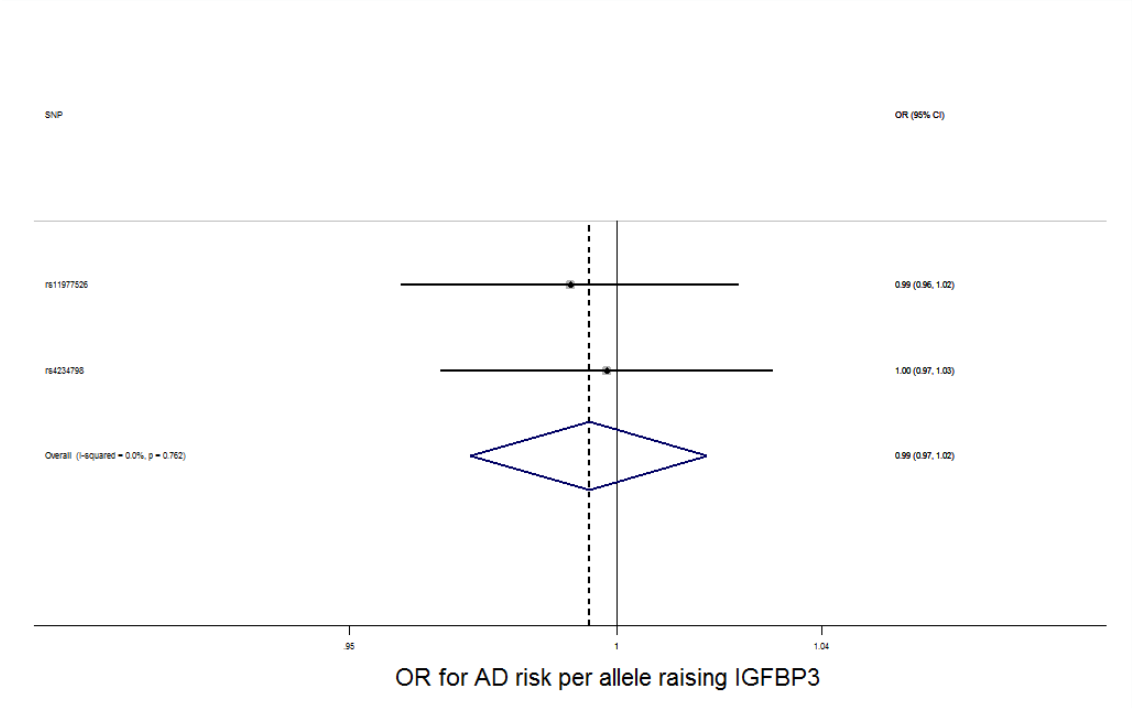
CMC – twins with genome-wide SNP genotyping performed using the CardioMetabochip microarray; HOE – twins with genome-wide SNP genotyping performed using the HumanOmniExpress microarray.

Figure e-2. Meta-analysis of SNP-AD associations in the sub-set of SNPs identified as determinants of IGF1 only (not of IGFBP3)



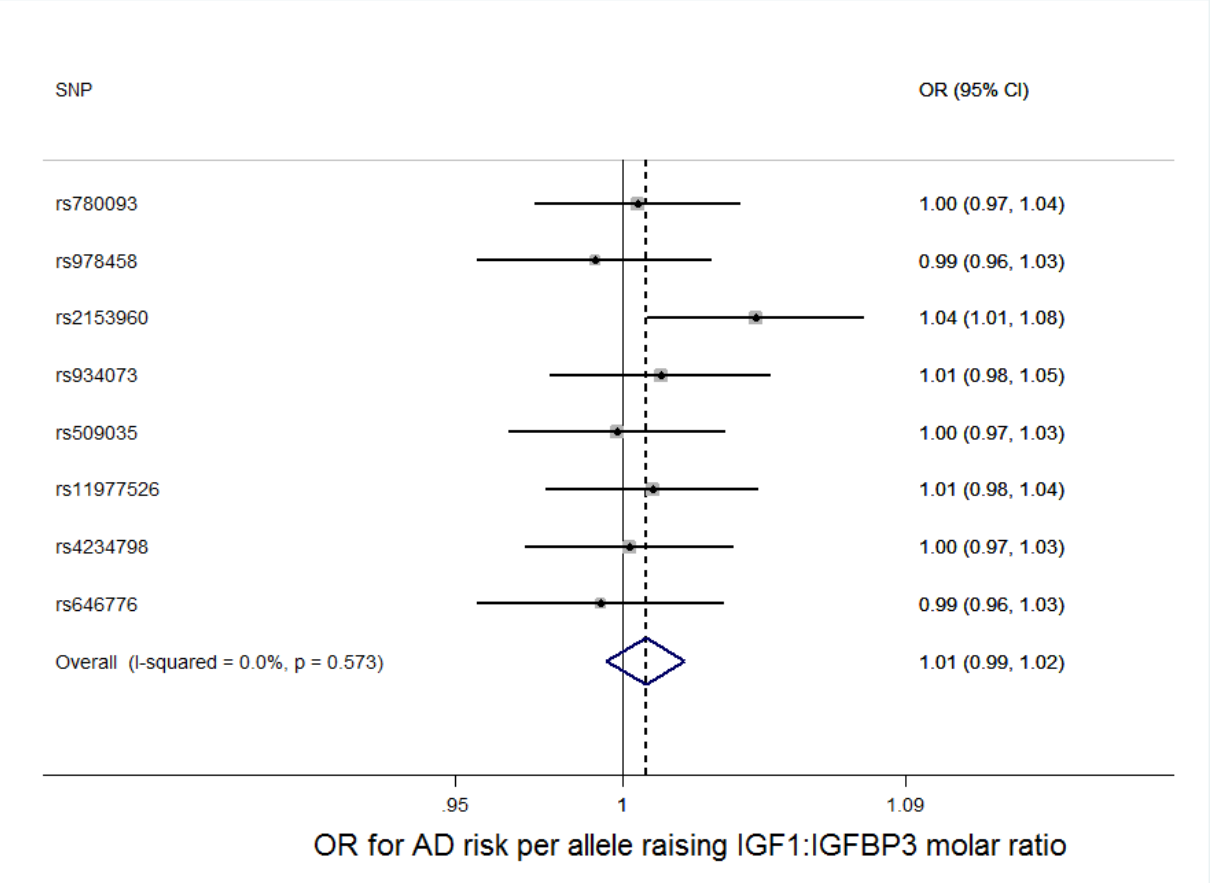
OR = odds ratio. A combined estimate and its 95% CI from fixed-effects meta-analysis is shown by the diamond's central position and lateral width, respectively, along with the test statistic of heterogeneity between individual estimates (I^2). Grey boxes around point estimates indicate the weighting of results in the overall estimate.

Figure e-3. Meta-analysis of SNP-AD associations in the sub-set of SNPs identified as determinants of IGFBP3 only (not of IGF1)



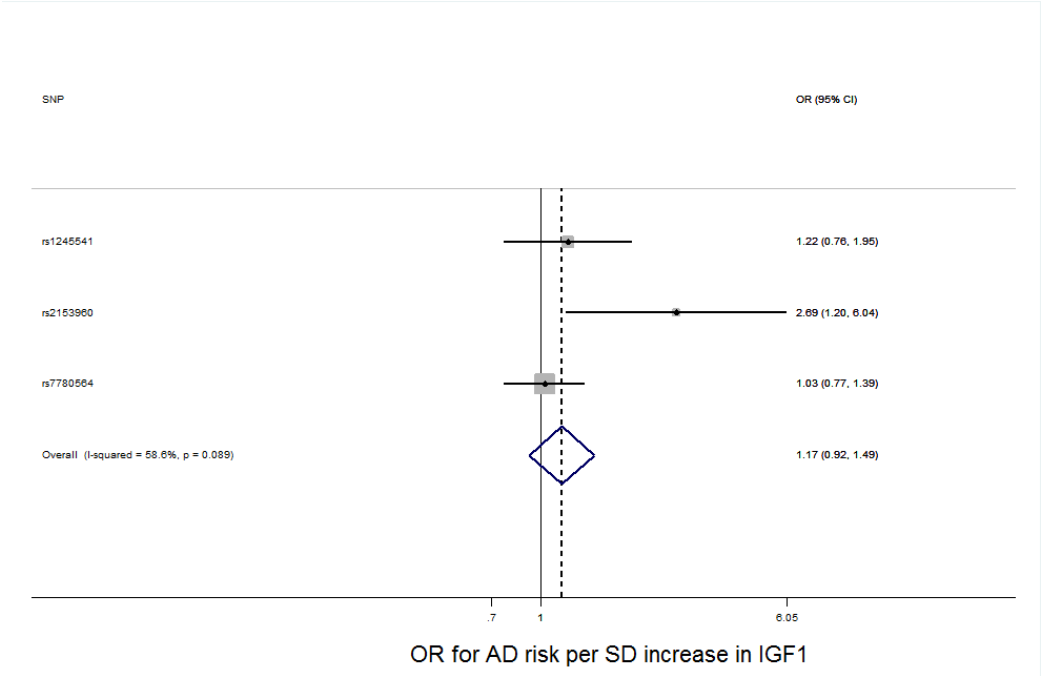
OR = odds ratio. A combined estimate and its 95% CI from fixed-effects meta-analysis is shown by the diamond's central position and lateral width, respectively, along with the test statistic of heterogeneity between individual estimates (I^2). Grey boxes around point estimates indicate the weighting of results in the overall estimate.

Figure e-4. Meta-analysis of SNP-AD associations according to alleles expected to raise the molar ratio of IGF1 to IGFBP3



OR = odds ratio. A combined estimate and its 95% CI from fixed-effects meta-analysis is shown by the diamond's central position and lateral width, respectively, along with the test statistic of heterogeneity between individual estimates (I^2). Grey boxes around point estimates indicate the weighting of results in the overall estimate.

Figure e-5. Mendelian randomization estimates of the magnitude of effect of variation in IGF1 on AD risk

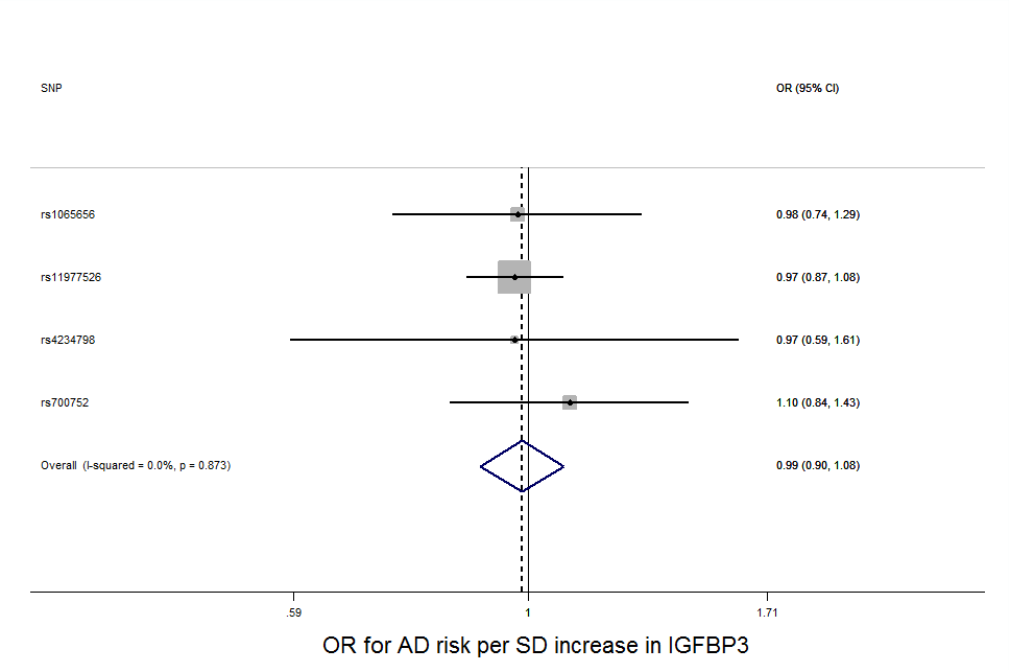


NB: Analysis a sub-set of three SNPs for which SNP-IGF1 association magnitudes were available in published literature [4]. It was not possible to retrieve such statistics for all nine variants used in the main analysis.

Grey boxes around the point estimates indicate the weighting of associations in the overall estimate, according to the strength of the variant's association with IGF1.

Wald estimators for AD risk difference per SD increase in IGF1 were calculated by dividing SNP-AD betas from IGAP data by SNP-IGF1 betas from one cohort in a GWAS meta-analysis of IGF1[4]. Standard errors were derived by the delta method[5].

Figure e-6. Mendelian randomization estimates of the magnitude of effect of variation in IGFBP3 on AD risk

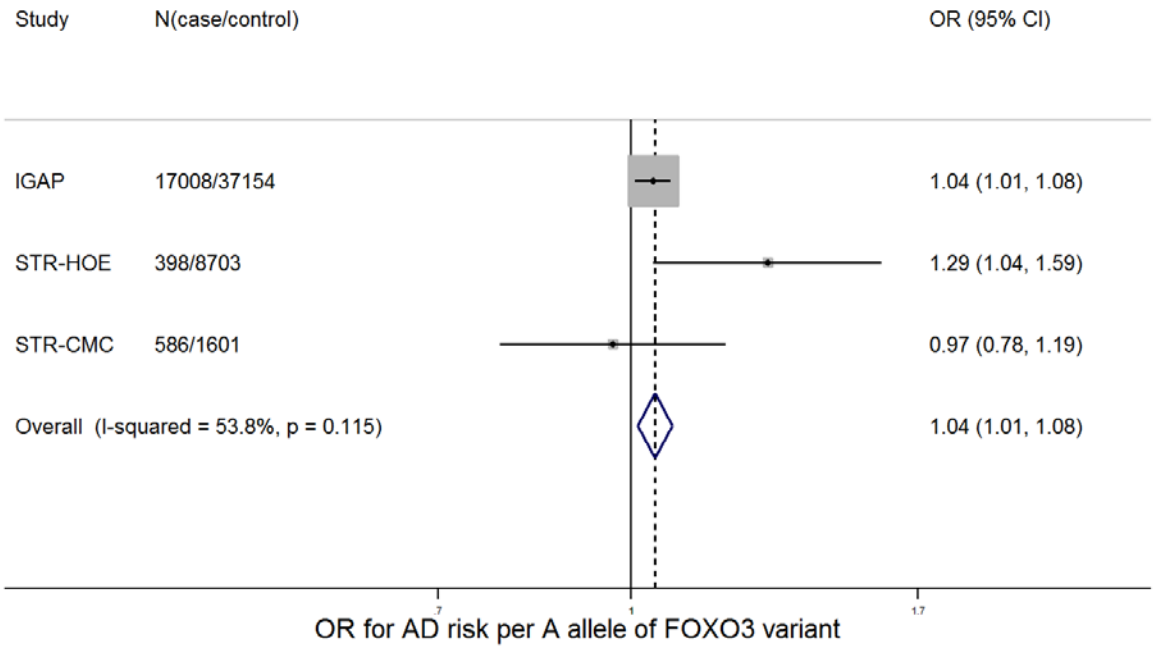


NB: Analysis a sub-set of four SNPs for which SNP-IGFBP3 association magnitudes were available in published literature [4]. It was not possible to retrieve such statistics for all nine variants used in the main analysis.

Grey boxes around the point estimates indicate the weighting of associations in the overall estimate, according to the strength of the variant's association with IGFBP3.

Wald estimators of AD risk difference per SD increase in IGFBP3 were calculated by dividing SNP-AD betas from IGAP data by SNP-IGFBP3 betas from one cohort in a GWAS meta-analysis of IGFBP3 (results from the Framingham Heart Study)[4]. Standard errors were derived by the delta method[5].

Figure e-7. Associations of *FOXO3* intron variant rs2153960 (or its proxy*) in the IGAP dataset and two STR samples of AD cases and controls



Overall meta-analysis result combines three estimates from IGAP, the STR twins genotyped with the HumanOmniExpress array (labelled STR-HOE), and STR twins genotyped with the CardioMetabochip array (STR-CMC).

* The individual-level analysis for STR-MC sample used variant rs3800229 as the independent variable, which was directly typed on the CardioMetabochip. This in high LD (r^2=1) with main variant rs2153960 that was tested in IGAP and STR-HOE samples.