

Supplementary File

Table 1. Leave Out Analysis for the Association Between AD and Stroke.

Leave out analysis	OR	lci	uci	p
SNP				
rs10790275	1.036604	0.972788	1.104605	0.267451
rs12144049	1.042417	0.972733	1.117092	0.239259
rs12188917	1.041947	0.978455	1.10956	0.200193
rs12334935	1.035133	0.970749	1.103787	0.291931
rs2212434	1.020007	0.955225	1.089182	0.554045
rs2477121	1.034137	0.969395	1.103203	0.308846
rs2918299	1.03132	0.96544	1.101695	0.359834
rs4151657	1.022324	0.959644	1.089097	0.494015
rs479844	1.016297	0.952313	1.08458	0.626072
rs6062486	1.011756	0.961976	1.064113	0.649796
rs61815704	1.030897	0.963773	1.102695	0.375715
rs6419573	1.031928	0.966049	1.1023	0.350428
rs8066625	1.024116	0.959297	1.093315	0.475022
All	1.029013	0.967481	1.094458	0.363285

OR: odds ratio; lci: lower confidence intervals; uci: upper confidence intervals

Table 2. Leave Out Analysis for the Association Between AD and Heart Failure.

Leave out analysis	OR	lci	uci	p
SNP				
rs10790275	1.045685	0.998383	1.095228	0.058563
rs12144049	1.040601	0.985861	1.098381	0.14888
rs12188917	1.039984	0.989537	1.093003	0.122254
rs12334935	1.049112	1.00675	1.093256	0.022613
rs2212434	1.029703	0.980293	1.081603	0.24335
rs2477121	1.04574	0.998462	1.095256	0.05812
rs2918299	1.03622	0.985465	1.089589	0.16496
rs4151657	1.031931	0.983738	1.082484	0.197717
rs479844	1.028488	0.978571	1.08095	0.268462
rs6062486	1.041393	0.991172	1.09416	0.107756
rs61815704	1.035809	0.984408	1.089894	0.175465
rs6419573	1.037437	0.987373	1.09004	0.145272
rs8066625	1.028608	0.981841	1.077604	0.234802
All	1.037797	0.990541	1.087308	0.118686

OR: odds ratio; lci: lower confidence intervals; uci: upper confidence intervals

Table 3. Leave Out Analysis for the Association Between AD and Coronary Artery Disease.

Leave out analysis				
SNP	OR	lci	uci	p
rs10790275	0.998822	0.953129	1.046706	0.960658
rs12144049	0.999948	0.950616	1.05184	0.998389
rs12188917	0.994383	0.948679	1.042289	0.814494
rs12334935	1.005797	0.962038	1.051546	0.798973
rs2212434	1.009113	0.964813	1.055448	0.692053
rs2477121	1.001785	0.95586	1.049915	0.940634
rs2918299	1.003518	0.957882	1.051329	0.88243
rs4151657	0.988936	0.951483	1.027864	0.572203
rs479844	0.988138	0.946092	1.032053	0.590661
rs6062486	1.002905	0.957254	1.050733	0.902869
rs61815704	1.008962	0.963617	1.056441	0.703724
rs6419573	0.999903	0.953663	1.048385	0.996795
rs8066625	1.002174	0.956419	1.050117	0.927441
All	1.000338	0.957371	1.045233	0.987967

OR: odds ratio; lci: lower confidence intervals; uci: upper confidence intervals

Table 4. Leave Out Analysis for the Association Between AD and Myocardial Infarction.

Leave out analysis				
SNP	OR	lci	uci	p
rs10790275	0.999032	0.997552	1.000513	0.199932
rs12144049	0.99909	0.997501	1.000681	0.262249
rs12188917	0.999546	0.998032	1.001061	0.556637
rs12334935	0.999523	0.998046	1.001002	0.527093
rs2212434	0.999239	0.997709	1.000772	0.330301
rs2477121	0.999383	0.997902	1.000866	0.414595
rs2918299	0.999211	0.997712	1.000712	0.302782
rs4151657	0.999099	0.997621	1.00058	0.232923
rs479844	0.999167	0.997629	1.000707	0.288732
rs6062486	0.999378	0.997897	1.000862	0.411388
rs61815704	0.999544	0.997987	1.001104	0.566673
rs6419573	0.999325	0.997826	1.000827	0.378057
rs8066625	0.998984	0.997499	1.00047	0.180141
All	0.99927	0.997827	1.000716	0.322364

OR: odds ratio; lci: lower confidence intervals; uci: upper confidence intervals

Table 5. Leave Out Analysis for the Association Between AD and Angina Pectoris.

Leave out analysis	OR	lci	uci	p
SNP				
rs10790275	1.000954	0.999344	1.002566	0.245799
rs12144049	1.001062	0.999283	1.002844	0.242133
rs12188917	1.000588	0.998863	1.002316	0.504061
rs12334935	1.001026	0.999524	1.00253	0.180897
rs2212434	1.000258	0.998796	1.001722	0.729742
rs2477121	1.000653	0.998952	1.002356	0.452234
rs2918299	1.000854	0.999161	1.002551	0.323015
rs4151657	1.00054	0.998912	1.00217	0.51587
rs479844	1.000581	0.998834	1.002331	0.514699
rs6062486	1.000607	0.998924	1.002292	0.480047
rs61815704	1.000857	0.999064	1.002653	0.349097
rs6419573	1.000952	0.99932	1.002587	0.253258
rs8066625	1.00064	0.998937	1.002347	0.461454
All	1.000735	0.999134	1.002338	0.368553

OR: odds ratio; lci: lower confidence intervals; uci: upper confidence intervals

Table 6: Characteristics of Population-Based Studies Reporting the Association Between AD and CVD

CVD main results											
Study	Study design and Period	Setting	Age, sample size (proportion of males)	Diagnosis of AD	Outcome definition	Statistical analysis	CAD	Angina	MI	HF	Stroke
Andersen, 2016 ¹	Cohort, (1997-2012)	Denmark	≥15 yrs, Mild: 26,898, Severe: 2,527 (46.1%), Control: 145372	Hospital diagnosis of AD, ICD-8, ICD-10 codes	ICD-8, ICD-10 codes	Poisson regression			Adjusted ¹ IRR: Mild: 0.82 (0.66-1.02), Severe: 1.39 (0.95-2.03); Fully adjusted ² IRR Mild: 0.73 (0.59-0.91), Severe: 1.06 (0.72-1.56)		Adjusted ³ IRR: Mild (0.78-1.11), Severe: 1.51 (1.08-2.10); Fully adjusted ⁴ IRR Mild: 0.82 (0.68-0.98), Severe: 1.19 (0.85-1.65)
Drucker, 2016 ²	Cross-sectional, (1989-2009)	USA	Total :78702, AD: 7916 (0%)	Self-reported clinician diagnosed eczema (AD)	self-reported, confirmed by medical record, letter or interview	Logistic regression			Adjusted ³ OR: 0.97 (0.69-1.36); MV-adjusted ⁴ OR 0.94 (0.67-1.32); MV-adjusted ⁵ OR 0.91 (0.65-1.28)		Adjusted ⁶ OR: 1.38 (1.03-1.85); MV-adjusted ⁷ OR 1.35 (1.00-1.80); MV-adjusted ⁸ OR 1.31 (0.98-1.76)
Drucker, 2017 ³	Cross-sectional, (2009 onwards)	Canada	30-74 yrs, Total: 259119, AD: 21379 (25%)	Self-reported a diagnosis of eczema	Self-reported a diagnosis of MI, stroke	Logistic regression			Adjusted ⁶ OR: 0.83 (0.72-0.95), MV-adjusted ⁷ model 1 OR: 0.75 (0.62-0.89); MV-adjusted ⁸ model 2 OR: 0.87 (0.75-1.00)		Adjusted ⁹ OR: 0.81 (0.68-0.97); MV-adjusted ¹⁰ model 1 OR: 0.75 (0.62-0.89); MV-adjusted ¹¹ model 2 OR: 0.79 (0.66-0.95)
Egeberg, 2016 ⁴	Cross-sectional, (1995-2012)	Denmark	≥18 yrs, AD: 7937 (38.2%), Control: 79370	Clinical diagnosis of AD ICD-10 codes	Administrative code	Logistic regression			Adjusted ⁹ OR: overall: 1.1 (0.92-1.33), mild: 0.88 (0.63-1.23); severe: 1.23 (0.98-1.54)		Adjusted ¹² OR: overall: 1.52 (1.32-1.74), mild: 1.23 (0.94-1.60); severe: 1.45 (1.19-1.77)

Ivert, 2019 ⁵	Case-control, (1968 -2016)	Sweden	≥15 yrs, AD: 104832, Non-severe: 95274 (33.8%), Severe: 9558 (35.7%), Control: 1022435	ICD-8: ICD- 9: ICD-10: codes	ICD codes	Conditional logistic regression	All cases: all crude ¹⁰ OR: 1.18 (1.13- 1.23), all fully adjusted ¹¹ OR: 1.13 (1.08-1.19), Men crude ^j OR: 1.15 (1.08-1.22), Men fully adjusted ^k OR: 1.10 (1.03-1.18), Women crude ^j OR: 1.21 (1.14-1.28), Women fully adjusted ^k OR: 1.16 (1.09-1.24). Non-severe cases: all crude ^j OR: 1.16 (1.10- 1.21), All fully adjusted OR: 1.13 (1.08- 1.19), Men crude ^j OR: 1.15 (1.07- 1.23), Men fully	All cases: all crude ^j OR: 1.10 (1.04-1.15), all fully adjusted ^k OR: 1.07 (1.02-1.12), Men crude ^j OR: 1.15 (1.07- 1.22), Men fully adjusted ^k OR: 1.12 (1.05-1.20), Women crude ^j OR: 1.03 (0.96- 1.11), Women fully adjusted ^k OR: 1.01 (0.94-1.08). Non-severe cases: all crude ^j OR: 1.08 (1.03- 1.14), All fully adjusted ^k OR: 1.07 (1.02-1.13), Men crude ^j OR: 1.16 (1.08-1.24), Men fully adjusted ^k OR: 1.15 (1.07-1.23), Women crude ^j OR: 0.99 (0.92- 1.08), Women fully	All cases: all crude ^j OR: 1.07 (1.02-1.13), all fully adjusted ^k OR: 1.04 (0.99-1.09). Men crude ^j OR: 1.13 (1.05-1.22), Men fully adjusted ^k OR: 1.09 (1.01-1.17). Women crude ^j OR: 1.03 (0.96-1.10), Women fully adjusted ^k OR: 1.00 (0.93-1.07). Non-severe cases: all crude ^j OR: 1.02 (0.97-1.08), All fully adjusted ^k OR: 1.00 (0.94-1.06), Men crude ^j OR: 1.09 (1.01-1.19), Men fully adjusted ^k OR: 1.06 (0.98-1.16), Women crude ^j OR: 0.96 (0.89-1.04), Women fully adjusted ^k OR: 0.95 (0.88-1.02). Severe cases: all crude ^j OR: 1.32 (1.19-1.47), All fully adjusted ^k OR: 1.19 (1.07-1.33), Men crude ^j OR: 1.32 (1.11-1.56), Men fully adjusted ^k OR: 1.20 (1.01-1.43), Women crude ^j OR: 1.33 (1.15-1.53), Women fully adjusted ^k OR: 1.19 (1.03-1.37)
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Table S6 (Continued)

CVD main results											
Study	Study design and Period	Setting	Age, sample size (proportion of males)	Diagnosis of AD	Outcome definition	Statistical analysis	CAD	Angina	MI	HF	Stroke
								adjusted ^k OR: 1.12 (1.04-1.20), Women crude ^l OR: 1.17 (1.09-1.25), Women fully adjusted ^k adjusted ^k OR: 1.15 (1.08-1.24). Severe cases: all crude ^l OR: 1.01 (0.87-1.18), Women 1.27 (1.15-1.40), All fully adjusted OR: 1.11 (1.00-1.24), Men crude ^l OR: 1.16 (1.00-1.34), Men fully adjusted ^k OR: 1.04 (0.89-1.21), Women crude ^l OR: 1.38 (1.20-1.57), Women fully adjusted ^k OR: 1.19 (1.04-1.37)	adjusted ^k OR: 0.98 (0.91-1.07). Severe cases: all crude ^l OR: 1.14 (1.03-1.27), All fully adjusted ^k OR: 1.03 (0.92-1.15), Men crude ^l OR: 1.09 (0.94-1.26), Men fully adjusted ^k OR: 1.01 (0.87-1.18), Women crude ^l OR: 1.20 (1.03-1.40), Women fully adjusted ^k OR: 1.06 (0.91-1.24)		

Jung, 2021 ⁶	Cohort, (2005-2016)	Korea	Total: 2780356 (49.6%), AD: 285468	ICD-10: one of the AD diagnostic codes and underwent two AD-related tests	prescribed medication ≥2 times (outpatient) or ≥1 time hospitalized, ICD-10 codes	Cox regression		Adjusted ¹² HR: 5.99 (4.96-7.25), Mild: 2.88 (1.07-7.75), Mod: 6.49 (1.61-26.18), Severe: 6.16 (5.0- 7.47)	Adjusted ¹ HR: 9.43 (7.28-12.20), Mild: 5.50 (2.41-12.57), Mod: 3.92 (0.55-28.15), Severe: 10.13 (7.7-13.17)	Adjusted ¹ HR: 10.61 (8.65-13.03), Mild: 10.35 (4.85-22.08), Mod: 12.72 (3.15-51.35), Severe 10.56 (8.59-12.98)
Kwa 2017 ⁷	Cross-sectional, (2002-2012)	USA	≥18 yrs, Total: 72651487, AD-E 164868	ICD-9 codes	Pre-coded by Association for Healthcare Research and Quality (AHRQ)	Logistic regression.	Crude OR: 0.75 (0.74-0.77), Propensity ¹³ OR: 0.67 (0.66-0.69).	Crude OR: 0.56 (0.53-0.58), PSM ^m OR: 0.52 (0.49-0.55)	Crude OR: 0.74 (0.71-0.77), PSM ^m OR: 0.71 (0.67-0.74)	
Nishida, 2019 ⁸	Cohort, (1988-2009)	Japan	aged 40-79 yrs, Total: 85,099 (41.7%)	self-reported	ICD-10 codes	Cox proportional hazard regression	Frequency of Eczema: Often/ Seldom or Sometimes: ¹⁴ Adjusted ¹⁴ HR: 1.39 (1.12-1.72), MV-adjusted ¹⁵ HR: 1.30 (1.05-1.61)	Often/ Seldom or Sometimes: Adjusted ⁿ HR: 1.14 (0.88-1.48), MV-adjusted ^o HR: 1.11 (0.80-1.27), MV-adjusted ^o HR: 1.01 (0.80-1.27), MV-adjusted ^o HR: 0.96 (0.76-1.21).	Often/Seldom or Sometimes: Total stroke: Adjusted ⁿ HR: 1.03 (0.87-1.22), MV-adjusted ^o HR: 0.98 (0.83-1.17). Ischemic stroke: Adjusted ⁿ HR: 1.01 (0.80-1.27), MV-adjusted ^o HR: 0.96 (0.76-1.21).	
Radtke, 2016 ⁹	Cross-sectional, (2009 onwards)	Germany	> 18 yrs, Total: 1349671, AD: 48140	ICD-10 codes	ICD-10 codes	Chi-square	Ischemic heart disease: Prevalence rate: (with/without AD): 0.83 (0.80-0.86)			

Table S6 (Continued)

CVD main results											
Study	Study design and Period	Setting	Age, sample size (proportion of males)	Diagnosis of AD	Outcome definition	Statistical analysis	CAD	Angina	MI	HF	Stroke
Rhee, 2021 ¹⁰	Cohort, (2009-2018)	Korea	>20 yrs, Total: 9548939, AD: 18557 (48.6%)	ICD-10 code, ≥3 times of physician diagnosis within 1 year	ICD-10 codes	Cox proportional hazards regression			Unadjusted HR: 1.51 (1.40-1.63), Adjusted ¹⁶ HR: 1.21 (1.12-1.31), MV-adjusted ¹⁷ HR: 1.14 (1.06-1.24)		
Riis, 2016 ¹¹	Cohort, (1977-2013)	Denmark	Danishi born 1947- 1977. Total 53210, AD: 4814 (45%)	Two clinical diagnoses of ICD-8 or ICD-10 codes	Clinical diagnoses of ICD-8 or ICD-10 codes	Cox proportional hazards regression			Crude HR: all: 1.79 (1.25-2.57), Men: 2.03 (1.32-3.12), Women: 1.39 (0.72-2.69), Mild: 1.62 (1.04-2.51), Severe: 2.38 (1.26-4.50), Adjusted ¹⁸ HR: 1.74 (1.21-2.49); Men: 2.01 (1.31-3.08), Women: 1.28 (0.66-2.48), Mild: 1.58 (1.02-2.45); Severe: 2.40 (1.27-4.45)		
Shalom, 2019 ¹²	cross-sectional, (1998-2016)	Israel	AD: 116816 patients (2.7% of total), Control: 116812	At least one documented diagnosis	"CHS Chronic Disease Register"	Logistic regression	Ischemic heart disease: AD n (%): 2252 (1.9) General population n (%): 2290 (2.0), p=0.568		AD n (%): 538 (0.5) General population n (%): 572 (0.5), p=0.306	AD n (%): 538 (0.5) General population n (%): 572 (0.5), p=0.306	AD n (%): 538 (0.5) General population n (%): 572 (0.5), p=0.306

Silverberg, 2015 ¹³	Cross-sectional, (2005-2006)	USA (NHANES)	≥20 yrs, Total: 4970 AD: 3.1% of total	self-reported	self-reported doctor diagnosis	Logistic regression	Crude OR: 2.57 (1.45-4.53), Model 1 adjusted ¹⁹ OR: 2.11 (1.14-3.91) Model 2 adjusted ²⁰ OR: 2.46 (1.37-4.43) Model 3 adjusted ²¹ OR: 1.96 (1.02-3.77)	Crude OR: 1.87 (0.98-3.57), Model 1 adjusted ^s OR: 1.63 (0.84-3.15) Model 2 adjusted ^t OR: 1.91 (0.98-3.69) Model 3 adjusted ^u OR: 1.35 (0.55-3.28)	Crude OR: 2.59 (1.35-4.96), Model 1 adjusted ^s OR: 2.33 (1.22-4.46); Model 2 adjusted ^t OR: 2.58 (1.31-5.06) Model 3 adjusted ^u OR: 1.98 (0.96-4.12)	Crude OR: 2.37 (1.27-4.41), Model 1 adjusted ^s OR: 2.01 (1.03-3.94) Model 2 adjusted ^t OR: 2.25 (1.17-4.32) Model 3 adjusted ^u OR: 1.01 (0.40-2.57)	Crude OR: 0.76 (0.31-1.86), Model 1 adjusted ^s OR: 0.71 (0.29-1.74) Model 2 adjusted ^t OR: 0.74 (0.30-1.82) Model 3 adjusted ^u OR: 0.61 (0.21-1.80)
	Cross-sectional, (2010)	USA, (NHIS)	≥18 yrs, Total: 27157, AD: 10.2% of total	self-reported	self-reported doctor diagnosis	Logistic regression	Crude OR: 1.48 (1.22-1.80), Model 1 adjusted ^s OR: 1.38 (1.13-1.69) Model 2 adjusted ^t OR: 1.41 (1.16-1.71) Model 3 adjusted ²² OR: 1.38 (1.12-1.70)	Crude OR: 1.87 (1.44-2.42), Model 1 adjusted ^s OR: 1.79 (1.37-2.35) Model 2 adjusted ^t OR: 1.58 (1.21-2.05) Model 3 adjusted ^v OR: 1.73 (1.30-2.31)	Crude OR: 1.73 (1.39-2.16), Model 1 adjusted ^s OR: 1.72 (1.36-2.17) Model 2 adjusted ^t OR: 1.65 (1.32-2.06) Model 3 adjusted ^v OR: 1.48 (1.15-1.90)	Crude OR: 1.61 (1.27-2.05), Model 1 adjusted ^s OR: 1.61 (1.25-2.07) Model 2 adjusted ^t OR: 1.53 (1.19-1.96) Model 3 adjusted ^v OR: 1.39 (1.05-1.83)	
	Cross-sectional, (2012)	USA (NHIS)	≥18 yrs, Total: 34525, AD: 7.2% of total	self-reported doctor diagnosis	self-reported doctor diagnosis	Logistic regression	Crude OR: 1.36 (1.09-1.69), Model 1 adjusted ^s OR: 1.50 (1.18-1.90) Model 2 adjusted ^t OR: 1.31 (1.06-1.64) Model 3 adjusted ^v OR: 1.32 (1.04-1.66)	Crude OR: 1.73 (1.18-2.54), Model 1 adjusted ^s OR: 1.81 (1.21-2.70) Model 2 adjusted ^t OR: 1.58 (1.09-2.30) Model 3 adjusted ^v OR: 1.77 (1.20-2.61)	Crude OR: 1.33 (1.03-1.70), Model 1 adjusted ^s OR: 1.44 (1.11-1.87) Model 2 adjusted ^t OR: 1.29 (1.01-1.66) Model 3 adjusted ^v OR: 1.26 (0.96-1.64)	Crude OR: 1.63 (1.27-2.09), Model 1 adjusted ^s OR: 1.75 (1.35-2.28) Model 2 adjusted ^t OR: 1.52 (1.19-1.95) Model 3 adjusted ^v OR: 1.73 (1.33-2.25)	

Table S6 (Continued)

CVD main results											
Study	Study design and Period	Setting	Age, sample size (proportion of males)	Diagnosis of AD	Outcome definition	Statistical analysis	CAD	Angina	MI	HF	Stroke
Silverwood, 2018 ¹⁴	Cohort, (1998-2015)	UK	≥18 yrs, AD: 387439 (36.1%) Match group: 1528477	At least one diagnosis code and two treatment codes on separate dates, ICD-10 codes	ICD-9 or ICD-10 codes	Cox regression		(Unstable angina) Unadjusted: HR: 1.22 (1.14-1.31) Mild: 1.22 (1.11-1.33) Mod: 1.20 (1.08-1.34) Severe: 1.47 (1.10-1.97), Adjusted ^{2,3} HR: 1.25 (1.11-1.41) Mild: 1.25 (1.10-1.43) Mod: 1.22 (1.06-1.42) Severe: 1.48 (1.08-2.03), Mediation model ^{2,4} HR: 1.17 (1.03-1.32), Mild: 1.19 (1.04-1.37), Mod: 1.11 (0.96-1.29), Severe: 1.41 (1.02-1.95)	Unadjusted HR: 1.10 (1.05-1.15) Mild: 1.03 (0.96-1.09) Mod: 1.15 (1.07-1.23) Severe: 1.46 (1.21-1.74) Adjusted ^w HR: 1.06 (0.98-1.15) Mild: 1.00 (0.91-1.10) Mod: 1.11 (1.01-1.23) Severe 1.41 (1.15-1.71), Mediation model ^x HR: 1.04 (0.96-1.13), Mild: 1.00 (0.91-1.10), Mod: 1.07 (0.97-1.18), Severe: 1.37 (1.12-1.68)	Unadjusted HR: 1.21 (1.16-1.26) Mild: 1.12 (1.05-1.19) Mod: 1.27 (1.19-1.35) Severe: 1.71 (1.43-2.05) Adjusted ^w HR: 1.19 (1.10-1.30) Mild: 1.12 (1.02-1.23) Mod: 1.25 (1.14-1.38) Severe: 1.69 (1.38-2.06), Mediation model ^x HR: 1.17 (1.08-1.28), Mild: 1.12 (1.02-1.24), Mod: 1.20 (1.09-1.33), Severe: 1.67 (1.36-2.05)	Unadjusted: HR 1.07 (1.03-1.12) Mild: 1.03 (0.98-1.09) Mod: 1.11 (1.04-1.18) Severe: 1.19 (1.00-1.42) Adjusted ^w HR: 1.10 (1.02-1.19) Mild: 1.07 (0.98-1.16) Mod: 1.14 (1.04-1.25) Severe: 1.22 (1.01-1.48), Mediation model ^x HR: 1.08 (1.00-1.16), Mild: 1.06 (0.97-1.15), Mod: 1.09 (1.00-1.20), Severe: 1.20 (0.99-1.46)

Standl, 2017 ¹⁵	Cross-sectional, (2012-2014)	Germany (AOK PLUS)	≥40 yrs, Total: 1180678, AD: 36606 (36.24%)	At least two clinical diagnoses of ICD-10 codes	ICD-10 codes	Linear regression		Model 1 adjusted ⁵ RR: All: 1.34 (1.28-1.41), Mild: 1.20 (1.10-1.31), Mod: 1.33 (1.25-1.42), Severe: 1.60 (1.45-1.77), Model 2 Adjusted ⁶ : RR: All: 1.32 (1.26-1.38), Mild: 1.18 (1.08-1.29), Mod: 1.31 (1.23-1.39), Severe: 1.57 (1.43-1.74)	Model 1 adjusted ⁷ RR: All: 0.98 (0.90-1.05), Mild AD: 0.94 (0.82-1.08), Mod: 0.95 (0.85-1.05), Severe: 1.12 (0.94-1.32), Model 2 Adjusted ⁸ RR: All 0.98 (0.91-1.06), Mild: 0.95 (0.82-1.09), Mod: 0.95 (0.86-1.06), Severe: 1.12 (0.94-1.33)	Model 1 adjusted ⁹ : RR: All: 1.06 (1.01-1.11), Mild: 1.03 (0.94-1.12), Mod: 1.06 (0.99-1.13), Severe: 1.08 (0.96-1.21), Model 2 Adjusted ¹⁰ RR: All: 1.05 (1.00-1.11), Mild: 1.03 (0.94-1.12), Mod: 1.05 (0.99-1.13), Severe: 1.08 (0.96-1.21)
	Cohort, (2005-2014)	Germany (AOK PLUS)	≥40 yrs, Total: 121413, AD: 33816 (35%)	At least two clinical diagnoses of ICD-10 codes	ICD-10 codes	Linear regression		Model 1 adjusted ¹¹ : RR: All: 1.18 (1.13-1.23), Mild: 0.94 (0.85-1.04), Mod: 1.21 (1.13-1.29), Severe: 1.38 (1.26-1.50), Model 2 adjusted ¹² : RR: All: 1.17 (1.12-1.23), Mild: 0.93 (0.84-1.03), Mod: 1.20 (1.12-1.28), Severe: 1.37 (1.25-1.49)	Model 1 adjusted ¹³ RR: All: 1.03 (0.98-1.07), Mild: 0.92 (0.84-1.01), Mod: 1.06 (1.00-1.13), Severe: 1.07 (0.98-1.17), Model 2 Adjusted ¹⁴ : RR: All: 1.02 (0.98-1.07), Mild: 0.92 (0.84-1.01), Mod: 1.05 (0.99-1.12), Severe: 1.06 (0.98-1.16)	Model 1 adjusted ¹⁵ : RR: All: 1.03 (0.98-1.07), Mild: 0.92 (0.84-1.01), Mod: 1.06 (1.00-1.13), Severe: 1.07 (0.98-1.17), Model 2 Adjusted ¹⁶ : RR: All: 1.02 (0.98-1.07), Mild: 0.92 (0.84-1.01), Mod: 1.05 (0.99-1.12), Severe: 1.06 (0.98-1.16)
Su, 2014 ¹⁶	Cohort, (2005-2009)	Taiwan	≥20 yrs, Total: 40646, AD: 20323 (38.1%)	ICD-9 codes, (newly diagnosed)	ICD-9 codes	Cox's proportional hazards regression		Adjusted ¹⁷ HR: 1.31 (0.88-1.95)	Adjusted ¹⁸ HR: 1.46 (1.10-1.93)	Adjusted ¹⁹ HR: 1.29 (1.09-1.54), Adjusted ²⁰ HR: 1.33 (1.12-1.59)

Table S6 (Continued)

CVD main results											
Study	Study design and Period	Setting	Age, sample size (proportion of males)	Diagnosis of AD	Outcome definition	Statistical analysis	CAD	Angina	MI	HF	Stroke
Sung, 2017 ¹⁷	Cohorts, (2000-2011)	Taiwan	Total: 75515, AD: 15103 (45.8%)	Outpatients received at least three consensus diagnoses, ICD-9 codes	Brain computed tomography or magnetic resonance imaging and at least three consensus diagnosis	Cox ⁷ proportional hazard regression					Crude HR: All stroke: 1.25 (1.13-1.39), Ischemic stroke: 1.30 (1.17-1.46), Hemorrhagic stroke: 1.00 (0.76-1.32), Adjusted ²⁸ HR: 1.17 (1.06-1.30), Ischemic stroke: 1.21 (1.08-1.36), Hemorrhagic stroke : 0.97 (0.74-1.29)
Treudler, 2017 ¹⁸	Cross-sectional, (2011-2014)	Germany	Logistic regression: Total: 4340, AD: 168	Physician-diagnosed AD (ever)	Physician diagnosis	Logistic regression	OR: 1.6 (0.8-3.0)		OR: 0.5 (0.2-1.6)		OR: 1.3 (0.6-2.9)
Tsai, 2016 ¹⁹	Cohort (2000-2011)	Taiwan	≥20 yrs. Total: 470440, AD: 235220 (41.87%)	ICD-9 codes, (at least two medical visits)	New diagnosis of stroke , ICD-9 codes	Cox's proportional hazard regression					Stroke: crude HR: 1.27 (1.23-1.3), Adjusted ²⁹ HR: Stroke: 1.13 (1.10-1.16), Ischemic stroke: 1.30 (1.27-1.34), Adjusted ³⁰ HR: 1.16 (1.12-1.19)
Varbo, 2017 ²⁰	Cohort, (2003-2014)	Denmark	Total: 84601, AD: 8484	self-reported	ICD-8 ICD-10 codes (two independent doctors)	Cox proportional hazard regression					Ischemic stroke: Adjusted ³⁰ HR: 1.24 (1.01-1.52), MV-adjusted ³¹ HR: 1.19 (0.96-1.48)

AD: atopic dermatitis, CVD: cardiovascular disease, CAD: coronary artery disease, MI: myocardial infarction, HF: heart failure, yrs: years old, ICD: International Classification of Diseases, RR: incident rate ratios, OR: odds ratio, HR: hazard ratio, RR: risk ratio. MV: multivariate, BMI: body mass index

¹ Adjusted for age and sex

² Adjusted for age and sex, socioeconomic status, smoking, comorbidities, and medication use

³ Adjusted for age

⁴ Adjusted for age, race, BMI, physical activity, alcohol, smoking, family history of MI, hormone replacement use

⁵ Adjusted for age, race, BMI, physical activity, alcohol, smoking, family history of MI, hormone replacement use, history of hypertension, hypercholesterolemia and diabete

- ⁶ Adjusted for age and sex
- ⁷ Adjusted for age, sex, ethnic background, body mass index, smoking 100 cigarettes, weekly alcohol intake, average daily sleep, weekly physical activity and history of asthma
- ⁸ The analysis for each outcome is additionally adjusted for all three other outcomes (hypertension, type 2 diabetes, MI, stroke)
- ⁹ Adjusted for age, sex, socioeconomic status, and number of dermatology visits
- ¹⁰ Adjusted for age and sex
- ¹¹ Adjusted for cardiovascular comorbidities (diabetes mellitus, hyperlipidemia, hypertension) and years of education
- ¹² Adjusted for sex, age, and other CVD and metabolic diseases
- ¹³ Adjusted for age, sex, race, mean annual household income, insurance status, number of chronic conditions, and hospital region
- ¹⁴ Adjusted for age and sex
- ¹⁵ Adjusted for age, sex, BMI, history of hypertension, diabetes, alcohol, smoking, perceived mental stress, daily walking time, participation in sports, sleep duration, education
- ¹⁶ Adjusted for age and sex
- ¹⁷ Adjusted for age and sex, smoking, alcohol, physical activity, low socioeconomic status, BMI, hypertension, diabetes mellitus, and dyslipidemia
- ¹⁸ Adjusted for birth-year categories, gender, educational level and history of diabetes, hypertension, hyperlipidaemia or stroke
- ¹⁹ Adjusted for age, highest level of education in the household, ethnicity, and sex
- ²⁰ Adjusted for 1-year history of asthma and hay fever
- ²¹ Adjusted for BMI, history of ever smoking cigarettes, consumption of alcohol in the past year, and vigorous activity in the past 30 days
- ²² Adjusted for BMI, history of ever smoking cigarettes, consumption of alcohol in the past year, and vigorous activity in the past week
- ²³ Adjusted for current calendar period (1997-99, 2000-04, 2005-09, 2010-15), time since diagnosis (0-4, 5-9, 10-14, 15-19, ≥20 years), index of multiple deprivation at cohort entry, and time-varying asthma
- ²⁴ Adjusted additionally for BMI and smoking at cohort entry, and time-varying hyperlipidaemia, hypertension, depression, anxiety, diabetes, and severe alcohol use
- ²⁵ Adjusted for sex and cubic age
- ²⁶ Adjusted for sex, cubic age, and socioeconomic status of region and access to health care
- ²⁷ Adjusted for age, sex, comorbidities and medication
- ²⁸ Adjusted for AD, age, sex, and comorbidity
- ²⁹ Adjusted for age, gender, treatment, and comorbidity
- ³⁰ Adjusted for age and sex
- ³¹ Adjusted for age, sex, smoking, lipid-lowering therapy, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetes, alcohol consumption, systolic and diastolic blood pressure, BMI, physical activity, atrial fibrillation

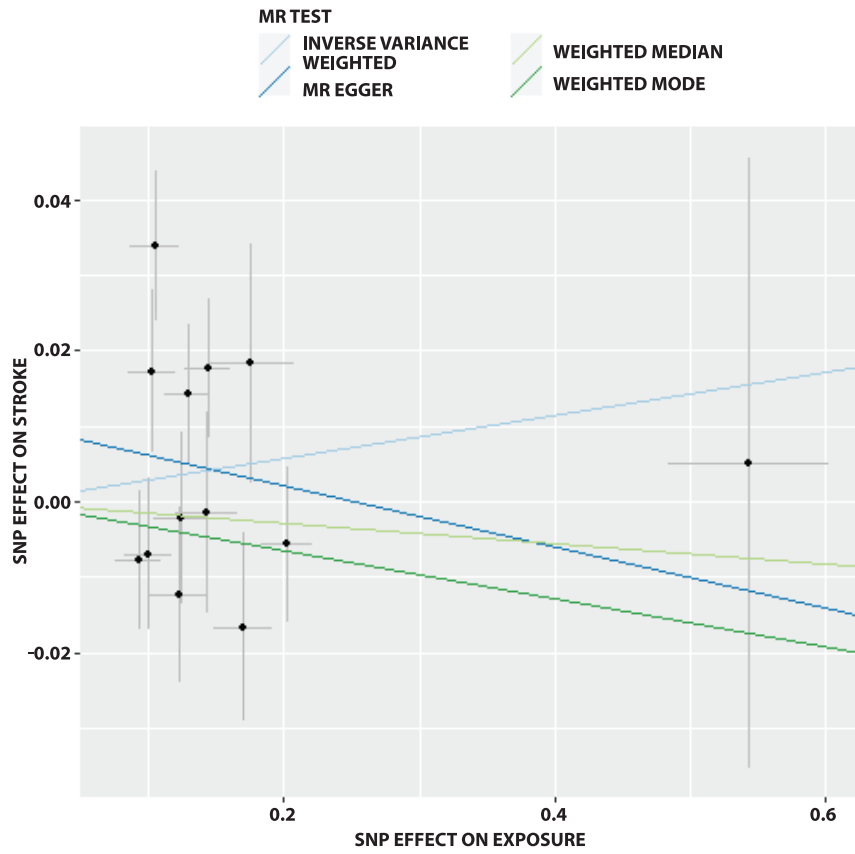


Figure 1. Scatter plot for Mendelian randomization analysis for AD on stroke.

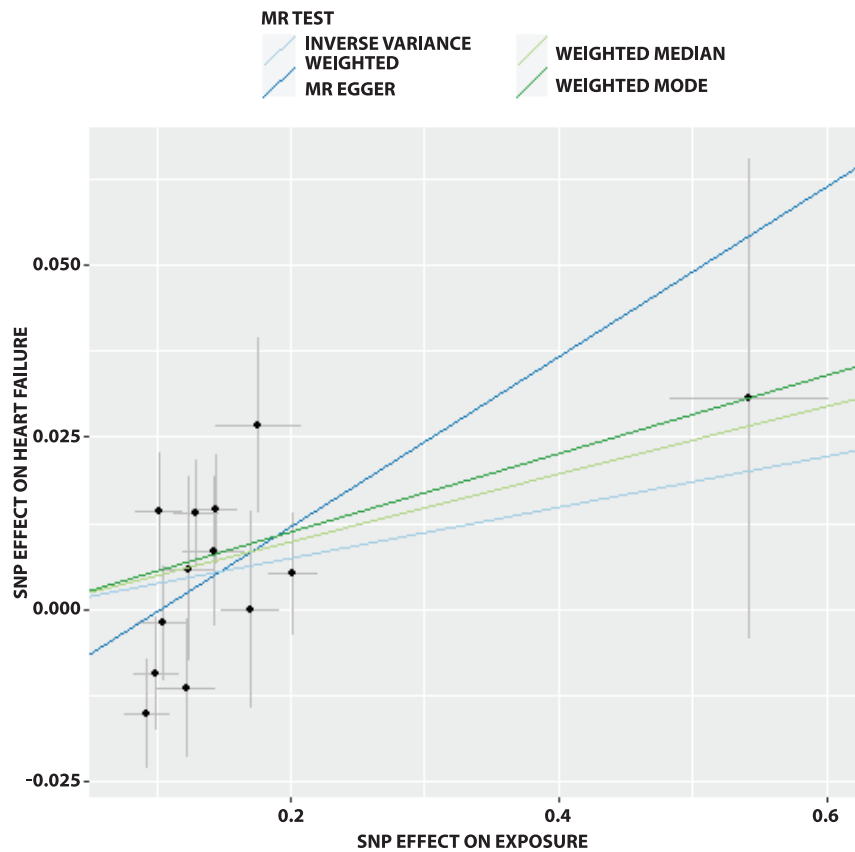


Figure 2. Scatter plot for Mendelian randomization analysis for AD on heart failure.

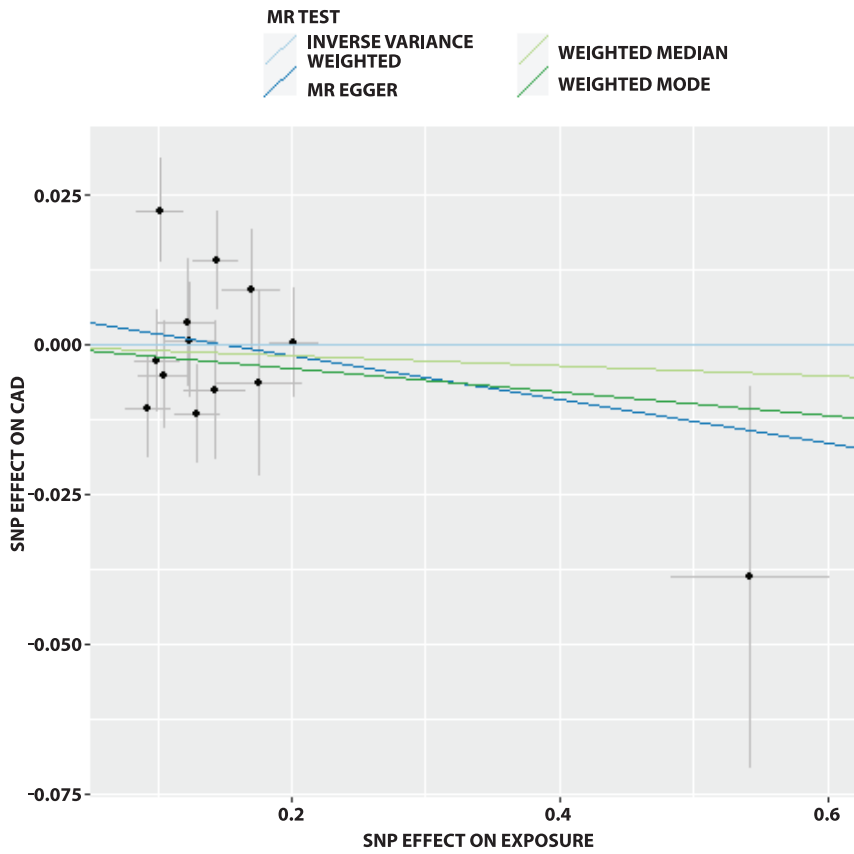


Figure 3. Scatter plot for Mendelian randomization analysis for AD on CAD.

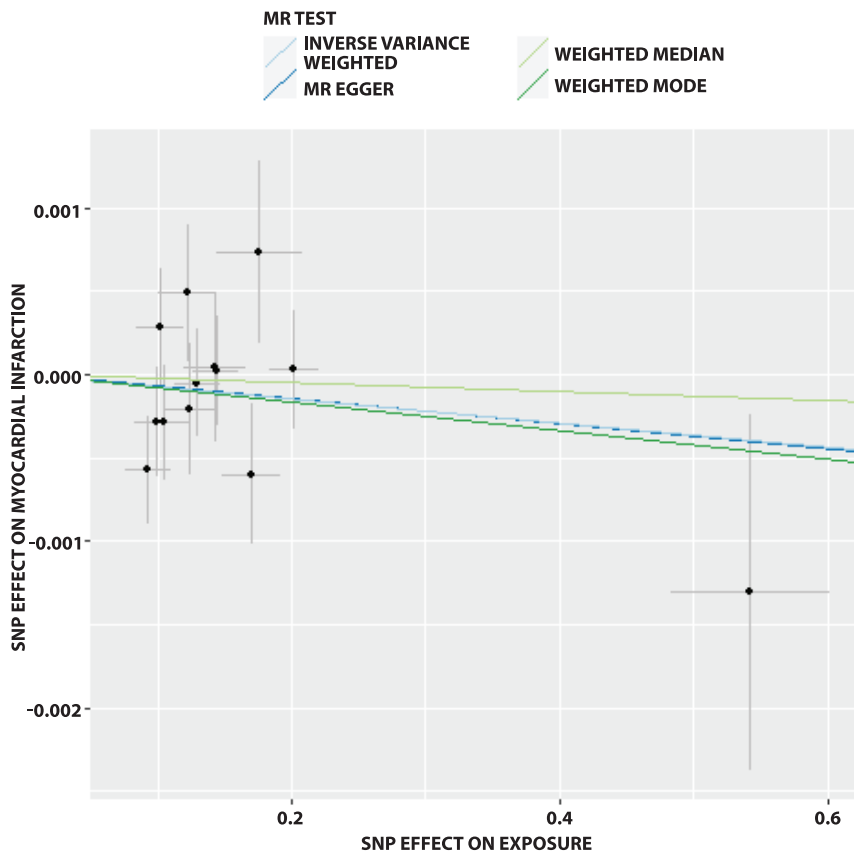


Figure 4. Scatter plot for Mendelian randomization analysis for AD on myocardial infarction.

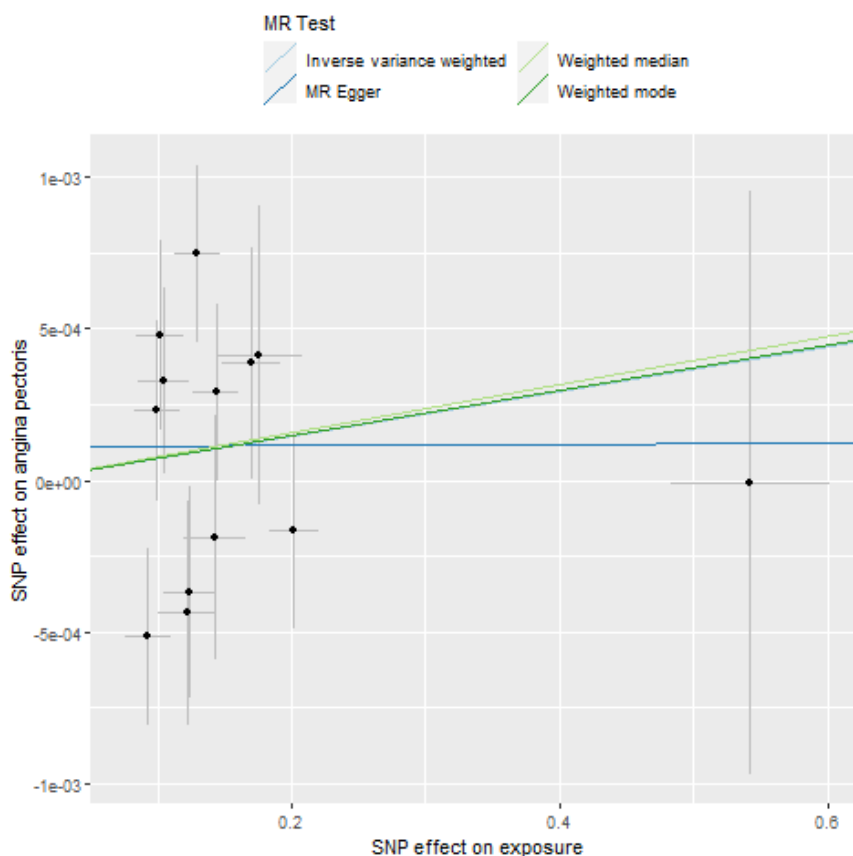


Figure 5. Scatter plot for Mendelian randomization analysis for AD on angina pectoris.

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