Figure S1: *GSMR analysis to test for effect of asthma on AD and vice versa when the APOE region had been removed.* **(A)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for asthma are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(B)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of asthma with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(C)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for asthma are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* **(D)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of asthma with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
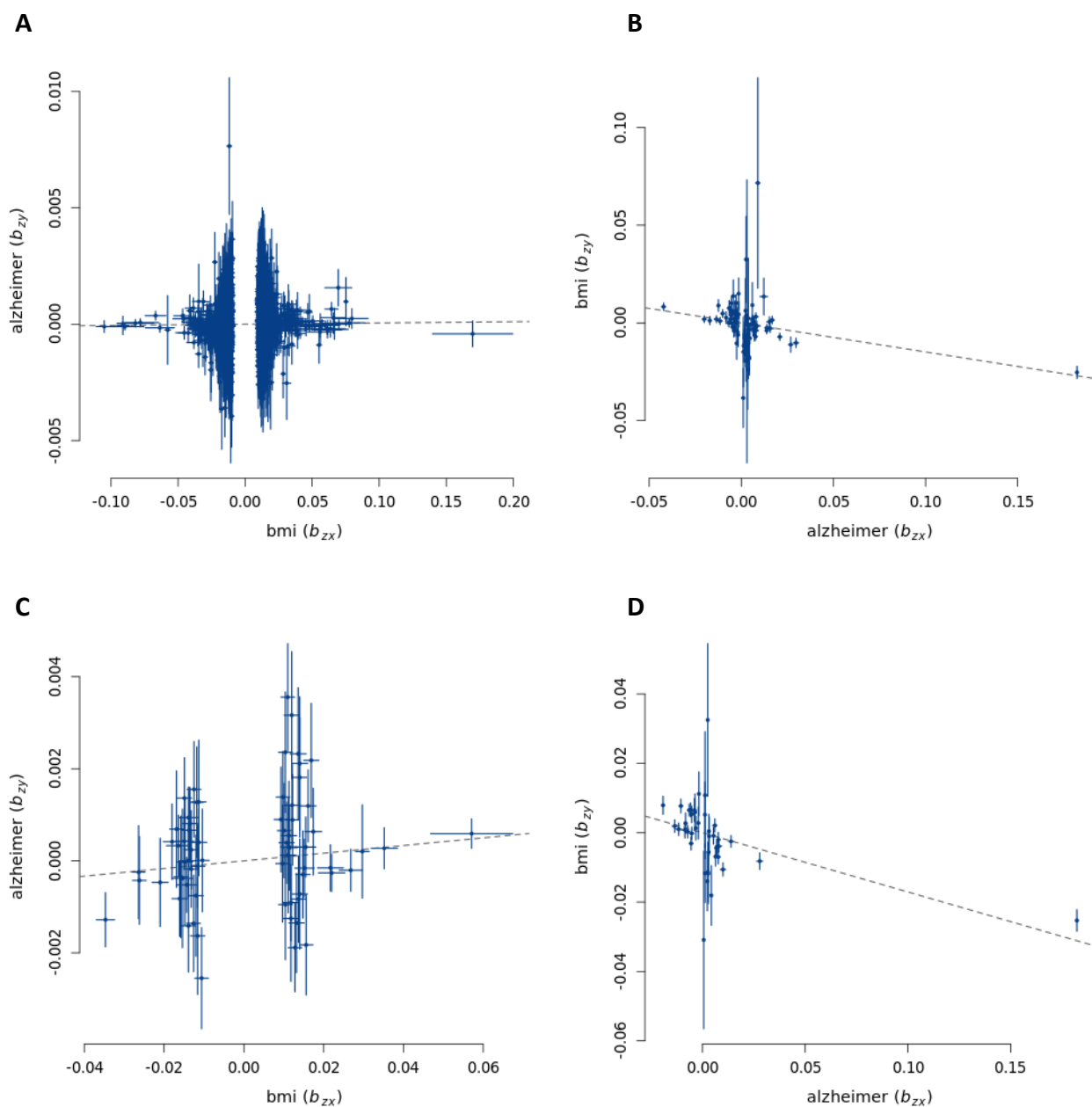
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Figure S2: *GSMR analysis to test for effect of BMI on AD and vice versa when the APOE region had been removed.* ***(A)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for BMI are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(B)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of BMI with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(C)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for BMI are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* ***(D)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of BMI with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
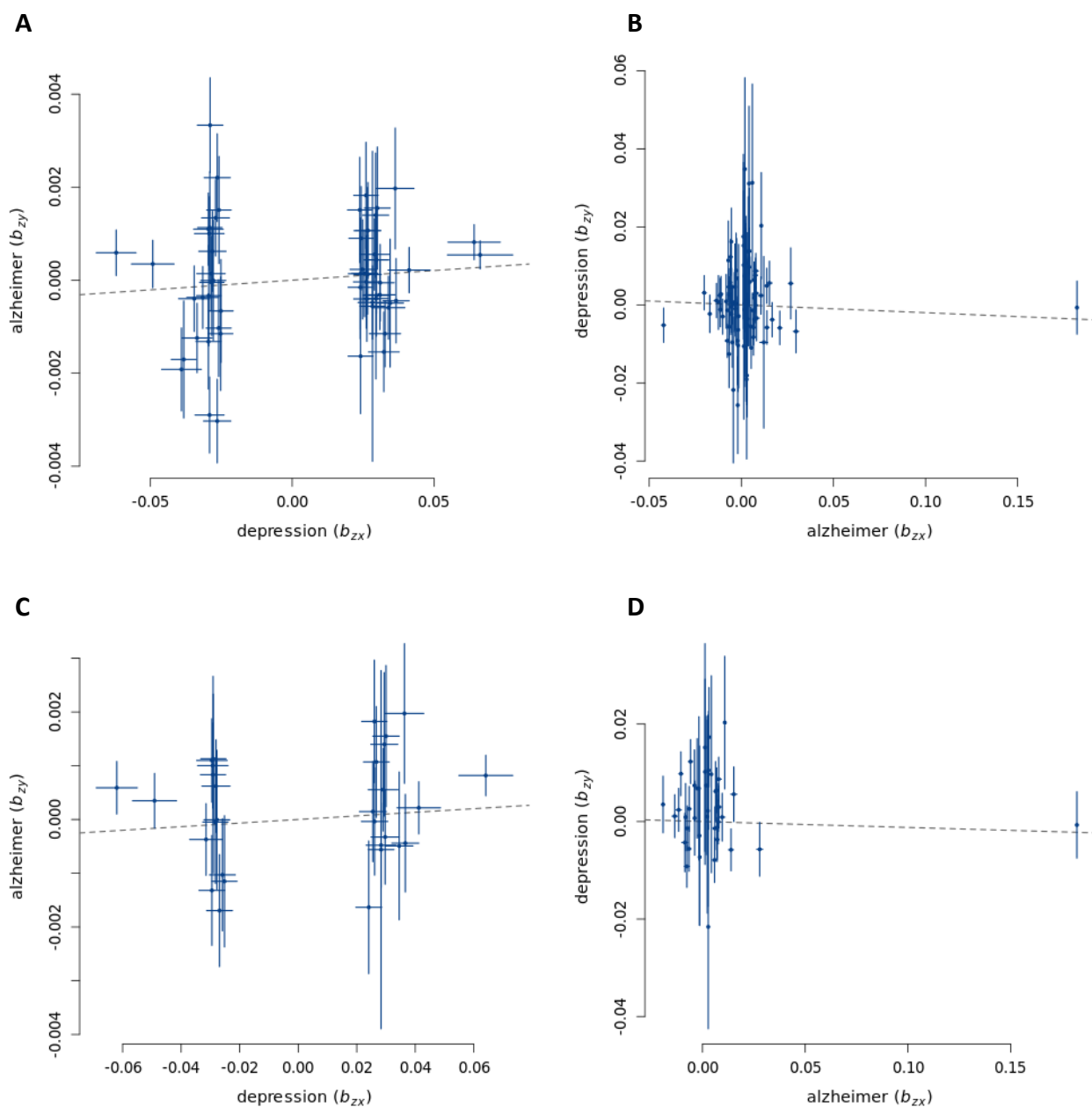
Figure S3: *GSMR analysis to test for effect of depression on AD and vice versa when the APOE region had been removed.* **(A)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for depression are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(B)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of depression with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(C)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for depression are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* **(D)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of depression with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
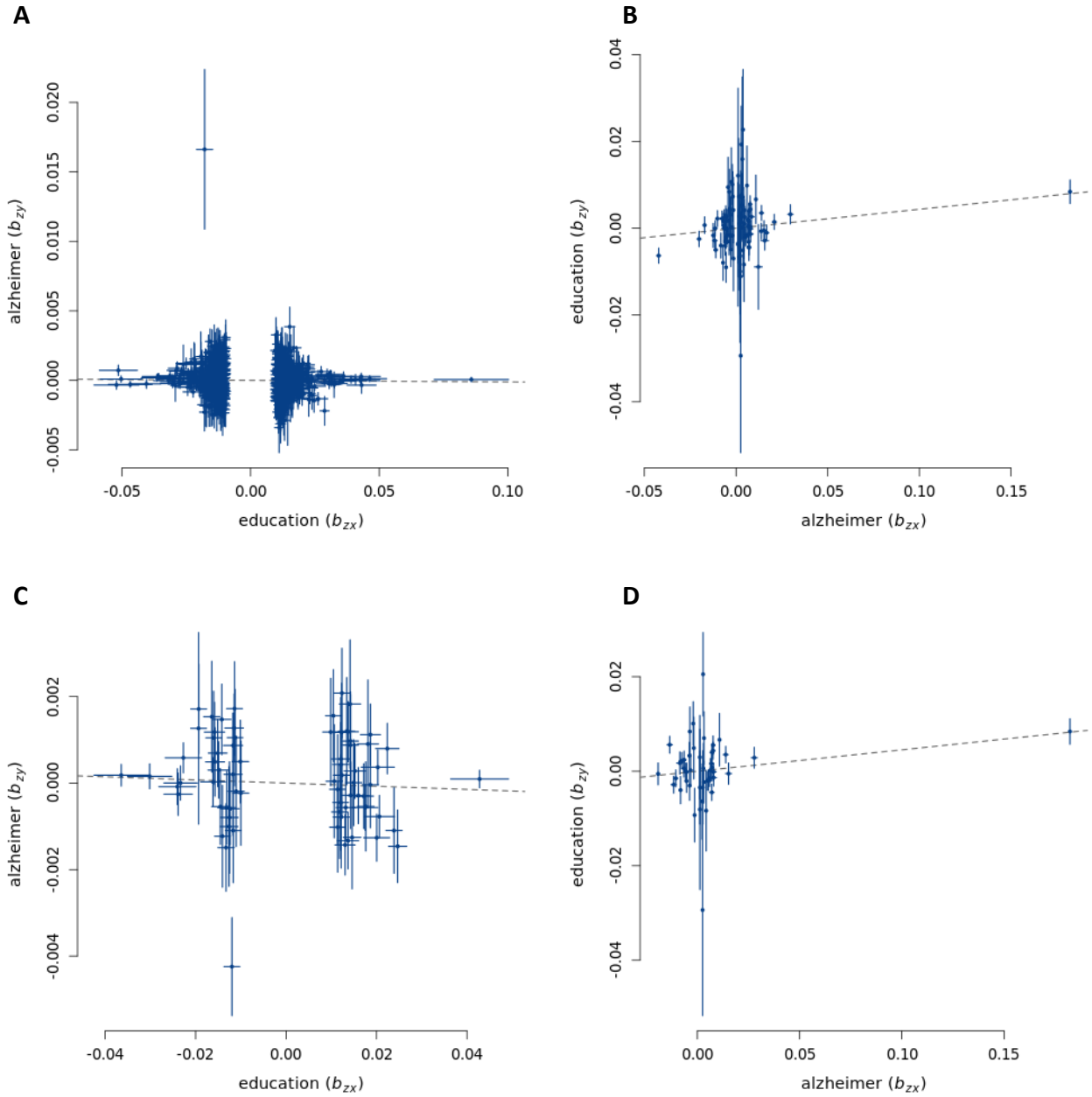
Figure S4: *GSMR analysis to test for effect of educational attainment on AD and vice versa when the APOE region had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for educational attainment are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of educational attainment with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for educational attainment are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of educational attainment with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
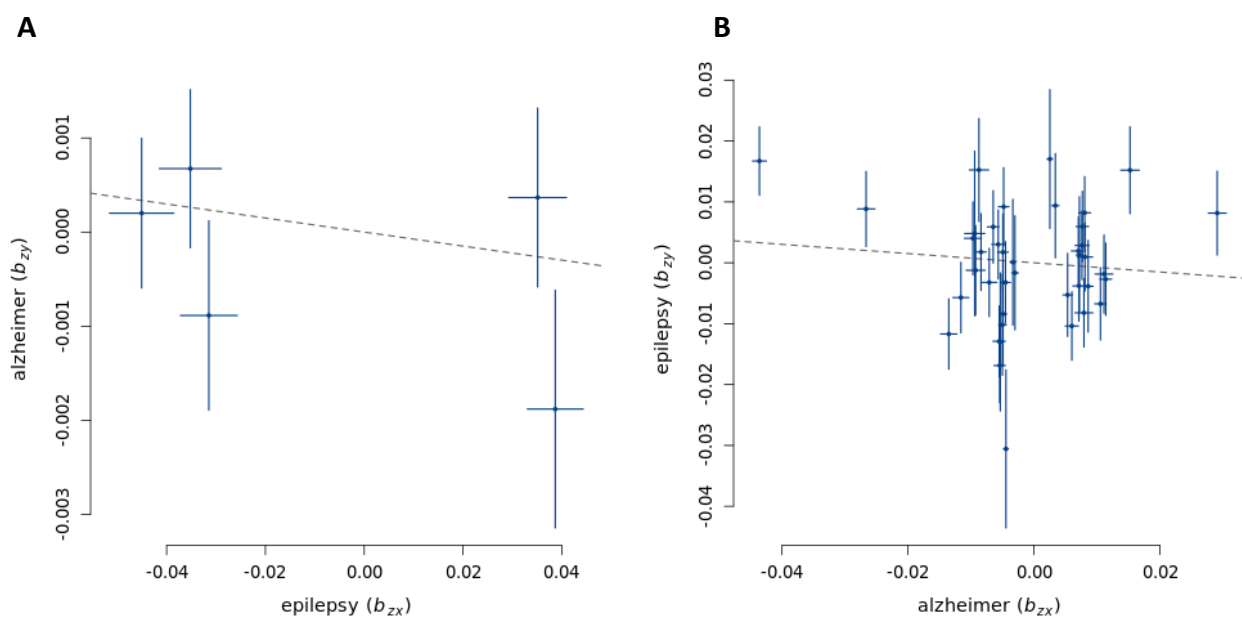
Figure S5: *GSMR analysis to test for effect of epilepsy AD and vice versa when the APOE region had been removed.* ***(A)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for epilepsy are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(B)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of epilepsy with HEIDI outlier filtering and a LD clumping threshold of 0.05.*
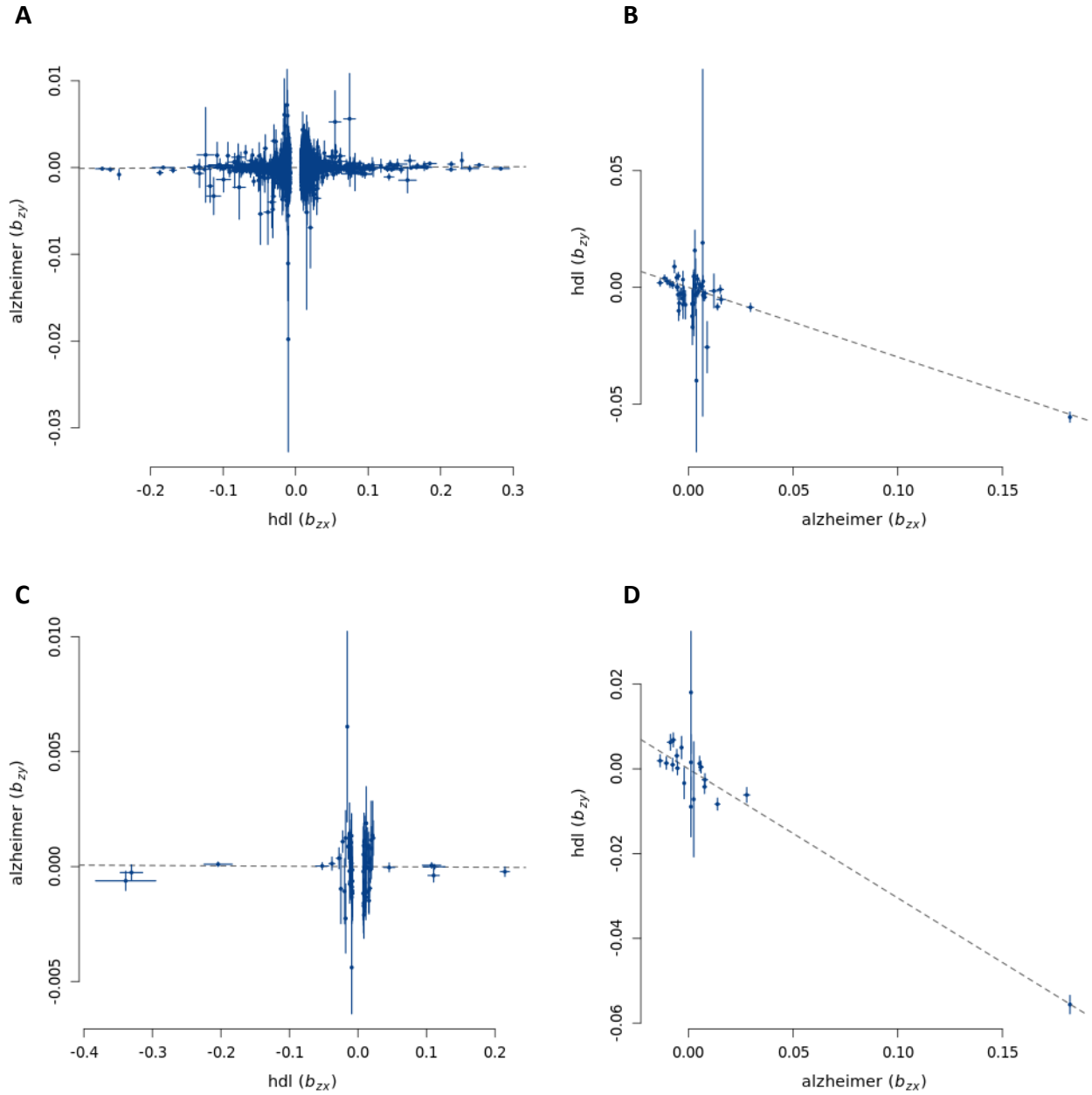
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Figure S6: *GSMR analysis to test for effect of HDL on AD and vice versa when the APOE region had been removed.* ***(A)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for HDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(B)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of HDL with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(C)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for HDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* ***(D)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of HDL with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
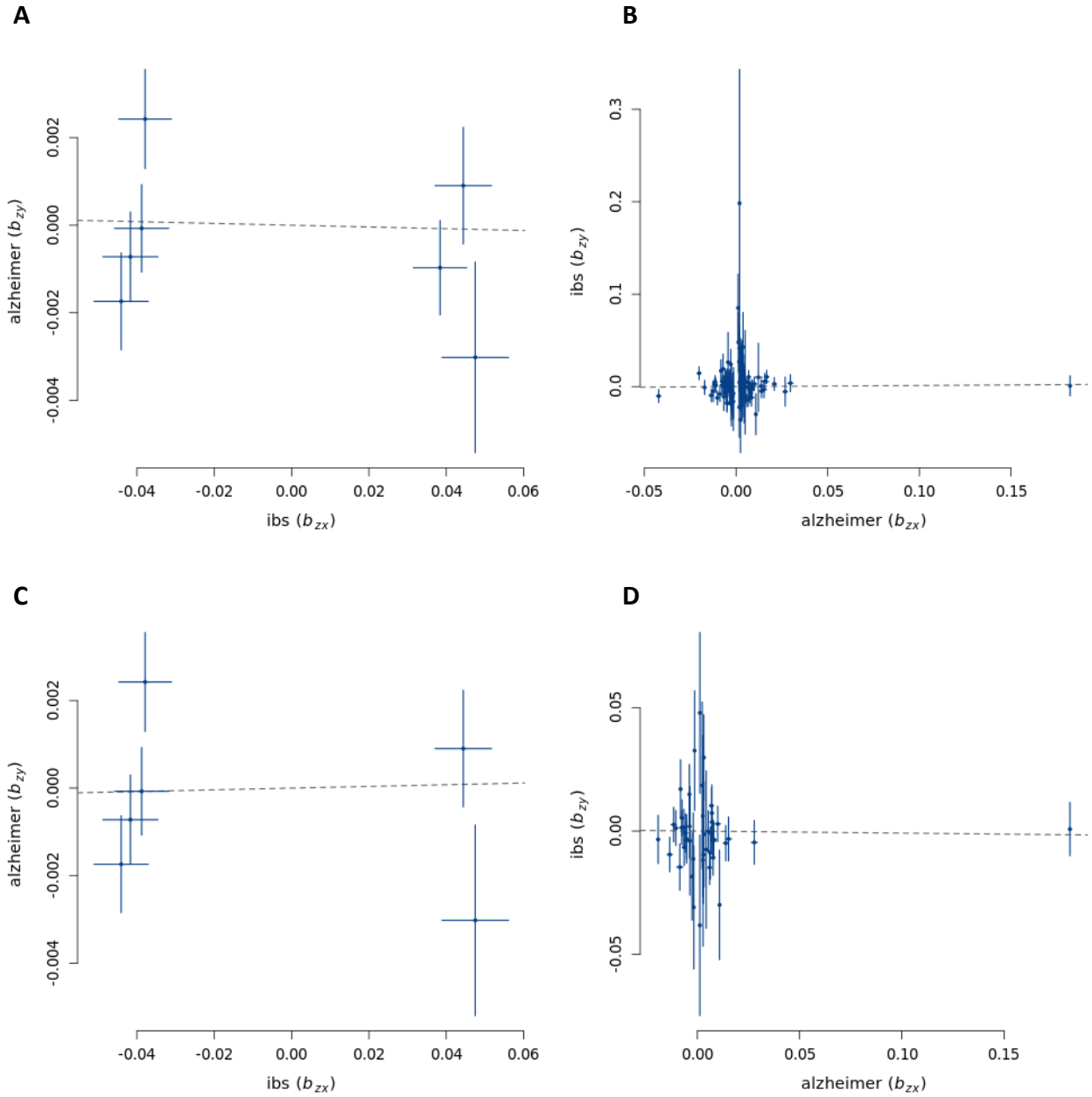
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*Figure S7: GSMR analysis to test for effect of IBS on AD and vice versa when the APOE region had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for IBS are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of IBS with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for IBS are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of IBS with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
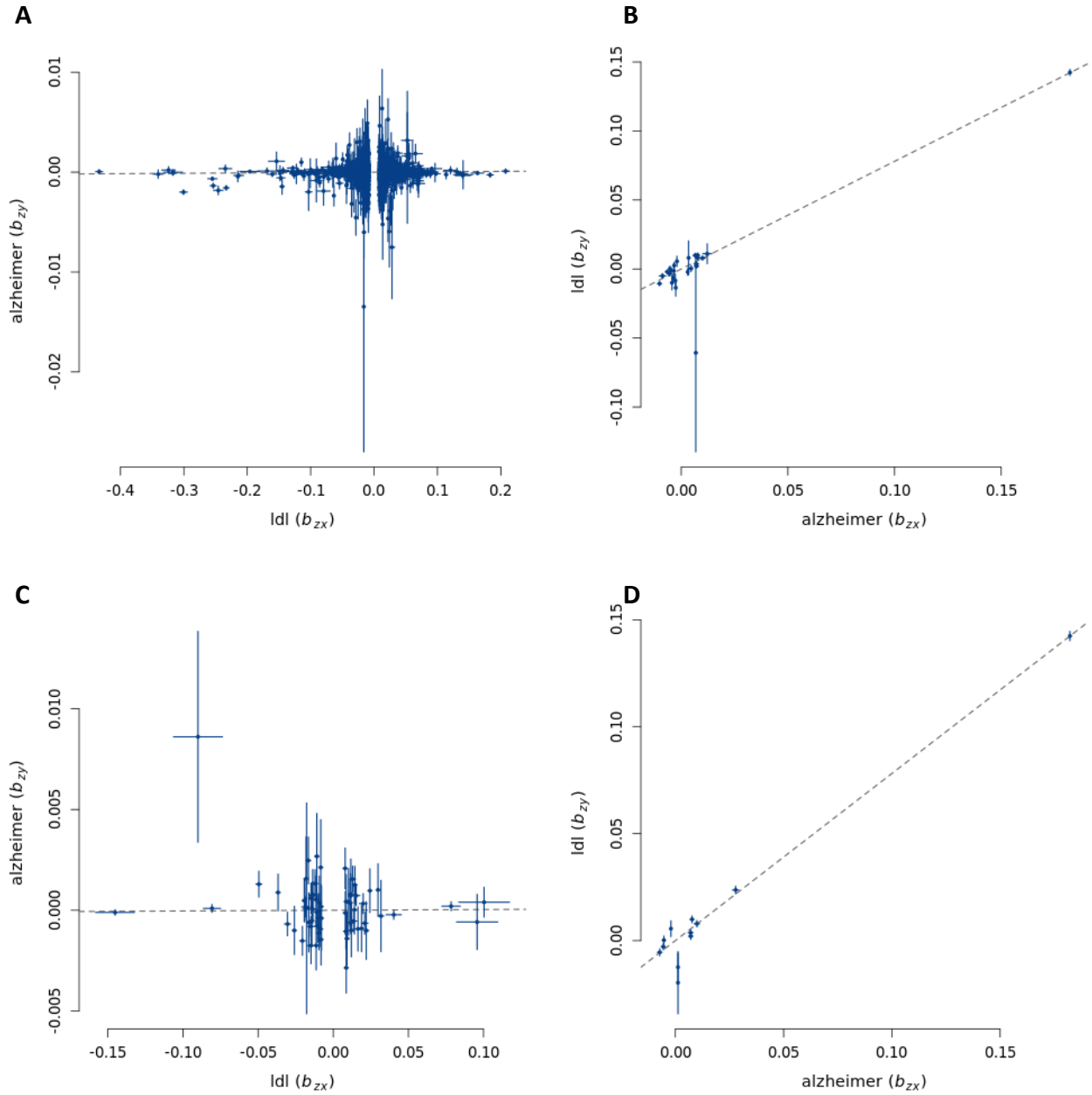
Figure S8: *GSMR analysis to test for effect of LDL on AD and vice versa when the APOE region had been removed.* **(A)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for LDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(B)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of LDL with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(C)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for LDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* **(D)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of LDL with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
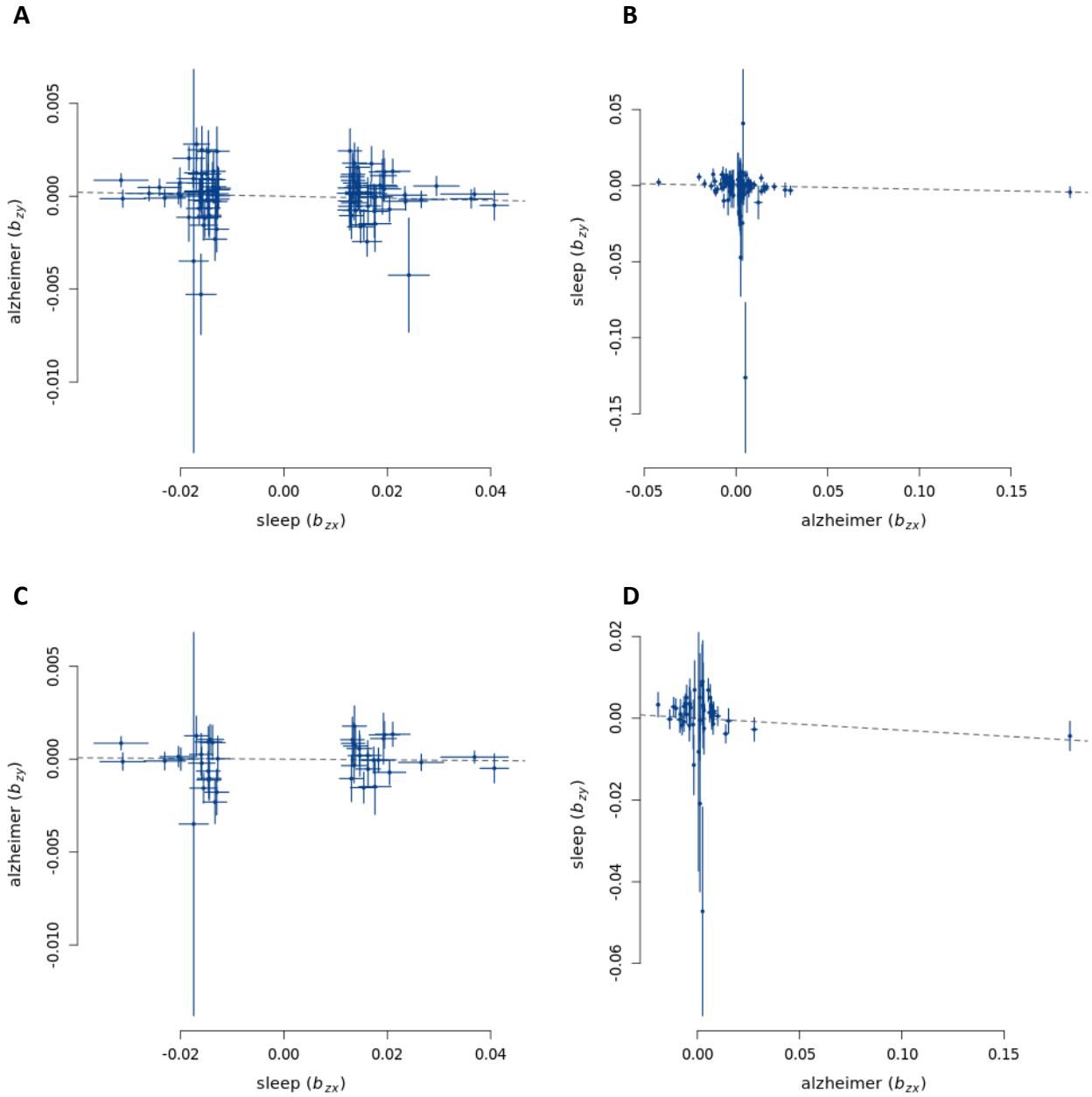
Figure S9: GSMR analysis to test for effect of sleep duration on AD and vice versa when the APOE region had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for sleep duration are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of sleep duration with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for sleep duration are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of sleep duration with HEIDI outlier filtering and a LD clumping threshold of 0.01.
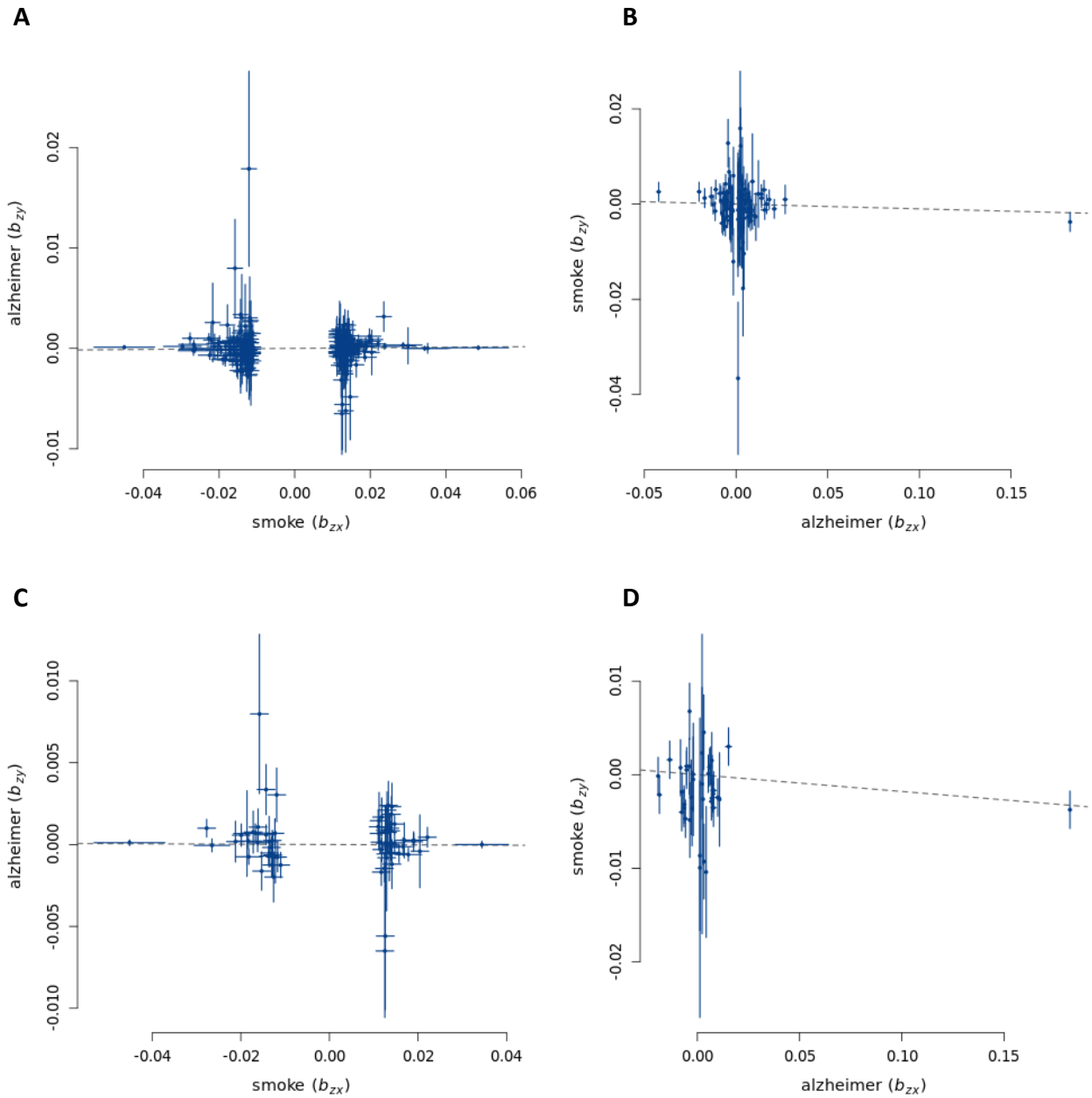
Figure S10: *GSMR analysis to test for effect of smoke initiation on AD and vice versa when the APOE region had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for smoke initiation are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of smoke initiation with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for smoke initiation are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of smoke initiation with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
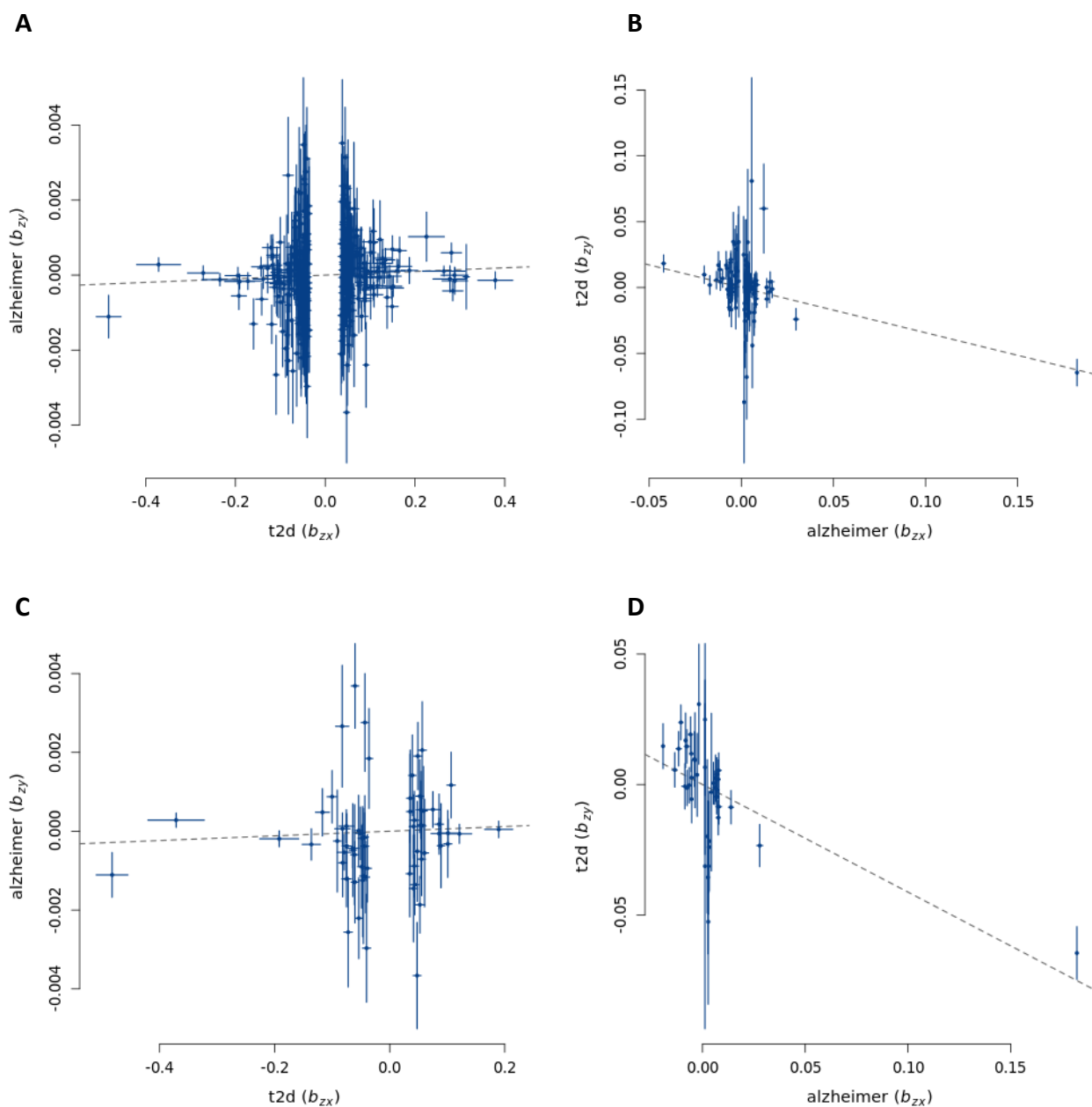
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Figure S11: *GSMR analysis to test for effect of type 2 diabetes on AD and vice versa when the APOE region had been removed. (A) GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for type 2 diabetes are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. (B) GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of type 2 diabetes with HEIDI outlier filtering and a LD clumping threshold of 0.05. (C) GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for type 2 diabetes are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. (D) GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of type 2 diabetes with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
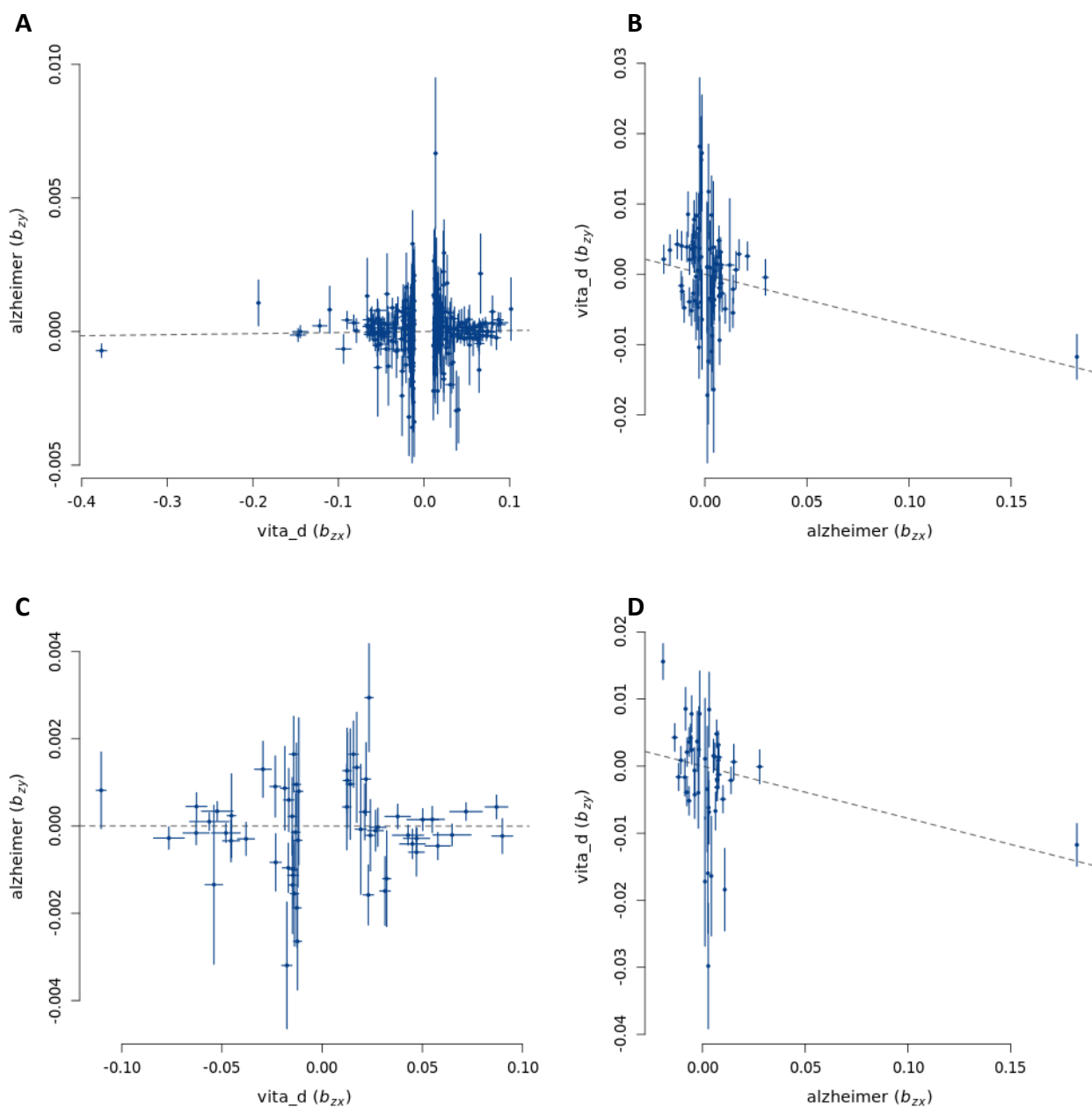
Figure S12: *GSMR analysis to test for effect of vitamin D on AD and vice versa when the APOE region had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for vitamin D are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of vitamin D with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for vitamin D are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of vitamin D with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
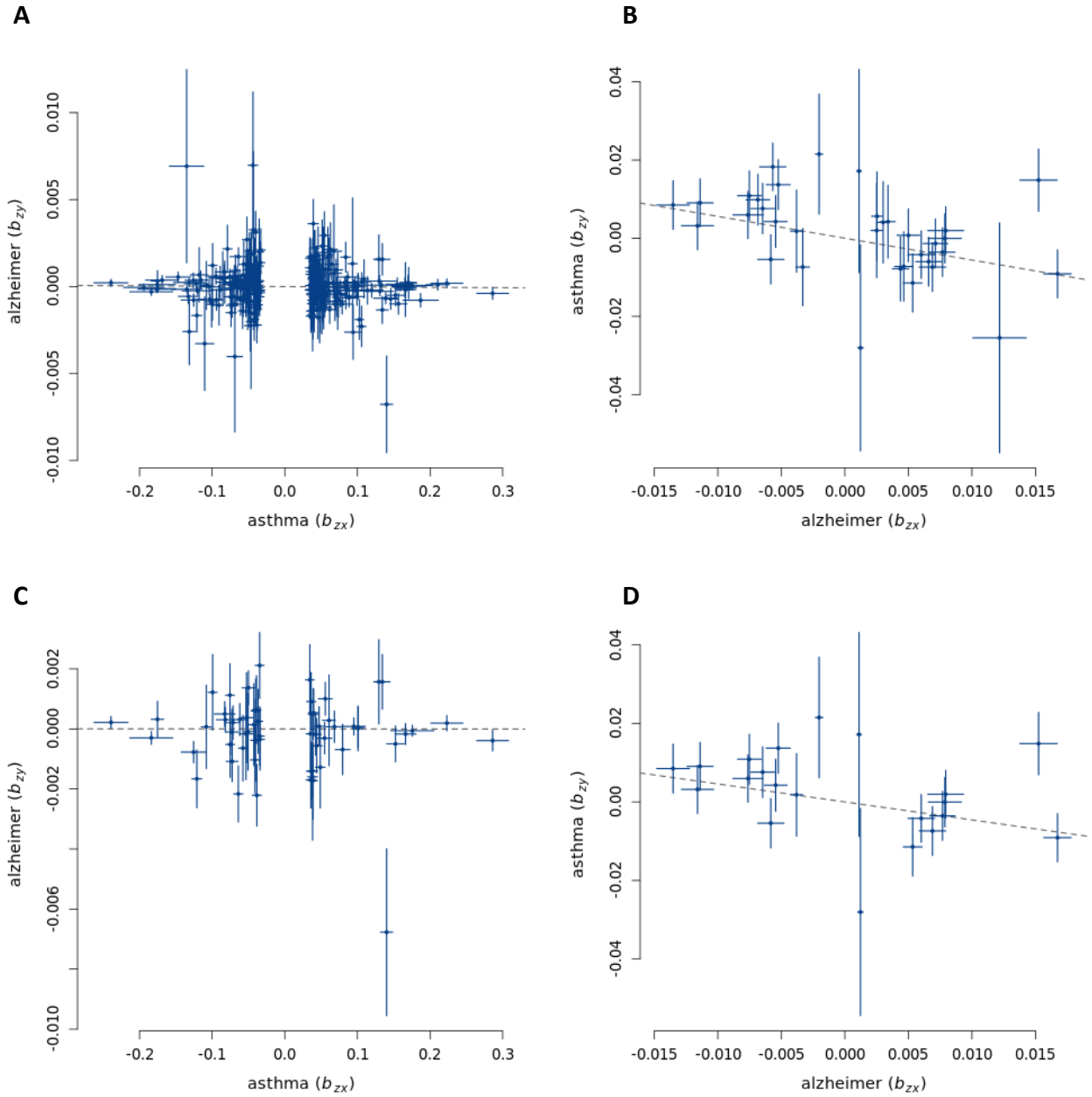
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Figure S13: *GSMR analysis to test for effect of asthma on AD and vice versa when chromosome 19 had been removed.* ***(A)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for asthma are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(B)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of asthma with HEIDI outlier filtering and a LD clumping threshold of 0.05.* ***(C)*** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for asthma are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* ***(D)*** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of asthma with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
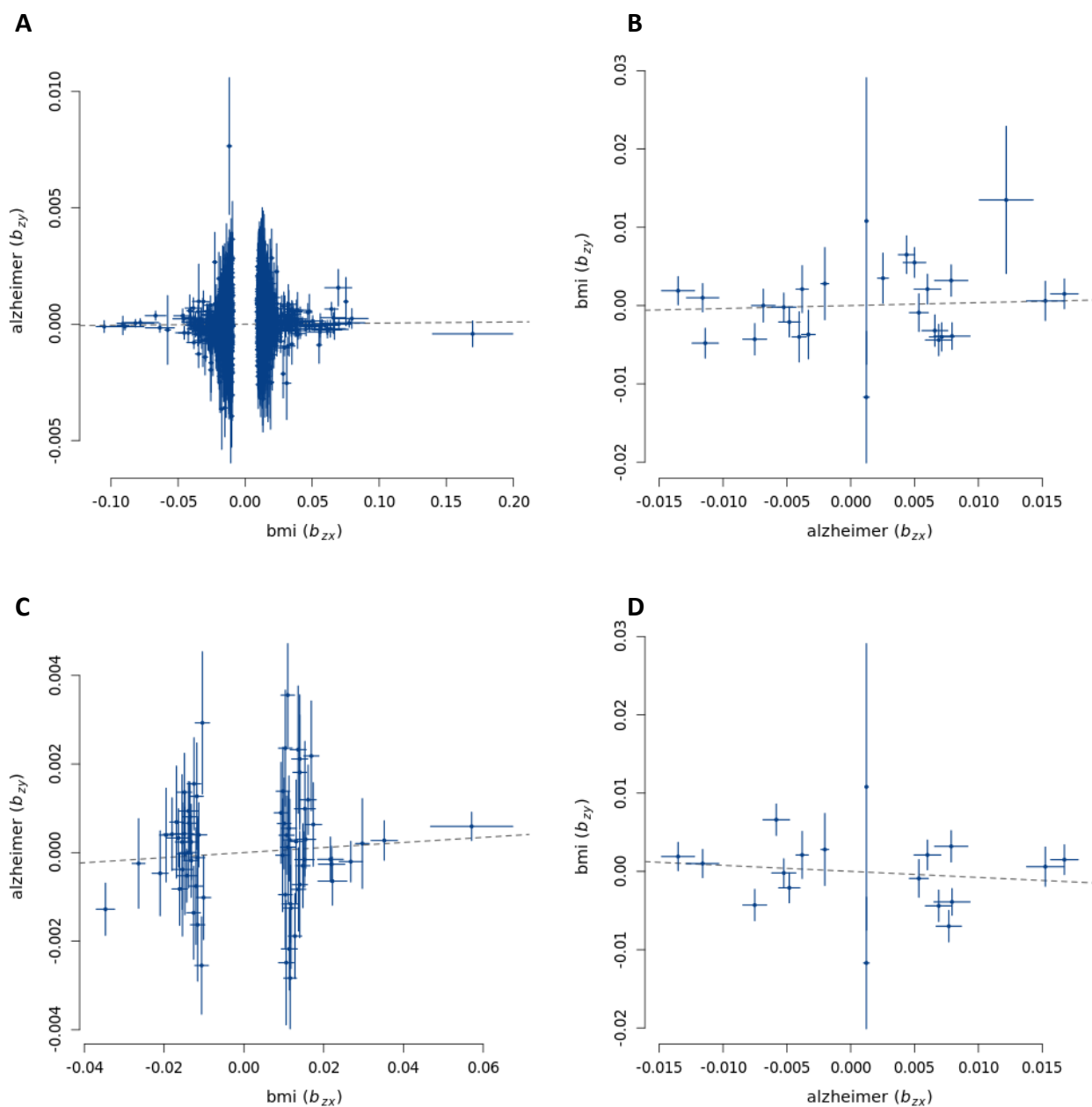
Figure S12: *GSMR analysis to test for effect of BMI on AD and vice versa when chromosome 19 had been removed.* **(A)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for BMI are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(B)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of BMI with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(C)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for BMI are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* **(D)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of BMI with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
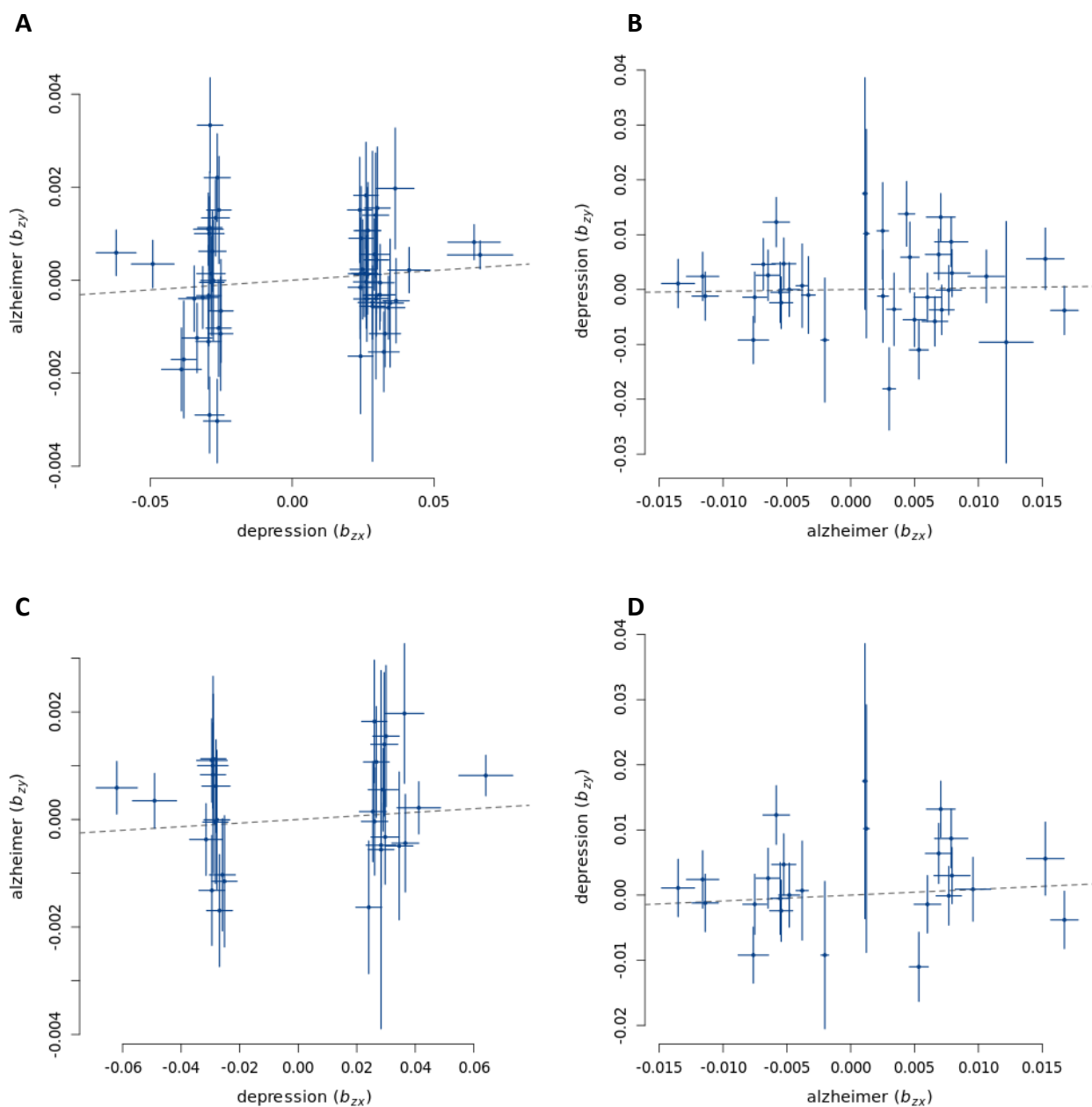
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Figure S15: GSMR analysis to test for effect of depression on AD and vice versa when chromosome 19 had been removed. (A) GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for depression are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. (B) GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of depression with HEIDI outlier filtering and a LD clumping threshold of 0.05. (C) GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for depression are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. (D) GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of depression with HEIDI outlier filtering and a LD clumping threshold of 0.01.
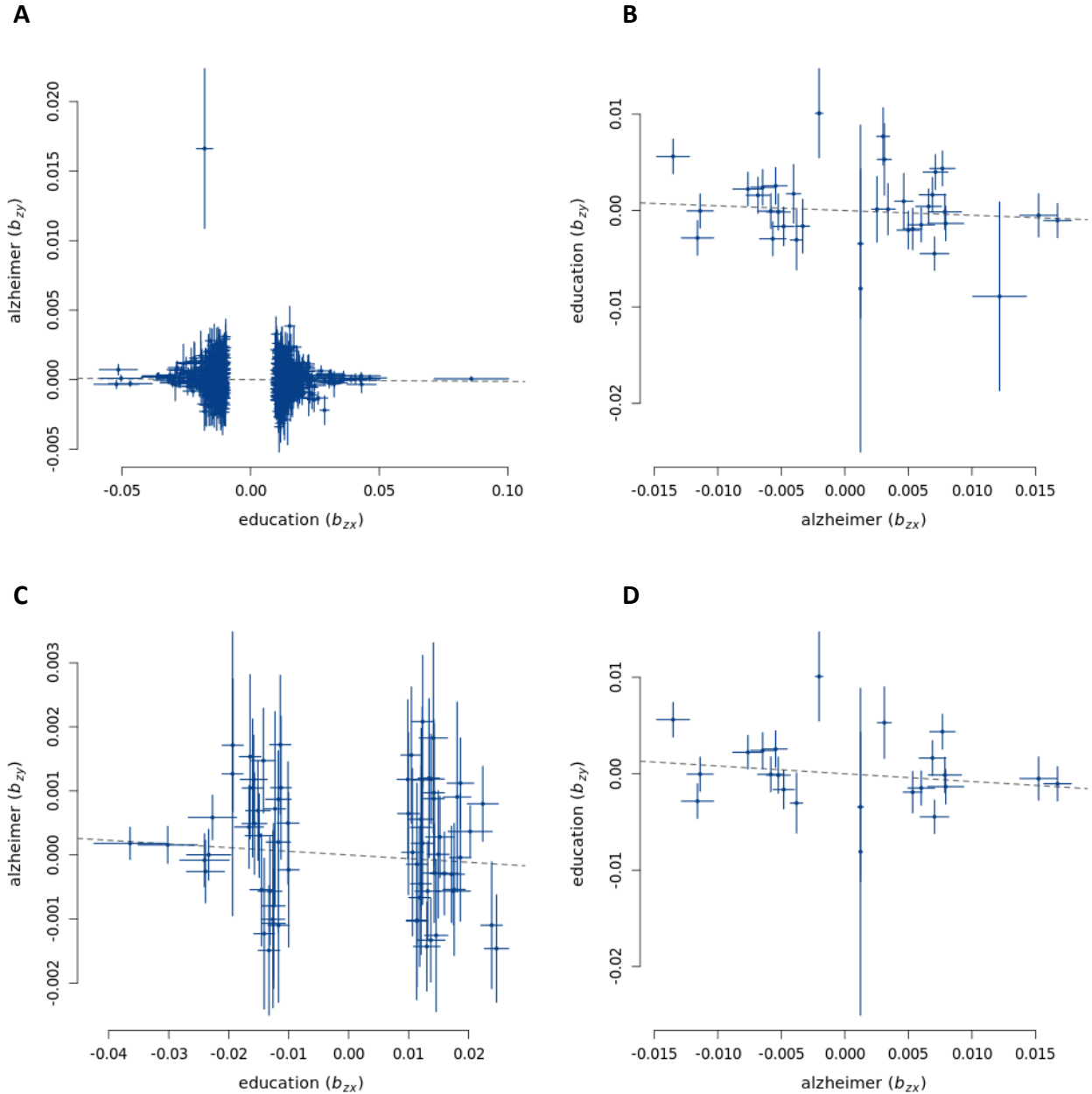
Figure S16: *GSMR analysis to test for effect of educational attainment on AD and vice versa when chromosome 19 had been removed.* **(A)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for educational attainment are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(B)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of educational attainment with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(C)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for educational attainment are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01.* **(D)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of educational attainment with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
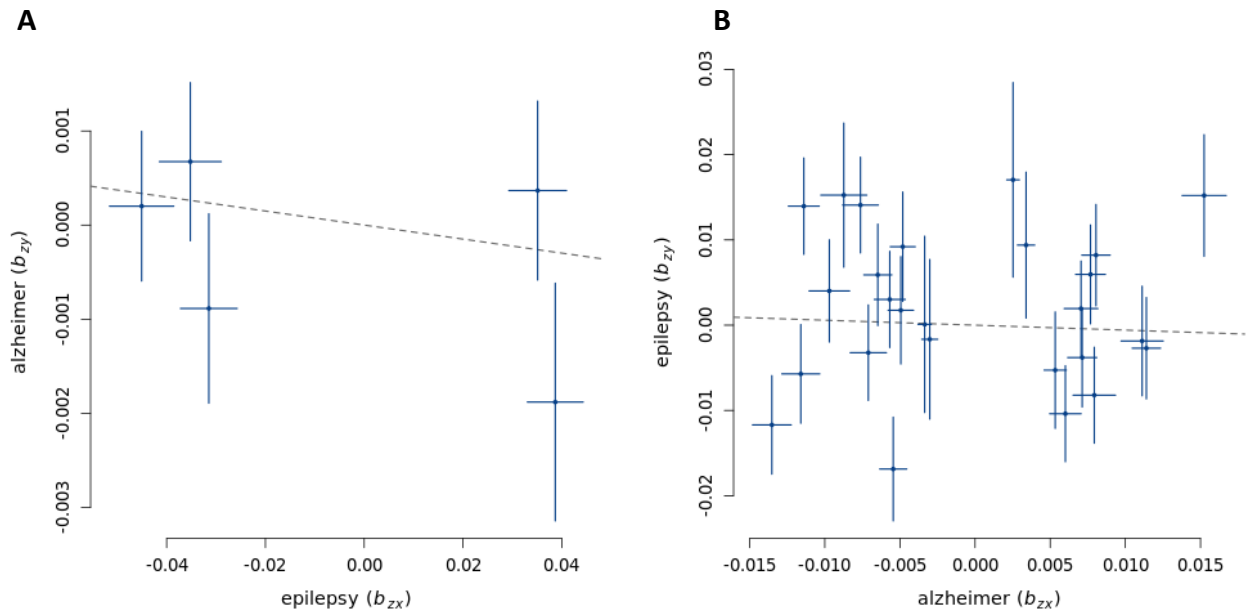
Figure S17: *GSMR analysis to test for effect of epilepsy AD and vice versa when chromosome 19 had been removed.* **(A)** *GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for epilepsy are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05.* **(B)** *GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of epilepsy with HEIDI outlier filtering and a LD clumping threshold of 0.05.*
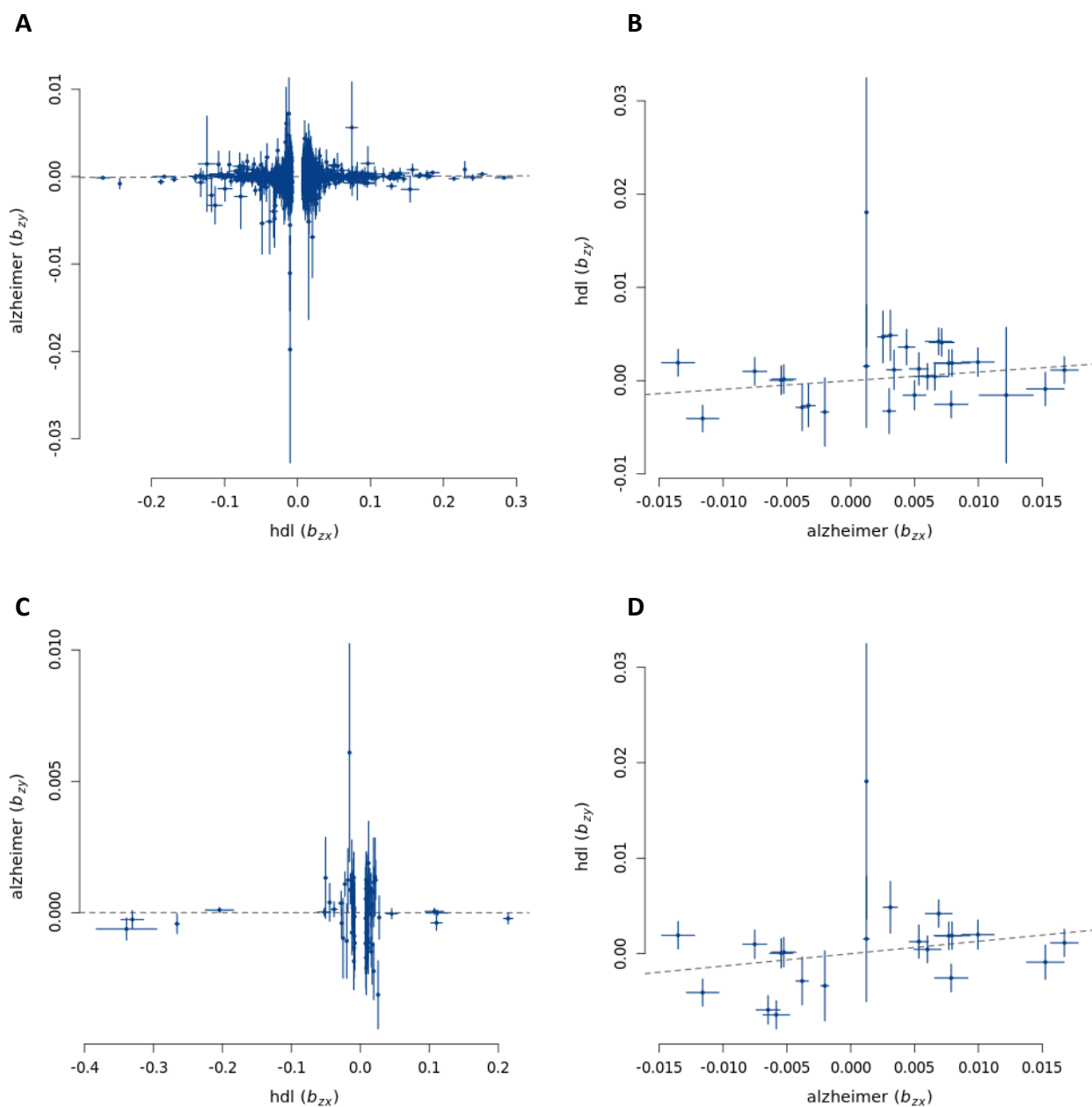
Figure S18: *GSMR analysis to test for effect of HDL on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for HDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of HDL with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for HDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of HDL with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
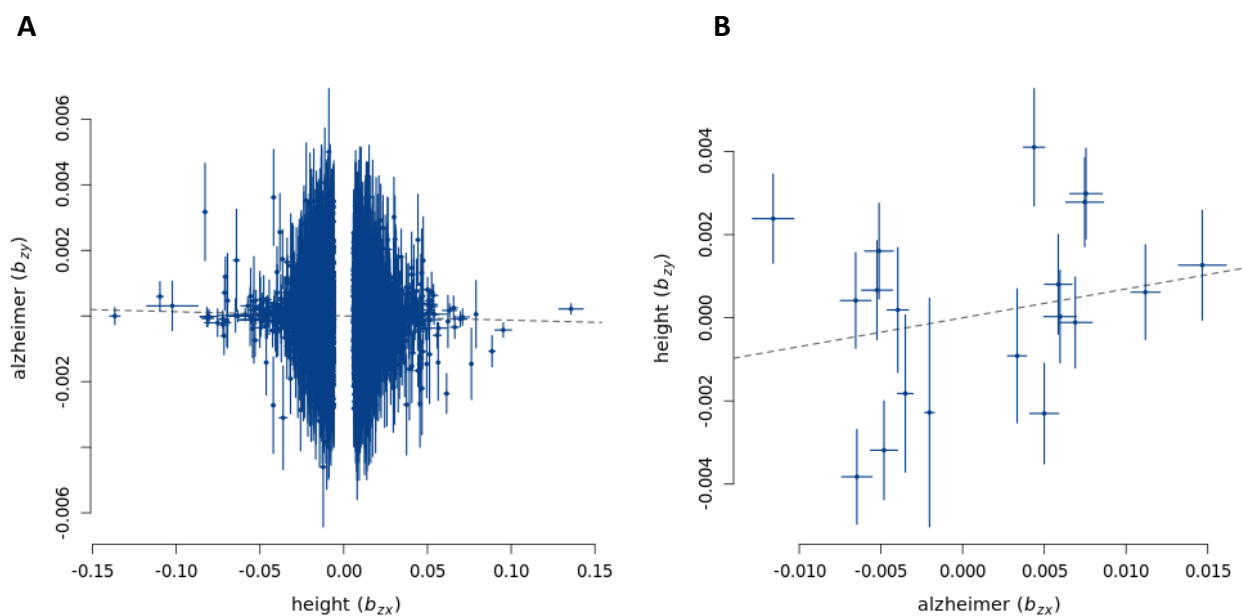
Figure S19: *GSMR analysis to test for effect of height AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for height are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of height with HEIDI outlier filtering and a LD clumping threshold of 0.05.*
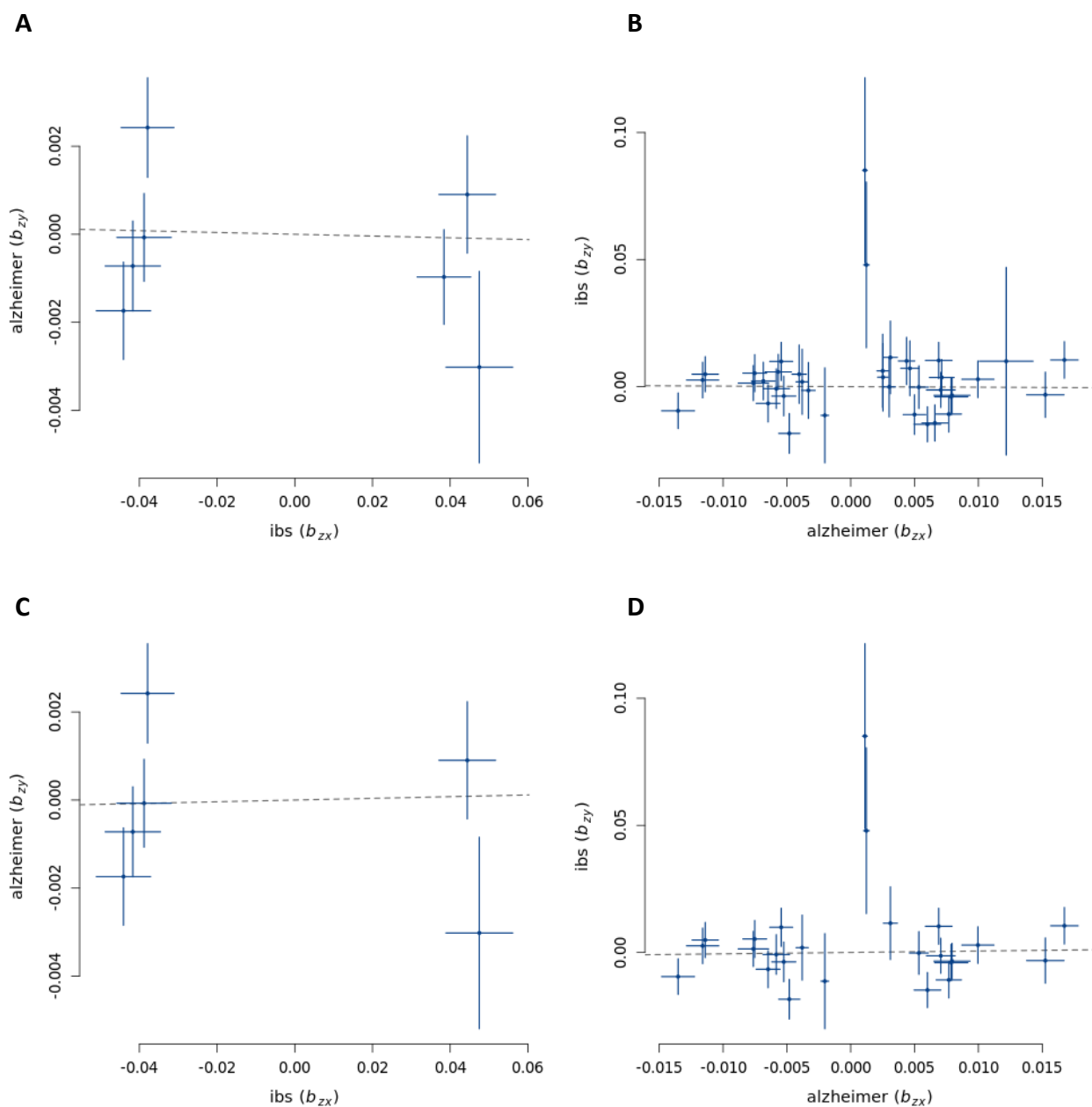
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Figure S20: *GSMR analysis to test for effect of IBS on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for IBS are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of IBS with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for IBS are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of IBS with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
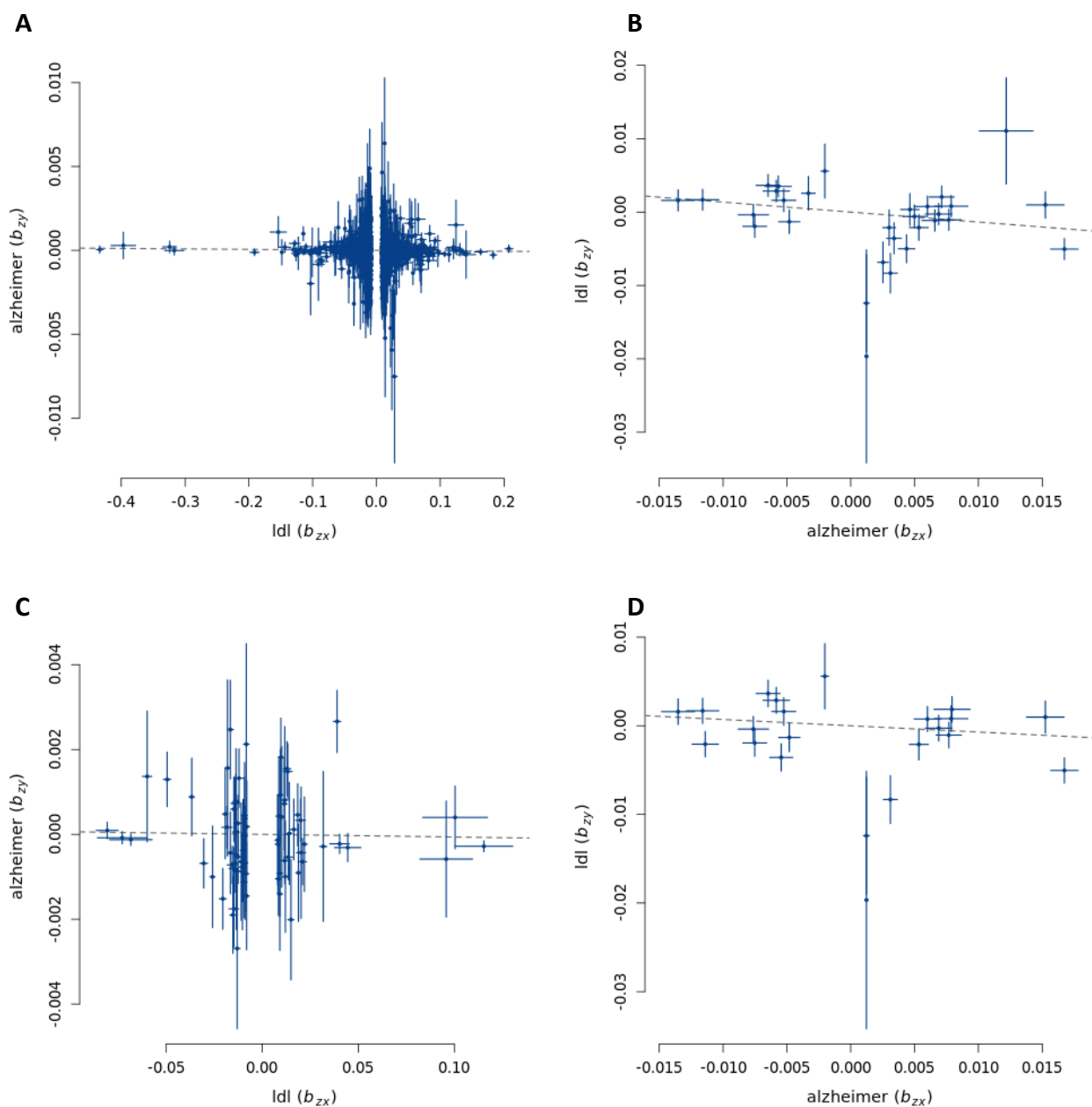
Figure S21: *GSMR analysis to test for effect of LDL on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for LDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of LDL with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for LDL are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of LDL with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
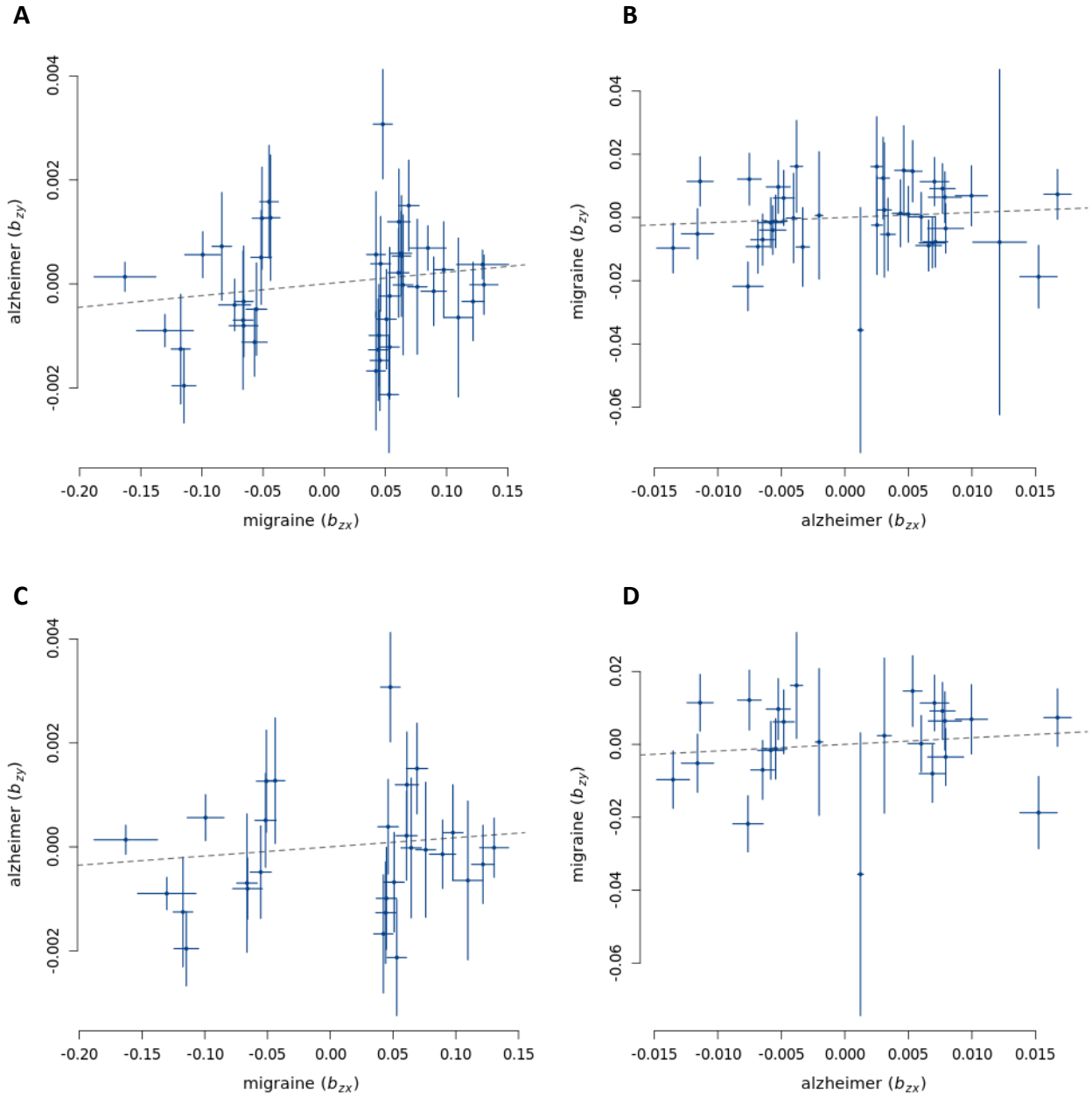
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Figure S22: *GSMR analysis to test for effect of migraine on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for migraine are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of migraine with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for migraine are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of migraine with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
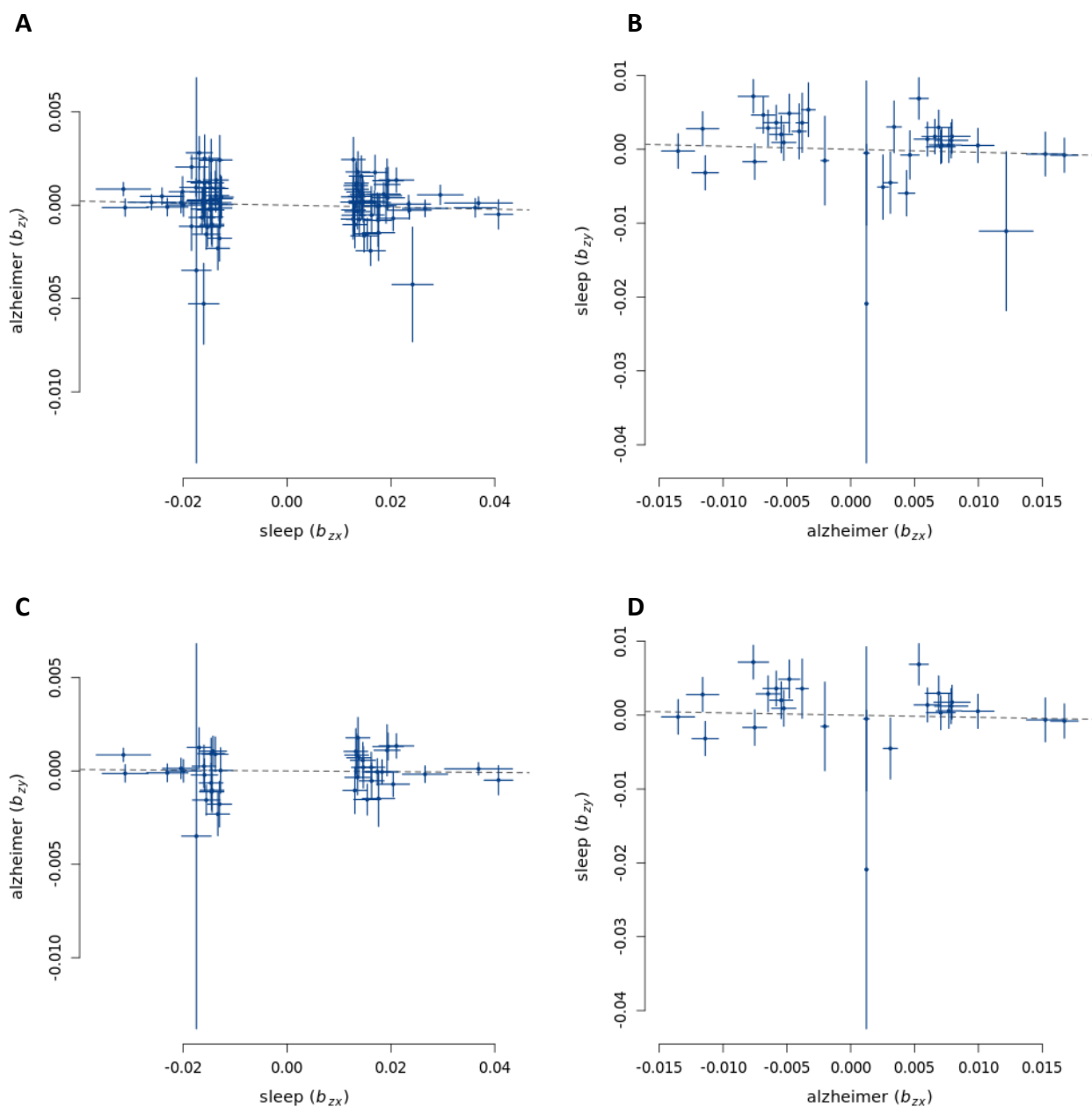
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Figure S23: *GSMR analysis to test for effect of sleep duration on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for sleep duration are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of sleep duration with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for sleep duration are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of sleep duration with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
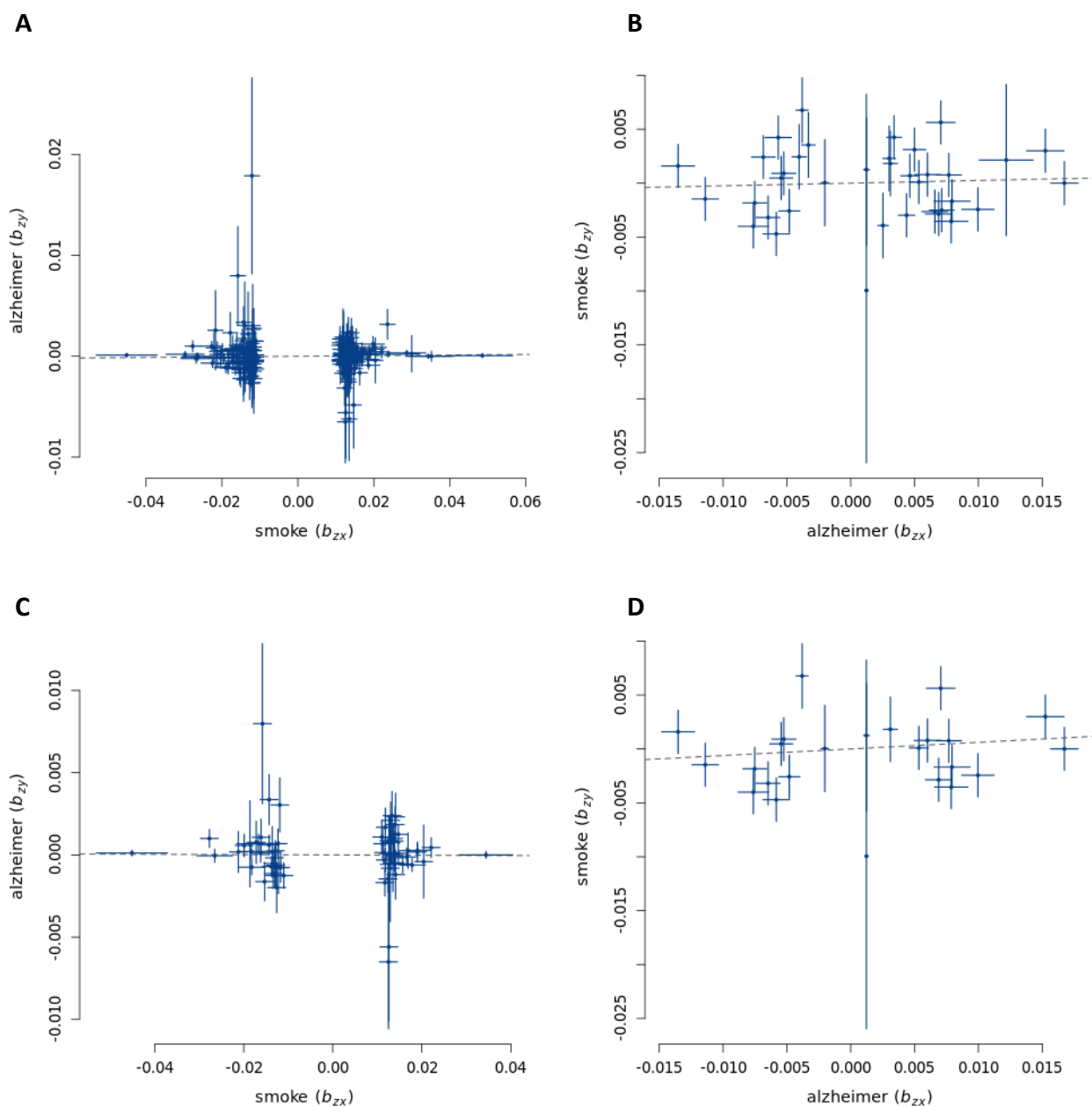
Figure S24: *GSMR analysis to test for effect of smoke initiation on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for smoke initiation are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of smoke initiation with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for smoke initiation are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of smoke initiation with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
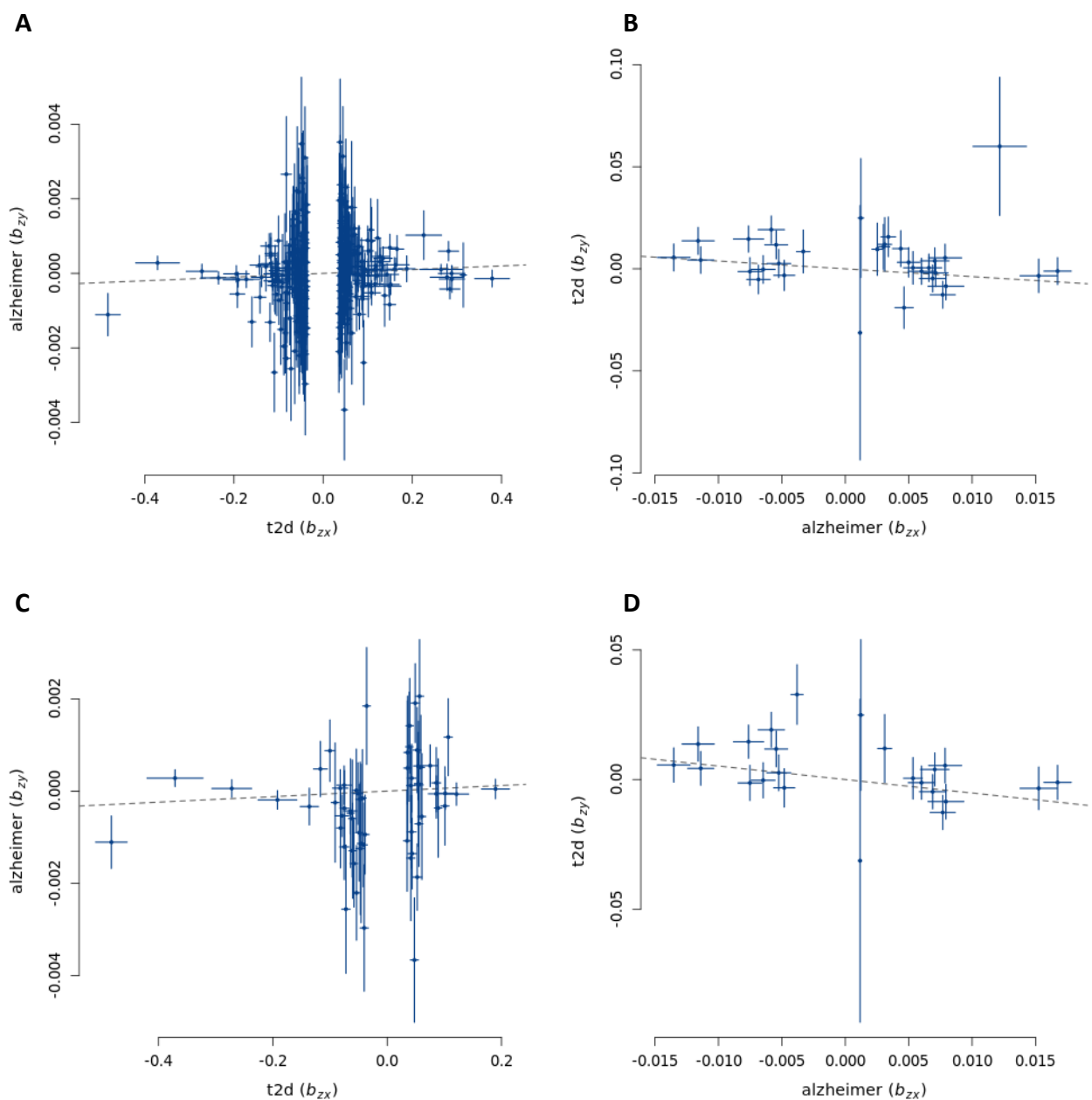
Figure S25: *GSMR analysis to test for effect of type 2 diabetes on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for type 2 diabetes are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of type 2 diabetes with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for type 2 diabetes are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of type 2 diabetes with HEIDI outlier filtering and a LD clumping threshold of 0.01.*
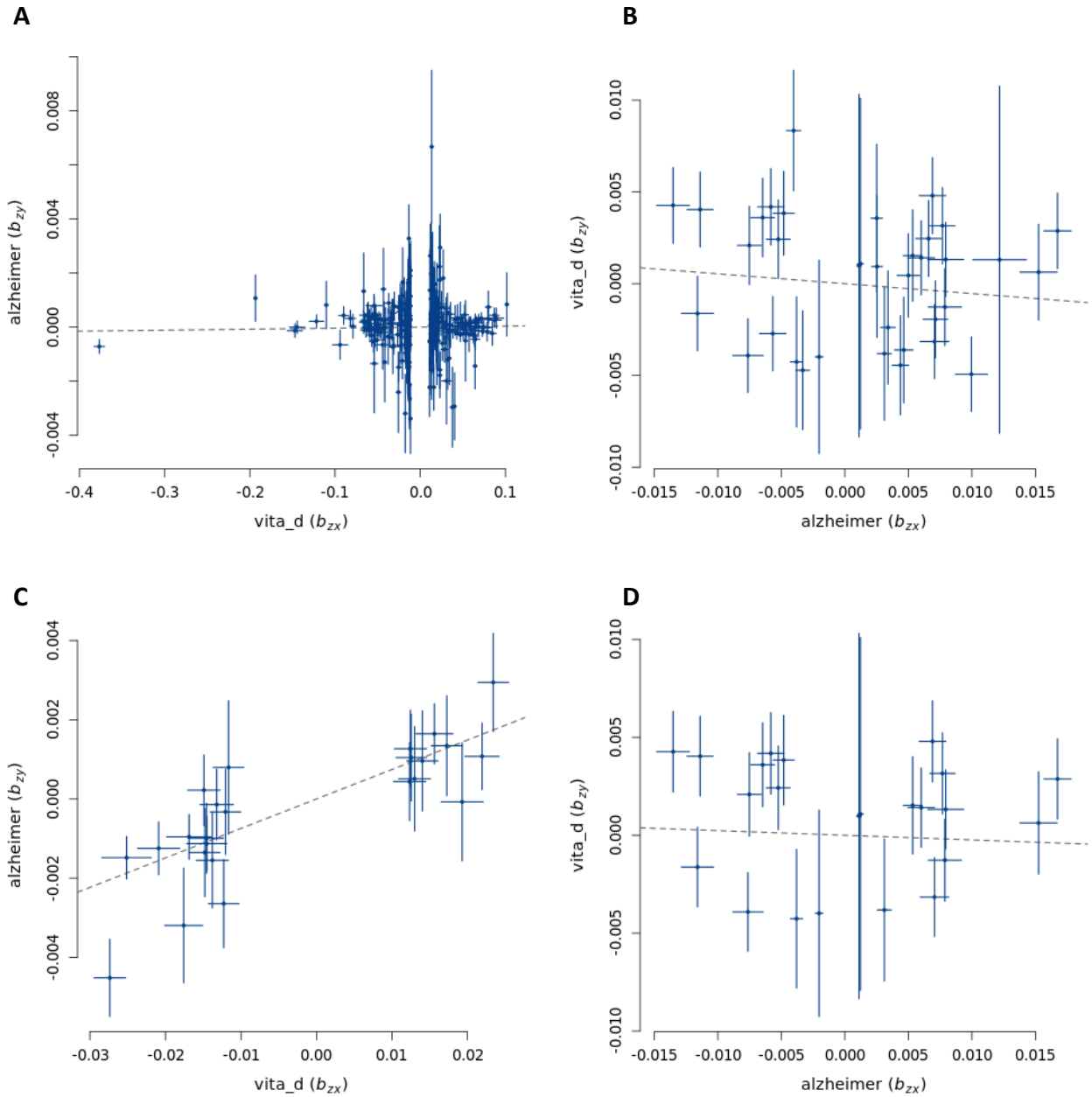
Figure S26: *GSMR analysis to test for effect of vitamin D on AD and vice versa when chromosome 19 had been removed. **(A)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for vitamin D are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(B)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of vitamin D with HEIDI outlier filtering and a LD clumping threshold of 0.05. **(C)** GSMR plot of the forward analysis, where effect sizes of all genetic instruments from a GWAS for vitamin D are plotted against those of AD with HEIDI outlier filtering and a LD clumping threshold of 0.01. **(D)** GSMR plot of the reverse analysis, where effect sizes of all genetic instruments from a GWAS for AD are plotted against those of vitamin D with HEIDI outlier filtering and a LD clumping threshold of 0.01.*