Supplementary material

Supplement to: Obesity partially mediates the diabetogenic effect of lowering low-density lipoprotein cholesterol.

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Supplementary Table 1: Genetic variants used to proxy LDLc.

SNP	CHR	BP	EA	NEA	EAF	BETA	SE
rs880315	1	10736809	T	C	0.660	0.015	0.002
rs6693893	1	109255141	T	C	0.965	0.075	0.006
rs4970834	1	109272258	C	T	0.813	0.105	0.003
rs115458560	1	109519352	T	C	0.981	0.050	0.008
rs77257036	1	150503710	C	T	0.648	0.012	0.002
rs4661359	1	16186658	C	T	0.377	-0.013	0.002
rs1434282	1	199041592	C	T	0.275	-0.015	0.002
rs2642438	1	220796686	A	G	0.297	-0.025	0.002
rs6678608	1	224511398	T	C	0.784	0.014	0.003
rs7551124	1	23459267	C	T	0.125	-0.019	0.003
rs10910476	1	234599210	C	T	0.445	-0.012	0.002
rs556107	1	234717312	C	T	0.477	-0.035	0.002
rs28631087	1	234973467	T	C	0.787	0.016	0.003
rs35189848	1	25461931	A	G	0.555	0.026	0.002
rs75460349	1	26853597	A	C	0.977	-0.056	0.007
rs55637835	1	55000630	C	T	0.879	0.019	0.003
rs11591147	1	55039974	G	T	0.983	0.349	0.008
rs472495	1	55055640	G	T	0.351	-0.043	0.002
rs111928762	1	55228515	A	G	0.960	-0.051	0.005
rs2994562	1	56332125	A	G	0.407	-0.013	0.002
rs1168086	1	62646718	A	G	0.352	-0.039	0.002
rs1556562	1	92568466	G	T	0.210	-0.019	0.002
rs2718717	2	108589683	A	G	0.857	-0.019	0.003
rs150474434	2	118087545	G	A	0.899	0.035	0.003
rs17050272	2	120548864	G	A	0.591	0.021	0.002
rs4954192	2	134875411	C	T	0.627	-0.015	0.002
rs4556933	2	157587377	G	A	0.603	0.011	0.002
rs2287622	2	168973818	A	G	0.397	0.021	0.002
rs7569317	2	202663256	T	C	0.469	-0.018	0.002
rs719148	2	20321886	G	A	0.224	0.018	0.002
rs77370158	2	20823505	A	G	0.916	-0.025	0.004
rs62122481	2	20993943	C	A	0.623	-0.066	0.002
rs72902590	2	21066196	G	A	0.955	0.080	0.005
rs62131701	2	21342131	A	G	0.927	-0.034	0.004
rs1250258	2	215435462	C	T	0.263	-0.014	0.002
rs11568318	2	233756852	C	A	0.934	-0.026	0.004
rs1731243	2	26707543	C	T	0.393	-0.013	0.002
rs1260326	2	27508073	T	C	0.396	0.035	0.002
rs56236159	2	3588888	T	G	0.869	-0.018	0.003
rs4299376	2	43845437	G	T	0.323	0.054	0.002

rs6709904	2	43853185	A	G	0.887	0.044	0.003
rs13020929	2	44100324	G	A	0.543	-0.015	0.002
rs4671050	2	62761034	G	T	0.684	0.020	0.002
rs12471768	2	64701469	T	C	0.296	-0.014	0.002
rs3732359	3	119817582	G	A	0.220	0.017	0.003
rs9841897	3	122563722	T	C	0.844	-0.019	0.003
rs13076933	3	12285932	T	G	0.741	0.021	0.002
rs78946096	3	132469319	A	G	0.942	0.039	0.004
rs3905668	3	136212744	A	G	0.724	-0.014	0.002
rs11709868	3	142930002	G	T	0.703	0.015	0.002
rs9834932	3	32493890	A	G	0.911	0.032	0.004
rs11706420	3	58406684	A	G	0.917	0.028	0.004
rs55921103	3	69761143	G	T	0.351	-0.014	0.002
rs13107325	4	102267552	C	T	0.925	0.025	0.004
rs2705453	4	155582205	A	G	0.479	0.012	0.002
rs13108218	4	3442204	A	G	0.385	0.018	0.002
rs9884390	4	68507689	T	C	0.766	-0.025	0.002
rs72663045	4	73311680	T	G	0.979	-0.037	0.007
rs1458038	4	80243569	C	T	0.709	0.019	0.002
rs1229984	4	99318162	T	C	0.027	-0.053	0.006
rs7734476	5	123513182	G	A	0.450	-0.019	0.002
rs1003533	5	132419959	C	T	0.812	0.018	0.003
rs58198139	5	156972028	C	T	0.366	-0.032	0.002
rs146433259	5	34713687	C	T	0.988	0.057	0.010
rs116734477	5	52799190	C	T	0.959	0.047	0.005
rs9686661	5	56565959	C	T	0.799	-0.015	0.003
rs889235	5	72658576	G	A	0.787	0.019	0.003
rs7707394	5	75177114	G	A	0.643	-0.041	0.002
rs12916	5	75360714	T	C	0.599	-0.062	0.002
rs17185536	6	100173055	C	T	0.754	0.017	0.002
rs3822855	6	115995719	G	T	0.598	-0.018	0.002
rs9491699	6	127150388	C	T	0.522	-0.014	0.002
rs12197047	6	130068066	G	A	0.330	-0.014	0.002
rs7776054	6	135097778	A	G	0.739	0.016	0.002
rs12208357	6	160122116	C	T	0.930	-0.057	0.004
rs146534110	6	160157037	G	T	0.987	-0.068	0.009
rs3127580	6	160289819	C	T	0.845	-0.036	0.003
rs12179053	6	160290534	C	T	0.748	0.017	0.002
rs117733303	6	160501838	A	G	0.982	-0.084	0.008
rs118039278	6	160564494	G	A	0.921	-0.084	0.004
rs2235215	6	16130925	T	C	0.696	0.023	0.002
rs79220007	6	26098246	T	C	0.924	0.057	0.004
rs2893936	6	27820406	T	C	0.913	0.035	0.004

rs28782316	6	29879365	T	G	0.451	-0.024	0.003
rs2187980	6	30255736	A	G	0.856	-0.027	0.003
rs2229094	6	31572779	T	C	0.746	-0.018	0.002
rs115563246	6	32521957	G	A	0.733	0.021	0.003
rs17205170	6	32634706	G	T	0.819	-0.038	0.003
rs76967117	6	34635914	G	A	0.885	0.028	0.003
rs913499	6	37070656	A	G	0.491	0.012	0.002
rs2758879	6	39281360	G	A	0.699	-0.012	0.002
rs9471975	6	42951484	T	C	0.417	0.013	0.002
rs11772705	7	100701281	T	C	0.712	0.017	0.002
rs869412	7	1034498	T	C	0.774	0.014	0.003
rs34927723	7	21383307	C	T	0.843	0.016	0.003
rs55696093	7	21566355	A	G	0.782	-0.033	0.003
rs4722551	7	25952206	T	C	0.841	-0.024	0.003
rs67050321	7	36129593	T	C	0.696	-0.015	0.002
rs2073547	7	44542732	A	G	0.816	-0.036	0.003
rs4148826	7	87445103	T	C	0.820	0.016	0.003
rs112758337	7	98347956	G	A	0.814	0.016	0.003
rs2737265	8	115655407	A	G	0.720	0.020	0.002
rs112875651	8	125494452	G	A	0.609	0.061	0.002
rs11997161	8	140728488	T	C	0.482	-0.012	0.002
rs11786083	8	143976190	G	A	0.626	-0.016	0.002
rs1495741	8	18415371	G	A	0.221	0.017	0.003
rs59328596	8	22070716	G	A	0.852	0.018	0.003
rs117139027	8	29167426	G	A	0.982	0.057	0.008
rs9298506	8	54524964	A	G	0.792	-0.019	0.003
rs4738684	8	58480714	A	G	0.335	0.032	0.002
rs1365041	8	6706347	G	T	0.316	-0.012	0.002
rs9987289	8	9325848	A	G	0.091	-0.045	0.004
rs4841146	8	9432835	C	A	0.791	-0.015	0.003
rs2066714	9	104824472	T	C	0.871	-0.021	0.003
rs11789603	9	104884738	C	T	0.892	-0.025	0.003
rs2740488	9	104899461	A	C	0.735	0.025	0.002
rs13289095	9	128704210	G	T	0.854	0.021	0.003
rs2519093	9	133266456	C	T	0.815	-0.056	0.003
rs10448340	9	136425617	T	G	0.680	0.015	0.002
rs6475606	9	22081851	C	T	0.516	0.020	0.002
rs3780181	9	2640759	A	G	0.932	0.028	0.004
rs6560499	9	76115850	G	A	0.424	0.012	0.002
rs2250802	10	112161596	G	A	0.276	0.018	0.002
rs72823013	10	114026474	G	A	0.874	0.022	0.003
rs12246352	10	122945791	A	G	0.896	-0.026	0.003
rs1277763	10	18206956	T	C	0.204	-0.015	0.003

rs79828839	10	50592671	C	T	0.801	-0.015	0.003
rs10822145	10	63174788	C	T	0.524	-0.012	0.002
rs16926246	10	69333636	C	T	0.870	0.020	0.003
rs2068888	10	93079885	G	A	0.549	0.019	0.002
rs10791660	11	104000311	C	A	0.815	0.016	0.003
rs61905084	11	116739578	T	C	0.819	0.018	0.003
rs3741298	11	116786845	C	T	0.192	0.042	0.003
rs6589939	11	122647817	A	G	0.622	-0.013	0.002
rs59379014	11	126358105	C	T	0.927	-0.055	0.004
rs10128711	11	18611437	T	C	0.261	-0.017	0.002
rs7108486	11	5655928	T	C	0.976	0.039	0.007
rs11601507	11	5679844	C	A	0.931	-0.032	0.004
rs174564	11	61820833	A	G	0.651	0.032	0.002
rs11227247	11	65655382	A	C	0.865	-0.018	0.003
rs74869459	11	66529098	T	C	0.761	0.017	0.002
rs3184504	12	111446804	T	C	0.483	-0.027	0.002
rs11066320	12	112468611	A	G	0.425	-0.022	0.002
rs11065385	12	120985583	A	G	0.309	0.024	0.002
rs11057397	12	123935181	C	T	0.663	0.012	0.002
rs112403212	12	124818708	C	T	0.859	-0.017	0.003
rs1007938	12	26649616	A	G	0.595	-0.012	0.002
rs2160994	12	50256274	T	C	0.353	-0.018	0.002
rs35882350	12	513963	A	G	0.739	-0.014	0.002
rs61754230	12	71785666	C	T	0.980	-0.043	0.007
rs78508096	12	8922110	G	A	0.774	-0.018	0.002
rs4771674	13	110386723	A	G	0.378	-0.013	0.002
rs6602912	13	113843576	T	G	0.715	-0.022	0.002
rs76428106	13	28029870	T	C	0.987	0.052	0.010
rs9534323	13	32376120	A	G	0.477	0.016	0.002
rs9316496	13	50467744	G	A	0.827	-0.014	0.003
rs11621792	14	24402720	C	T	0.547	-0.019	0.002
rs8008068	14	63766999	A	G	0.840	-0.016	0.003
rs6573971	14	70544752	G	A	0.445	0.013	0.002
rs61988555	14	72972127	T	C	0.915	0.022	0.004
rs12435583	14	74740989	G	A	0.557	0.011	0.002
rs145730801	14	94301859	T	C	0.956	-0.036	0.005
rs72733982	15	57275452	G	T	0.940	-0.026	0.004
rs1532085	15	58391167	A	G	0.386	0.017	0.002
rs261332	15	58435126	A	G	0.210	0.022	0.003
rs62011285	15	63498864	T	C	0.657	-0.012	0.002
rs6495122	15	74833304	A	C	0.409	-0.014	0.002
rs12445804	16	11612244	G	A	0.925	-0.023	0.004
rs62033400	16	53777876	A	G	0.605	0.014	0.002

rs3764261	16	56959412	C	A	0.676	0.033	0.002
rs56212732	16	70896467	C	T	0.915	0.024	0.004
rs62053078	16	71609769	G	T	0.626	-0.017	0.002
rs3794695	16	72063928	C	T	0.810	-0.048	0.003
rs7202323	16	72183214	T	G	0.770	0.026	0.002
rs11149612	16	83947360	C	T	0.540	0.016	0.002
rs4328458	16	86390687	G	A	0.556	-0.011	0.002
rs58926386	16	88505398	G	A	0.958	-0.029	0.005
rs704	17	28367840	G	A	0.524	-0.015	0.002
rs12453884	17	29533588	T	C	0.146	-0.016	0.003
rs12603885	17	31139704	G	A	0.300	-0.018	0.002
rs8065099	17	47556119	T	C	0.485	0.026	0.002
rs3110609	17	48676181	T	C	0.658	0.015	0.002
rs1801689	17	66214462	A	C	0.969	-0.062	0.006
rs77542162	17	69085137	A	G	0.978	-0.128	0.007
rs72853625	17	69209833	G	A	0.985	0.056	0.009
rs77049332	17	69230009	A	G	0.947	0.029	0.005
rs55714927	17	7176997	C	T	0.810	0.026	0.003
rs3744263	17	7710390	T	C	0.362	0.013	0.002
rs12948394	17	78386710	C	T	0.518	0.018	0.002
rs77960347	18	49583585	A	G	0.987	-0.071	0.009
rs7241918	18	49634583	G	T	0.176	-0.016	0.003
rs183143244	19	10554345	A	C	0.976	0.045	0.007
rs11668368	19	10609019	G	T	0.903	-0.029	0.004
rs10423733	19	11075243	T	C	0.820	0.103	0.003
rs72981271	19	11154116	C	T	0.709	-0.040	0.002
rs8101801	19	11224801	C	A	0.964	0.045	0.006
rs12986015	19	15693940	C	T	0.498	-0.013	0.002
rs62120394	19	18227899	G	A	0.708	-0.016	0.002
rs58542926	19	19268740	C	T	0.925	0.106	0.004
rs188247550	19	19285807	C	T	0.987	0.121	0.010
rs144984216	19	20369092	C	T	0.975	0.037	0.007
rs56113850	19	40847202	T	C	0.423	-0.013	0.002
rs145130411	19	43485383	T	G	0.893	0.019	0.003
rs187870654	19	43753872	G	A	0.988	0.062	0.010
rs62119267	19	44631381	A	C	0.978	0.251	0.007
rs62119282	19	44642317	C	T	0.938	-0.033	0.004
rs113330691	19	44792629	G	A	0.965	0.211	0.006
rs148933445	19	44799247	G	A	0.978	0.438	0.008
rs77196615	19	44877078	T	C	0.984	-0.045	0.008
rs72654437	19	44912842	G	A	0.970	-0.054	0.007
rs12691088	19	44915229	G	A	0.979	-0.178	0.008
rs138692741	19	44963875	C	T	0.964	-0.059	0.006

rs150262789	19	45933306	C	T	0.984	0.099	0.008
rs516246	19	48702915	C	T	0.492	-0.030	0.002
rs35081008	19	58150868	C	T	0.852	0.032	0.003
rs438568	20	12978039	A	G	0.391	-0.013	0.002
rs969075	20	17811678	T	C	0.335	-0.012	0.002
rs2618566	20	17864040	G	T	0.340	0.025	0.002
rs6050463	20	25228354	G	A	0.507	-0.013	0.002
rs224424	20	35560231	A	G	0.788	0.021	0.003
rs117113213	20	40537052	G	A	0.967	-0.098	0.006
rs1997833	20	41061702	T	C	0.700	-0.022	0.002
rs6065347	20	41393319	T	C	0.782	-0.016	0.003
rs1800961	20	44413724	C	T	0.969	0.060	0.006
rs6073958	20	45923216	T	C	0.801	-0.017	0.003
rs73075609	20	5600143	C	T	0.973	-0.037	0.007
rs2256814	20	63742630	G	A	0.802	-0.015	0.003
rs6090101	20	64278167	G	A	0.802	-0.018	0.003
rs11911615	21	36180834	T	G	0.672	0.012	0.002
rs4818025	21	39337245	A	G	0.428	-0.014	0.002
rs960596	22	40997516	C	T	0.661	-0.013	0.002
rs5770859	22	50435332	A	G	0.655	-0.013	0.002

Table Legend: Genetic variants for LDLc obtained from a GWAS for lipid levels in Richardson TG *et al* PLoS Med 2020. Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base position based on genome assembly GRCh38p12; EA, effect allele; NEA, Non-effect allele; EAF, effect allele frequency.

Supplementary Table 2: Genetic variants used to proxy BMI.

SNP	CHR	BP	EA	NEA	EAF	BETA	SE
rs11165643	1	96458541	C	T	0.425	-0.022	0.003
rs12401738	1	77981077	A	G	0.425	0.021	0.003
rs12566985	1	74536509	G	A	0.425	0.024	0.003
rs17024393	1	109612066	C	T	0.042	0.066	0.009
rs2820292	1	201815159	A	C	0.492	-0.020	0.003
rs3101336	1	72285502	T	C	0.351	-0.033	0.003
rs543874	1	177920345	G	A	0.267	0.048	0.004
rs657452	1	49124175	A	G	0.417	0.023	0.003
rs1016287	2	59078490	T	C	0.325	0.023	0.003
rs10182181	2	24927427	A	G	0.500	-0.031	0.003
rs11126666	2	26705943	G	A	0.692	-0.021	0.003
rs11688816	2	62825913	A	G	0.542	-0.017	0.003
rs12986742	2	58748008	C	T	0.500	0.021	0.004
rs13021737	2	632348	A	G	0.125	-0.060	0.004
rs1528435	2	180686235	T	C	0.583	0.018	0.003
rs2121279	2	142285716	T	C	0.117	0.025	0.004
rs7599312	2	212548507	G	A	0.708	0.022	0.003
rs13078960	3	85758440	T	G	0.817	-0.030	0.004
rs1516725	3	186106215	T	C	0.092	-0.045	0.005
rs16851483	3	141556594	G	T	0.908	-0.048	0.008
rs2365389	3	61250788	C	T	0.658	0.020	0.003
rs3849570	3	81742961	A	C	0.367	0.019	0.003
rs6804842	3	25064946	A	G	0.425	-0.019	0.003
rs10938397	4	45180510	A	G	0.567	-0.040	0.003
rs11727676	4	144737912	C	T	0.075	-0.036	0.006
rs13107325	4	102267552	C	T	0.883	-0.048	0.007
rs2112347	5	75719417	G	T	0.375	-0.026	0.003
rs13191362	6	162612318	A	G	0.800	0.028	0.005
rs2033529	6	40380914	G	A	0.258	0.019	0.003
rs205262	6	34595387	A	G	0.733	-0.022	0.004
rs2207139	6	50877777	G	A	0.100	0.045	0.004
rs9400239	6	108656460	C	T	0.703	0.019	0.003
rs1167827	7	75533848	A	G	0.458	-0.020	0.003
rs2245368	7	76978826	T	C	0.758	-0.032	0.006
rs17405819	8	75894349	C	T	0.367	-0.022	0.003
rs2033732	8	84167474	C	T	0.758	0.019	0.004
rs10733682	9	126698635	A	G	0.425	0.017	0.003
rs10968576	9	28414341	G	A	0.292	0.025	0.003
rs1928295	9	117616205	C	T	0.425	-0.019	0.003
rs4740619	9	15634328	T	C	0.533	0.018	0.003

rs6477694	9	109170062	C	T	0.358	0.017	0.003
rs11191560	10	103109281	T	C	0.942	-0.031	0.005
rs17094222	10	100635683	C	T	0.208	0.025	0.004
rs7899106	10	85651147	A	G	0.950	-0.040	0.007
rs7903146	10	112998590	T	C	0.250	-0.023	0.003
rs10840100	11	8647890	G	A	0.725	0.021	0.003
rs11030104	11	27662970	A	G	0.800	0.041	0.004
rs12286929	11	115151684	G	A	0.433	0.022	0.003
rs2176598	11	43842728	T	C	0.200	0.020	0.004
rs3817334	11	47629441	C	T	0.550	-0.026	0.003
rs11057405	12	122297350	A	G	0.092	-0.031	0.006
rs7138803	12	49853685	G	A	0.558	-0.032	0.003
rs12429545	13	53528071	G	A	0.900	-0.033	0.005
rs7992289	13	27462293	A	G	0.758	-0.026	0.004
rs10132280	14	25458973	A	C	0.333	-0.023	0.003
rs11847697	14	30045906	T	C	0.042	0.049	0.008
rs12885454	14	29267632	C	A	0.633	0.021	0.003
rs7141420	14	79433111	T	C	0.617	0.024	0.003
rs16951275	15	67784830	C	T	0.225	-0.031	0.004
rs3736485	15	51456413	A	G	0.425	0.018	0.003
rs12446632	16	19924067	A	G	0.133	-0.040	0.005
rs1421085	16	53767042	C	T	0.450	0.081	0.003
rs3888190	16	28878165	A	C	0.358	0.031	0.003
rs758747	16	3577357	C	T	0.733	-0.023	0.004
rs879620	16	3965728	C	T	0.408	-0.024	0.004
rs9925964	16	31118574	G	A	0.392	-0.019	0.003
rs1000940	17	5379957	G	A	0.225	0.019	0.003
rs12940622	17	80641771	A	G	0.458	-0.018	0.003
rs17066856	18	60382423	C	T	0.133	-0.040	0.006
rs1808579	18	23524924	T	C	0.475	-0.017	0.003
rs6567160	18	60161902	C	T	0.283	0.056	0.004
rs17724992	19	18344015	A	G	0.692	0.019	0.004
rs2287019	19	45698914	C	T	0.850	0.036	0.004
rs29941	19	33818627	A	G	0.333	-0.018	0.003
rs3810291	19	47065746	A	G	0.625	0.028	0.004

Table Legend: Genetic variants for BMI obtained from a GWAS for anthropometric measures in Locke AE *et al* Nature 2015.
Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base position based on genome assembly GRCh38p12; EA, effect allele; NEA, Non-effect allele; EAF, effect allele frequency.

Supplementary Table 3: Characteristics of participants included in individual-level MR analyses.

	CARDIA	CHS	GESUS	EPIC	FamHS	FHS	HCHS/SOL	JHS	GeneSTAR	MDC-CC	MESA	MGBB	RS	WGHS
Age, y	54 (5)	72 (5)	55 (13)	50 (9)	55 (13)	58 (16)	46 (14)	61 (13)	49 (13)	57 (6)	69 (10)	62 (16)	64 (7)	55 (7)
Gender, Female n (%)	1,012 (58.6)	2,346 (61.3)	3,946 (55.4)	1,444 (62.3)	1,369 (58.2)	2895 (53.9)	7,062 (59.7)	1,862 (61.8)	1,520 (57.7)	2,880 (60.5)	2,621 (52.6)	7,312 (52.5)	1,574 (59.5)	23,294 (100)
BMI, kg/m2	29.8 (7.1)	26.6 (4.7)	26.6 (4.6)	26.1 (4.3)	28.7 (5.8)	27.9 (5.6)	29.7 (6.0)	32.2 (7.5)	30.5 (7.0)	25.6 (3.9)	28.1 (5.7)	28.4 (6.1)	27.2 (4.2)	25.9 (5.0)
Fasting glucose, mmol/L	5.61 (1.56)	6.06 (1.88)	N/A	5.78 (1.37)	5.42 (1.20)	5.59 (1.24)	5.8 (2.0)	5.90 (2.03)	5.42 (1.75)	5.63 (0.79)	5.55 (1.53)	N/A	5.77 (1.34)	N/A
Prevalence of dyslipidemia, n (%)	N/A	2,088 (54.5)	2,234 (31.9)	599 (25.9)	869 (36.9)	2653 (49.4)	5,274 (44.6)	N/A	1,029 (39.3)	3,184 (66.8)	2,550 (51.2)	N/A	1313 (50.2)	6,961 (30.0)
Total cholesterol, mmol/L	4.94 (0.9)	5.49 (1.01)	5.49 (1.02)	5.30 (1.10)	4.93 (0.98)	4.80 (0.94	5.20 (1.11)	5.09 (1.07)	5.13 (1.07)	6.15 (1.08)	4.83 (0.97)	4.50 (1.12)	5.79 (0.98)	5.48 (1.08)
LDL-cholesterol, mmol/L	2.90 (0.10)	3.36 (0.92)	3.14 (0.89)	3.15 (0.91)	2.93 (0.86)	2.64 (0.79)	3.20 (0.93)	3.11 (0.96)	3.08 (0.98)	4.17 (0.99)	2.82 (0.85)	2.40 (0.90)	3.66 (0.9)	3.21 (0.88)
HDL-cholesterol, mmol/L	1.51 (0.50)	1.44 (0.41)	1.57 (0.47)	1.45 (0.39)	1.28 (0.37)	1.56 (0.48)	1.30 (0.31)	1.45 (0.42)	1.43 (0.44)	1.4 (0.37)	1.48 (0.44)	1.50 (0.50)	1.41 (0.44)	1.39 (0.39)
Triglycerides, mmol/L	2.90 (1.00)	1.54 (0.83)	1.79 (1.22)	3.48 (2.51)	1.60 (1.02)	1.29 (0.84)	1.64 (1.31)	1.19 (1.11)	1.36 (0.79)	1.30 (0.63)	1.27 (0.86)	1.42 (0.81)	1.53 (0.82)	3.72 (2.38)

Note: Values are mean (SD) for continuous variables; numbers and (percentages) for categorical variables.

Abbreviation: BMI, body mass index; LDLc low lipoprotein density cholesterol; HDLc, high lipoprotein density cholesterol.

Coronary Artery Risk Development in Young Adults (CARDIA), USA; Cardiovascular Health Study (CHS), USA; Danish General Suburban Population Study (GESUS), Denmark; European Prospective Investigation into Cancer and Nutrition-Potsdam (EPIC-Potsdam) study, Germany; Family Heart Study (FamHS), USA; Framingham Heart Study (FHS), USA; Hispanic Community Health Study / Study of Latinos (HCHS/SOL), USA; Jackson Heart Study (JHS), USA; Johns Hopkins Genetic Study of Atherosclerosis Risk (GeneSTAR), USA; Malmö Diet and Cancer-Cardiovascular Cohort study (MDC-CC), Sweden; Multi-Ethnic Study of Atherosclerosis (MESA), USA; Partners HealthCare Biobank (PHBB), USA; the Rotterdam Study (RS), The Netherlands; Women's Genome Health Study (WGHS), USA.

Supplementary Table 4: Genetic variants used in the multivariable MR analysis to proxy LDLc and BMI.

SNP	CHR	BP	EA	NEA	EAF
rs880315	1	10736809	T	C	0.660
rs4970834	1	109272258	C	T	0.813
rs4370783	1	109503258	A	C	0.886
rs4661359	1	16186658	C	T	0.377
rs543874	1	177920345	A	G	0.795
rs1434282	1	199041592	C	T	0.275
rs2820292	1	201815159	A	C	0.435
rs2642438	1	220796686	A	G	0.297
rs7517754	1	224356827	A	G	0.217
rs556107	1	234717312	C	T	0.477
rs16844296	1	234972561	G	A	0.788
rs35589882	1	25480604	T	C	0.554
rs657452	1	49124175	A	G	0.391
rs11591147	1	55039974	G	T	0.983
rs2495477	1	55052794	A	G	0.606
rs11206517	1	55060755	T	G	0.967
rs1168086	1	62646718	A	G	0.352
rs3101336	1	72285502	T	C	0.396
rs12566985	1	74536509	G	A	0.438
rs12401738	1	77981077	G	A	0.622
rs1556562	1	92568466	G	T	0.210
rs11165643	1	96458541	C	T	0.410
rs826681	2	108615619	C	T	0.857
rs12464355	2	118092274	A	G	0.898
rs17050272	2	120548864	G	A	0.591
rs4954192	2	134875411	C	T	0.627
rs2121279	2	142285716	C	T	0.875
rs4556933	2	157587377	G	A	0.603
rs2287622	2	168973818	A	G	0.397
rs1528435	2	180686235	C	T	0.379
rs11693335	2	20170652	G	A	0.523
rs7569317	2	202663256	T	C	0.469
rs13392272	2	20994618	C	T	0.497
rs7567653	2	21054090	G	A	0.955
rs7599312	2	212548507	G	A	0.733
rs13396400	2	21279855	A	G	0.554
rs1250229	2	215439661	T	C	0.261
rs11568318	2	233756852	C	A	0.934
rs10182181	2	24927427	A	G	0.514
rs11126666	2	26705943	G	A	0.744

rs1260326	2	27508073	T	C	0.396
rs4850047	2	3587163	T	C	0.132
rs745763	2	43228515	T	C	0.837
rs4299376	2	43845437	G	T	0.323
rs6709904	2	43853185	A	G	0.887
rs12986742	2	58748008	T	C	0.524
rs1016287	2	59078490	T	C	0.299
rs4671050	2	62761034	G	T	0.684
rs13021737	2	632348	A	G	0.172
rs12471768	2	64701469	T	C	0.296
rs3732359	3	119817582	G	A	0.220
rs9289196	3	122549659	T	C	0.826
rs13076933	3	12285932	T	G	0.741
rs9883745	3	132513479	G	A	0.669
rs6439629	3	136182428	G	A	0.728
rs16851483	3	141556594	G	T	0.934
rs4683438	3	142933717	G	T	0.666
rs1516725	3	186106215	T	C	0.137
rs6804842	3	25064946	A	G	0.426
rs9834932	3	32493890	A	G	0.911
rs11706420	3	58406684	A	G	0.917
rs2365389	3	61250788	C	T	0.592
rs9838601	3	69824633	C	T	0.354
rs3849570	3	81742961	C	A	0.654
rs13078960	3	85758440	T	G	0.798
rs13107325	4	102267552	C	T	0.925
rs11727676	4	144737912	T	C	0.904
rs1842896	4	155590307	G	T	0.479
rs6831256	4	3471412	A	G	0.577
rs10938397	4	45180510	A	G	0.566
rs2708699	4	68475319	T	C	0.593
rs1458038	4	80243569	C	T	0.709
rs7734476	5	123513182	G	A	0.450
rs1003533	5	132419959	C	T	0.812
rs6874202	5	156964617	T	C	0.366
rs2936574	5	52826192	T	G	0.736
rs9686661	5	56565959	C	T	0.799
rs3010239	5	72714474	G	A	0.790
rs12916	5	75360714	T	C	0.599
rs17185536	6	100173055	C	T	0.754
rs9400239	6	108656460	T	C	0.295
rs3822855	6	115995719	G	T	0.598
rs9491699	6	127150388	C	T	0.522

rs12197047	6	130068066	G	A	0.330
rs7776054	6	135097778	A	G	0.739
rs2297359	6	160071581	T	C	0.984
rs456598	6	160117889	G	A	0.859
rs10455872	6	160589086	A	G	0.921
rs6459450	6	16124329	T	C	0.693
rs13191362	6	162612318	A	G	0.876
rs1800562	6	26092913	G	A	0.923
rs13217599	6	27618451	T	C	0.912
rs3118362	6	28817308	C	T	0.095
rs3115626	6	29854284	C	T	0.194
rs2187980	6	30255736	A	G	0.856
rs2229094	6	31572779	T	C	0.746
rs6457614	6	32684123	T	G	0.880
rs3800406	6	35165297	A	G	0.896
rs913499	6	37070656	A	G	0.491
rs2033529	6	40380914	A	G	0.712
rs2296805	6	42961020	T	G	0.412
rs2207139	6	50877777	A	G	0.831
rs3757868	7	100885099	G	A	0.817
rs2107448	7	21445484	C	T	0.410
rs5008148	7	21564060	A	G	0.752
rs4722551	7	25952206	T	C	0.841
rs11772280	7	36146501	C	T	0.813
rs2073547	7	44542732	A	G	0.816
rs1167827	7	75533848	A	G	0.434
rs2245368	7	76978826	C	T	0.169
rs4148826	7	87445103	T	C	0.820
rs12701220	7	983092	T	C	0.789
rs10953259	7	98383795	A	C	0.184
rs2737252	8	115651671	G	A	0.720
rs2954021	8	125469835	A	G	0.495
rs11997161	8	140728488	T	C	0.482
rs11136343	8	143984818	A	G	0.616
rs1495741	8	18415371	G	A	0.221
rs9298506	8	54524964	A	G	0.792
rs4738684	8	58480714	A	G	0.335
rs17405819	8	75894349	T	C	0.702
rs2033732	8	84167474	T	C	0.255
rs9987289	8	9325848	A	G	0.091
rs2066714	9	104824472	T	C	0.871
rs11789603	9	104884738	C	T	0.892
rs1883025	9	104902020	C	T	0.745

rs6477694	9	109170062	C	T	0.352
rs1928295	9	117616205	T	C	0.569
rs10733682	9	126698635	A	G	0.473
rs9697210	9	128706461	G	A	0.854
rs507666	9	133273983	G	A	0.815
rs10448340	9	136425617	T	G	0.680
rs4740619	9	15634328	T	C	0.551
rs6475606	9	22081851	C	T	0.516
rs3780181	9	2640759	A	G	0.932
rs10968576	9	28414341	A	G	0.678
rs10869595	9	75598309	G	A	0.596
rs17094222	10	100635683	T	C	0.786
rs11191560	10	103109281	T	C	0.923
rs2250802	10	112161596	G	A	0.276
rs4132670	10	113008012	G	A	0.687
rs1106056	10	122953445	A	G	0.896
rs1277763	10	18206956	T	C	0.204
rs17496403	10	50591054	T	C	0.801
rs7077256	10	63576425	A	G	0.527
rs16926246	10	69333636	C	T	0.870
rs7899106	10	85651147	A	G	0.950
rs2068888	10	93079885	G	A	0.549
rs10791660	11	104000311	C	A	0.815
rs12286929	11	115151684	A	G	0.473
rs3741298	11	116786845	C	T	0.192
rs7112937	11	117009740	T	C	0.911
rs6589939	11	122647817	A	G	0.622
rs624259	11	126317973	G	A	0.554
rs4937122	11	126358764	T	G	0.925
rs10128711	11	18611437	T	C	0.261
rs11030104	11	27662970	A	G	0.797
rs2176598	11	43842728	T	C	0.247
rs3817334	11	47629441	C	T	0.592
rs11601507	11	5679844	C	A	0.931
rs174583	11	61842278	C	T	0.646
rs11227247	11	65655382	A	C	0.865
rs3819247	11	66526308	T	C	0.761
rs10840100	11	8647890	A	G	0.346
rs3184504	12	111446804	T	C	0.483
rs11066320	12	112468611	A	G	0.425
rs11065385	12	120985583	A	G	0.309
rs11057405	12	122297350	G	A	0.895
rs11057397	12	123935181	C	T	0.663

rs11057830	12	124822507	G	A	0.859
rs1007938	12	26649616	A	G	0.595
rs7138803	12	49853685	G	A	0.631
rs10876044	12	50512622	C	T	0.361
rs1805738	12	8924734	A	G	0.774
rs9521732	13	110381474	C	A	0.617
rs6602909	13	113849020	T	C	0.672
rs7992289	13	27462293	G	A	0.206
rs7330025	13	32394470	A	G	0.477
rs9316496	13	50467744	G	A	0.827
rs12429545	13	53528071	G	A	0.871
rs6573778	14	24403003	T	C	0.481
rs10132280	14	25458973	C	A	0.699
rs12885454	14	29267632	C	A	0.645
rs11847697	14	30045906	C	T	0.956
rs17101394	14	63765668	G	A	0.840
rs6573971	14	70544752	G	A	0.445
rs8022782	14	72975314	C	T	0.914
rs12431412	14	74753392	G	A	0.553
rs7141420	14	79433111	C	T	0.483
rs1395901	15	49557477	C	T	0.635
rs3736485	15	51456413	A	G	0.461
rs3803452	15	57287548	T	C	0.938
rs1532085	15	58391167	A	G	0.386
rs261332	15	58435126	A	G	0.210
rs2937856	15	63077543	G	A	0.139
rs10152515	15	63778180	C	A	0.696
rs16951275	15	67784830	T	C	0.773
rs6495122	15	74833304	A	C	0.409
rs12445804	16	11612244	G	A	0.925
rs12446632	16	19924067	G	A	0.858
rs3888190	16	28878165	C	A	0.601
rs9925964	16	31118574	A	G	0.640
rs758747	16	3577357	C	T	0.722
rs879620	16	3965728	C	T	0.387
rs1421085	16	53767042	T	C	0.597
rs3764261	16	56959412	C	A	0.676
rs4788547	16	71600641	G	A	0.627
rs2000999	16	72074194	G	A	0.810
rs7202323	16	72183214	T	G	0.770
rs4782863	16	83948855	A	G	0.360
rs1552657	16	86391091	G	A	0.554
rs12447718	16	88503726	G	A	0.958

rs704	17	28367840	G	A	0.524
rs548731	17	29555040	C	T	0.855
rs12603885	17	31139704	G	A	0.300
rs11870935	17	47655239	G	A	0.485
rs3110609	17	48676181	T	C	0.658
rs1000940	17	5379957	A	G	0.698
rs1801689	17	66214462	A	C	0.969
rs2886232	17	69154035	T	C	0.123
rs3826408	17	7197973	C	T	0.543
rs4366775	17	78385998	C	T	0.501
rs12940622	17	80641771	G	A	0.560
rs1808579	18	23524924	C	T	0.518
rs7241918	18	49634583	G	T	0.176
rs6567160	18	60161902	T	C	0.767
rs17066856	18	60382423	T	C	0.908
rs892078	19	10612343	T	G	0.903
rs9305020	19	11076035	T	C	0.819
rs4804576	19	11220678	G	T	0.965
rs626223	19	15691876	C	T	0.477
rs2302209	19	18213519	C	T	0.711
rs17724992	19	18344015	A	G	0.732
rs10401969	19	19296909	T	C	0.924
rs29941	19	33818627	A	G	0.326
rs2854496	19	43564041	C	T	0.813
rs2965157	19	44673068	T	C	0.970
rs3208856	19	44793549	C	T	0.965
rs10402271	19	44825957	T	G	0.677
rs8108762	19	45149969	G	A	0.681
rs34851490	19	45881296	A	G	0.883
rs3810291	19	47065746	G	A	0.325
rs516246	19	48702915	C	T	0.492
rs12981684	19	58120777	A	G	0.779
rs438568	20	12978039	A	G	0.391
rs1977107	20	17863180	T	C	0.173
rs8115257	20	25227295	A	G	0.507
rs224424	20	35560231	A	G	0.788
rs4810296	20	40563677	C	T	0.612
rs17820943	20	40639876	C	T	0.595
rs6016534	20	41250316	C	T	0.520
rs1800961	20	44413724	C	T	0.969
rs6065906	20	45925376	T	C	0.814
rs3208008	20	63694757	A	C	0.250
rs1060347	20	64276168	G	T	0.798

rs2835299	21	36180950	C	T	0.672
rs2836986	21	39330210	A	C	0.429
rs138352	22	40872921	T	G	0.341
rs5770859	22	50435332	A	G	0.655

Note: Genetic variants from the univariable analysis were used again after undertaking further LD clumping to account for correlation between LDLc and BMI genetic instruments (LD cutoff of r^2<0.001 within a 1Mb clumping window). Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base position based on genome assembly GRCh38p12; EA, effect allele; NEA, Non-effect allele; EAF, effect allele frequency.

Supplementary Table 5: Mendelian randomization estimates in sensitivity analyses.

Exposure (# SNPs)	Outcome	Sensitivity analysis	Odds ratio or Beta [95% CI]	P value
LDLc (232)	T2D	Weighted median	1.18 [1.05-1.33]	0.006
		MR Egger	1.18 [1.01-1.39]	0.039
		MR-PRESSO*	1.14 [1.04-1.21]	0.004
		FTO exclusion	1.10 [1.00-1.21]	0.044
		MVMR adjusting for HDL-c and TG$	1.18 [1.05-1.33]	0.005
LDLc (195)	BMI	Weighted median	0.05 [0.01-0.08]	0.010
		MR Egger	0.02 [-0.07-0.10]	0.710
		MR-PRESSO**	0.06 [0.03-0.09]	<0.001
		FTO exclusion	0.05 [0.02-0.09]	0.002
		MVMR adjusting for HDL-c and TG$$	0.07 [0.02-0.11]	0.006

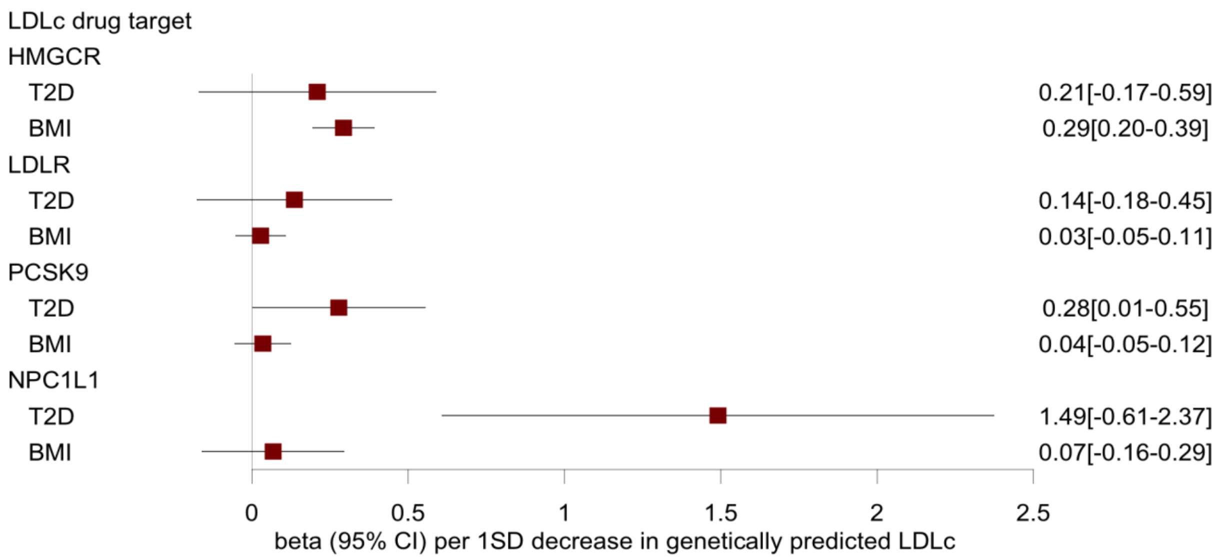
Note: Estimates reflect the effect of a 1-SD reduction in genetically predicted LDLc on the respective outcomes. BMI: body mass index; CI: confidence interval; LDLc: low-density lipoprotein cholesterol; MR: Mendelian randomization; T2D: type 2 diabetes; MVMR, Multivariable MR.
These analyses included 227*, 223**, 827$, and 692$ genetic instruments, respectively.

Supplementary Table 6: Sensitivity analysis to investigate potential causal reversal effects on MR estimates.

Exposure (# SNPs)	Outcome	Mediation contribution	Odds ratio or Beta [95% CI]	P value
LDLc (223) #	T2D	Total effect	1.11 [1.02-1.21]	0.017
LDLc (192) $	BMI	Indirect effect	1.05 [1.02-1.08]	0.002
BMI (73) %	T2D	Indirect effect	2.31 [1.96-2.74]	<0.001
		Indirect effect	1.04 [1.01-1.07]	0.003

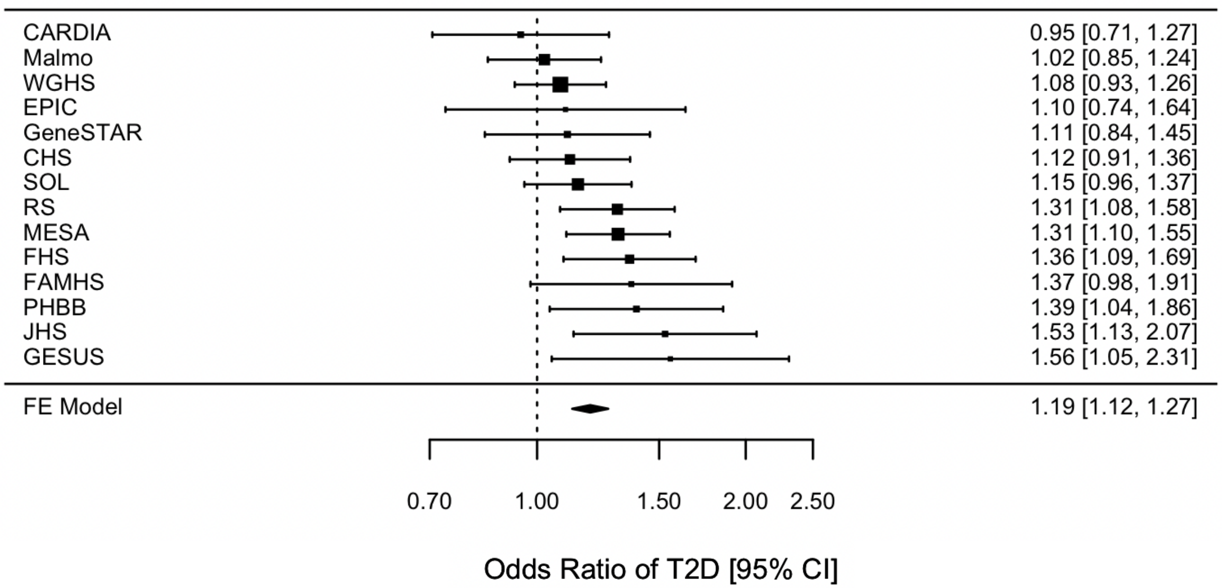
Note: MR-Steiger was used to identify and filter out genetic instruments that explained more of the variance in the outcome trait than in the exposure. The number of filtered variants were 9#, 3$, and 2%, respectively. Estimates reflect the effect of a 1-SD change in genetically driven exposures on outcomes. The indirect effect of LDLc on T2D was calculated using the product method (methods). The proportion mediated was 39% of the total effect (p=0.003).

Supplementary Figure 1: Association of LDLc lowering genetic variants at LDLc drug targets with T2D and BMI.



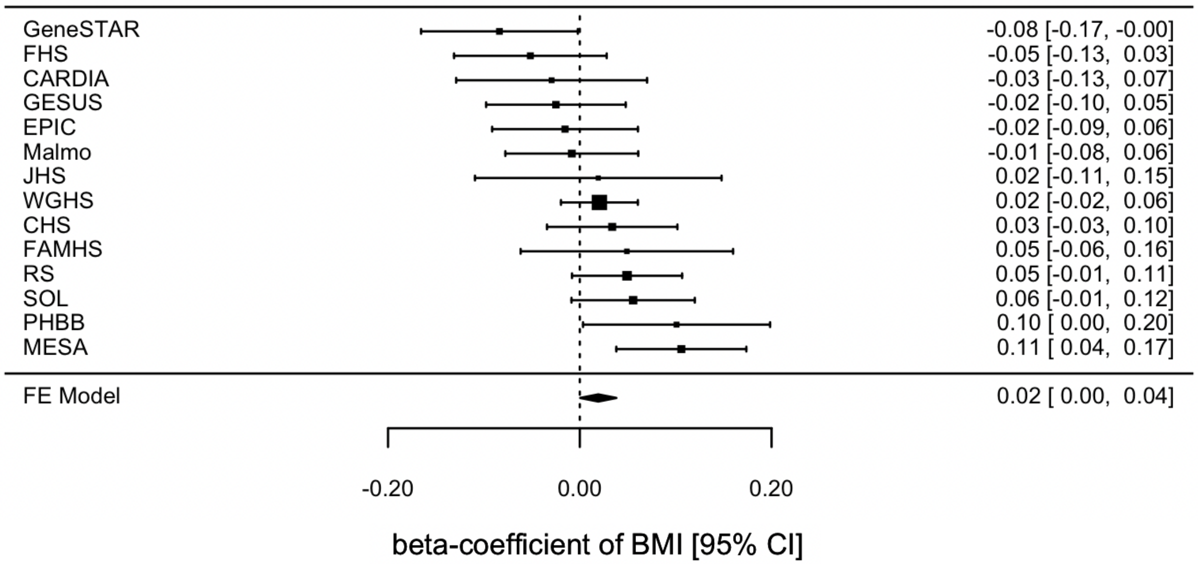
Note: MR estimates for 1SD decrease in genetically predicted LDLc on T2D and BMI based on genetic variation for LDLc drug targets. Instrument selection for LDLc drug targets was based on all genome-wide significant variants within 100kb on either side of each gene (*HMGCR*, *LDLR*, *PCSK9*, *NPC1L1*) and that were in a pair-wise LD cutoff of $r^2<0.001$ within a 1Mb clumping window. Variants included were rs12916 at *HMGCR*; rs10423733, rs72981271, and rs8101801 at *LDLR*; rs11206517, rs11591147, and rs472495 at *PCSK9*; and rs2073547 at *NPC1L1*. T2D data are from 26,676 T2D cases and 132,532 controls from the DIAGRAM consortium. BMI data are from 322,154 participants from the GIANT consortium. All results are scaled to represent the odds ratio or beta coefficient per 1-SD genetically predicted reduction in LDLc.

Supplementary Figure 2: Effect of a genetically predicted low LDLc on T2D odds in individual-level MR analyses.



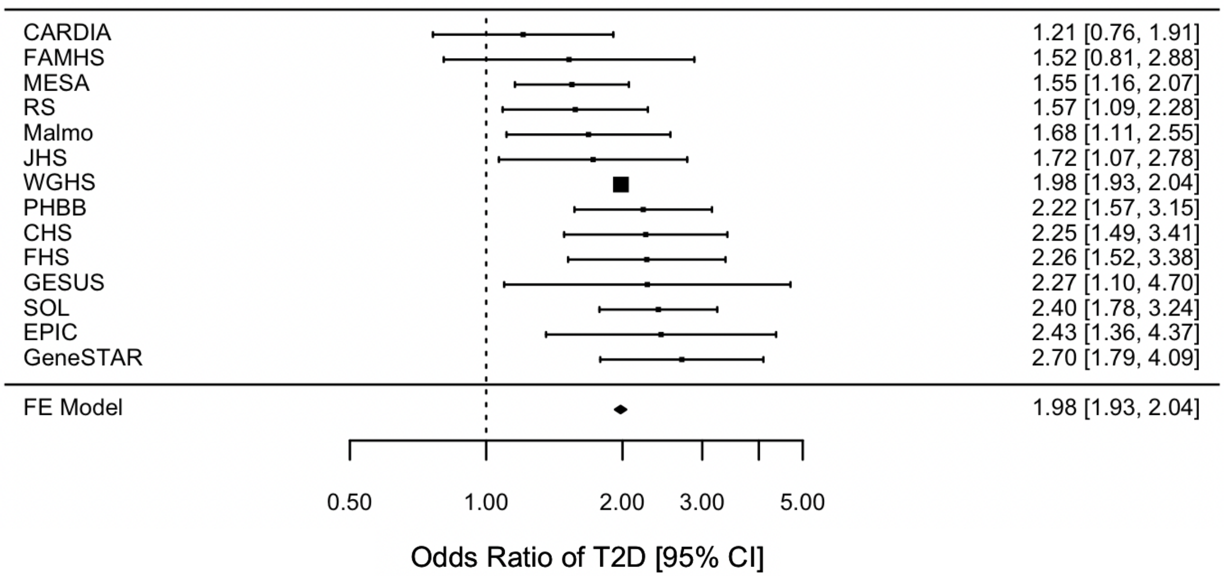
Note: Forest plot of MR estimates from individual-level data analyses for the combined effect of 1SD decrease in genetically predicted LDLc on T2D odds (black diamond) using fixed-effects inverse-variance weighted meta-analysis. Also, shown for each cohort the estimate of the association and the 95% confidence interval of the estimate.

Supplementary Figure 3: Effect of a genetically predicted low LDLc on BMI in individual-level MR analyses.



Note: Forest plot of MR estimates from individual-level data analyses for the combined effect of 1SD decrease in genetically predicted LDLc on BMI (black diamond) using fixed-effects inverse-variance weighted meta-analysis. Also, shown for each cohort the estimate of the association and the 95% confidence interval of the estimate.

Supplementary Figure 4: Effect of a genetically predicted BMI on T2D odds in individual-level MR analyses.



Note: Forest plot of MR estimates from individual-level data analyses for the combined effect of 1SD in genetically predicted BMI on T2D odds (black diamond) using fixed-effects inverse-variance weighted meta-analysis. Also, shown for each cohort the estimate of the association and the 95% confidence interval of the estimate.

Appendix 1

Description of the participating cohorts and exposure and outcome ascertainment

Participants for the current individual-level data MR study were drawn from 14 cohort studies, including the Coronary Artery Risk Development in Young Adults (CARDIA), the Cardiovascular Health Study (CHS), the Danish General Suburban Population Study (GESUS), the European Prospective Investigation into Cancer and Nutrition-Potsdam (EPIC-Potsdam) study, the Family Heart Study (FamHS), the Framingham Heart Study (FHS), the Hispanic Community Health Study / Study of Latinos (HCHS/SOL), the Jackson Heart Study (JHS), the Johns Hopkins Genetic Study of Atherosclerosis Risk (GeneSTAR), the Malmö Diet and Cancer-Cardiovascular Cohort study (MDC-CC), the Multi-Ethnic Study of Atherosclerosis (MESA), the Partners HealthCare Biobank (PHBB), the Rotterdam Study (RS) and the Women's Genome Health Study (WGHS).

The **Coronary Artery Risk Development in Young Adults** (CARDIA) study is a study examining the development and determinants of clinical and subclinical cardiovascular disease and its risk factors. It began in 1985 with a group of 5,115 black and white men and women aged 18-30 years, recruited from four communities in the USA, with follow-up visits every 2–5 years for approximately 30 years.

For these analyses we included 1,717 participants (253 T2D cases) with available genome-wide genetic data. LDLc was calculated using the Friedewald equation, and BMI was computed using weight and height determinations obtained at regular clinical visits. T2D was ascertained based on a) use of diabetes medication (assessed at every visit); b) a fasting blood glucose level of ≥6.99 mmol/l (126 mg/dl) (measured at visits in 1992, 1995, 2000, 2005); c) 2 h post-challenge glucose ≥11.1 mmol/l (200 mg/dl) (performed at the 1995 and 2005 visits); and/or d) a HbA1c ≥6.5% (48 mmol/mol) (assessed at the 2005 visit).

The **Cardiovascular Health Study** (CHS) is a population-based prospective cohort study of cardiovascular disease in adults older than 65 years and includes 5,888 participants ≥ 65 years of age identified from four U.S. communities using Medicare eligibility lists (Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA). The original cohort included 5,201 participants recruited in 1989–1990 and 687 additional subjects were recruited in 1992–1993 to enhance the racial/ethnic diversity of the cohort.

For these analyses, we included 4,276 (448 prevalent T2D cases) individuals free of cardiovascular disease. LDLc was calculated using the Friedewald equation after excluding individuals with triglycerides > 400mg/dl. Weight and eight were used to calculate BMI. Participants were classified as having T2D based on medication with oral hypoglycemic therapy or insulin or having fasting glucose level ≥7.0mmol/L.

The **Danish General Suburban Population Study** (GESUS). The cohort included 21,205 Danish participants (20-100 years) between 2010-2013 in Naestved Municipality located approximately 70km south of Copenhagen. Participants in the study completed a general questionnaire and a health examination including a non-fasting blood sample. In this study, we included 7120 participants (321 T2D cases) who were genotyped using the Infinium Global Screening Array v2 (Illumina). In the questionnaire, participants reported diabetes medication. Body mass index (BMI) was calculated as measured weight(kg) divided by measured height(meter) squared. From lithium-heparin plasma, nonfasting total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and blood glucose(mmol/L) were measured at health examination on Cobas. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald equation among participants with triglycerides≤4.0 mmol/L. From whole blood EDTA, HbA1c was measured on Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh Corporation) (an automated high-pressure liquid chromatography instrument). Participants were classified as having T2D based on self-reported diabetes (with onset after 30-years old), medication with oral hypoglycemic therapy, nonfasting glucose level ≥11.1mmol/L, or HbA1c>48 mmol/mol.

The **European Prospective Investigation into Cancer and Nutrition-Potsdam** (EPIC-Potsdam) study consists of 27,548 participants recruited between 1994 and 1998 from the general population in Potsdam and surroundings, Germany. The baseline examination involved a personal interview including questions on prevalent diseases, self-administered questionnaires, interviewer-conducted anthropometric measurements and a blood sample collection.

A random sub-cohort of 2,500 individuals was randomly selected from 26,444 participants who provided blood samples at baseline. Of these, participants with prevalent myocardial infarction or stroke were excluded. Further exclusion criteria were missing genetic data and missing lipid measurements, leaving 2,316 (93 prevalent T2D cases) individuals for analyses in the sub-cohort. LDLc was calculated using the Friedewald equation and BMI was computed using weight and height measured by trained interviewers. Prevalent type 2 diabetes at baseline was evaluated by a physician with information from self-reported diabetes diagnosis and/or diabetes medication at baseline. All participants provided written informed consent. The EPIC-Potsdam study was approved by the ethics committee of the State of Brandenburg, Germany. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The **Family Heart Study** (FamHS) is a multicenter, population-based study of genetic and nongenetic determinants of coronary heart disease, atherosclerosis, and cardiovascular risk factors. The study began in 1992 with the ascertainment of 1,200 families, half randomly sampled, and half selected because of an excess of coronary heart disease or risk factor abnormalities. A broad range of phenotypes were assessed at a clinic examination including height, weight, blood lipids and cardiovascular risk factors. Approximately 8 years later, study participants belonging to the largest pedigrees were invited for a second clinical exam, and a total of 2,756 Caucasian participants were examined.

All 2,756 participants consented for genetic studies and have genome-wide genetic data. We included 2,353 participants (n=256 T2D cases) for these analyses. LDLc was calculated using the Friedewald equation after excluding individuals with triglycerides > 400mg/dl. T2D was defined by a fasting glucose ≥ 126 mg/dl or taking diabetes medications, self-report of T2D, or having doctor diagnosis of T2D. An age of onset ≥ 40 years was also required to diagnose T2D.

The **Framingham Heart Study** (FHS) is a community-based longitudinal study designed to examine CVD risk in the offspring of the Original Cohort participants of the Framingham Heart Study and their spouses. In 1971, 5,124 individuals were enrolled; since then, the Offspring Cohort has been examined every 3–4 y. between 1998 and 2001, during the 7th examination cycle, 3,539 adults, with a mean age of 61y, underwent a standardized medical history and physical examination. Beginning in 2002, 4,095 Gen III participants, who had at least one parent in the offspring cohort, were enrolled in the Framingham Heart Study. At the first cycle of the Gen III study, 4,095 individuals with a mean age of 40 y, underwent the standard clinic examination. For the present study both cohorts were combined for the analysis.

A total of 5,368 adults with available DNA and consent to share genetic data were eligible for the current study. LDLc concentrations were estimated using the Friedewald formula. Participants with serum triglycerides above 400 mg/dL were excluded from the analyses. BMI was computed using weight and height determinations obtained at regular clinical visits. Diabetes was defined as a fasting plasma glucose ≥7.0 mmol/L, non-fasting glucose > 11.1 mmol/L, hba1c > 6.5, or treatment with either insulin or a hypoglycemic medication. Chart review was conducted to identify participants with type 1 diabetes mellitus; those individuals were excluded from the analyses.

The Hispanic Community Health Study / Study of Latinos (HCHS/SOL) is a multi-center epidemiologic study in Hispanic/Latino populations established in 2006 to assess the role of acculturation in the prevalence and development of disease. The target population of 16,000 persons of Hispanic/Latino origin, specifically Cuban, Puerto Rican, Dominican, Mexican, and Central/South American, were recruited through four Field Centers in Miami, San Diego, Chicago and the Bronx area of New York. During 2008-2011 study participants aged 18-74 years underwent an extensive clinic exam and assessments. During the 2014-2017 second clinic visit participants were re-examined to again collect data predictive of various health outcomes of interest.

For this analysis we included 11,822 out of the ~13,000 participants with available genome-wide genetic data who did not have cardiovascular disease at baseline. In HCSS/SOL, LDLc was quantified using the Friedewald equation. BMI was computed from weight and height measured at the clinic visit. T2D was defined according to the American Diabetes Association criteria which includes fasting glucose levels ≥126 mg/dL; or fasting ≤8 hours and fasting glucose ≥200 mg/dL; or post-oral glucose tolerance test (OGTT) glucose ≥200 mg/dL; or hemoglobin A1C (HbA1C) ≥6.5%; or if on current treatment with a hypoglycemic agent.

The **Jackson Heart Study** (JHS), is community-based epidemiologic investigation of environmental and genetic factors associated with cardiovascular disease among African Americans, recruiting 5,306 men and women ≥21 years of age from the Jackson, Mississippi metropolitan area (Hinds, Madison, and Rankin counties). The baseline exam was conducted from 2000 – 2004, with Exam 2 conducted from 2005 - 2008 and Exam 3 conducted from 2009 – 2013, with a 4^{th} exam ongoing (data for this study was drawn from Exams 1-3). All participants included in this analysis provided written, informed consent for use of genetic data, and all study protocols conform to the 1975 Declaration of Helsinki guidelines. The study was approved by the Institutional Review Boards of the participating institutions (University of Mississippi Medical Center, Jackson State University and Tougaloo College).

For this analysis we included 2,992 participants with post-quality control GWAS data from Affymetrix 6.0 array (imputed to 1000G phase 3 v5 on the Michigan imputation server) and relevant phenotype data. Lipid profiles were assessed at the University of Minnesota as previously described; LDL was calculated using the Friedewald equation, with those with triglycerides > 400 mg/dL excluded. Prevalent diabetes was defined according to the American Diabetes Association (ADA) criteria as fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or self-reported use of a diabetes medication within 2 weeks prior to the clinic visit. BMI was calculated in kg/m^2 from height to the nearest centimeter and weight to the nearest .1 kilogram in light clothing and in stocking feet. LDL, BMI, and diabetes were assessed at Exams 1-3 in individuals participating in each exam.

The **Johns Hopkins Genetic Study of Atherosclerosis** (GeneSTAR) is an ongoing prospective family study that begun in 1983 to explore the causes of premature cardiovascular disease. Briefly, probands with a premature coronary disease event prior to 60 years of age were identified at the time of hospitalization in any of 10 Baltimore area hospitals. Their apparently healthy 30–59-year-old siblings without known coronary artery disease were initially recruited and screened between 1983 and 2006; offspring of the siblings and probands, as well as the co-parent of these offspring, were recruited and assessed between 2003 and 2006.

In this study, 2,526 European- and African American participants with available genome-wide genetic data who did not have cardiovascular disease were included. LDLc was estimated using the Friedewald formula for participants with triglycerides < 400 mg/dl. BMI was calculated from height and weight measured at the clinical screening visit. T2D was defined as fasting glucose levels ≥126 mg/dl, current hypoglycemic treatment, and/or self-reported history at clinical screening visit.

The **Malmö Diet and Cancer-Cardiovascular Cohort study** (MDC-CC**)** consists of individuals randomly (50%) invited to be involved in additional baseline examinations between 1991 and 1994. In total 6,103 individuals (46-68 y, 58% females) participated in the additional examinations.

For this analysis, we included 4,764 individuals for whom data on genotype were available. Levels of LDL-C were calculated according to Friedewald's formula, with the assignment of missing values to subjects with a triglyceride level of more than 4.5 mmol/L. BMI was calculated in kg/m^2 from height and weight obtained at clinical exams. T2D cases were defined as individuals with fasting plasma glucose ≥7.0mmol/L, glucose ≥ 11.0mmol/L 2-h after OGTT, under diabetes medication (A10 drugs), or who have reported having diabetes in a questionnaire were identified as incident diabetes cases. In addition, T2D cases were identified via at least one of seven registries or at examinations during follow-up. Cases were also identified via registries from the National Board of Health and Welfare: The Swedish National Inpatient Registry, the Swedish Hospital-based outpatient care, the Cause-of-death Registry and the Swedish Prescribed Drug Registry.

The **Mass General Brigham Biobank** (MGBB) is a hospital-based cohort including data from 30,000 ethnically diverse consented patients seen at Partners HealthCare hospitals. Patients were recruited in the context of clinical care appointments at more than 40 sites and clinics. Biobank subjects provide consent for the use of their samples and data in broad-based research. A total of 15,061 individuals had available genomic data.

For this analysis, we included 13,925 individuals with available genome-wide genetic data and exposure and outcome information. LDLc was determined directly or calculated using the Friedewald equation. BMI was calculated from weight and height obtained during the clinical visits. T2D status was defined based on “curated phenotypes” developed by the Biobank Portal team using both structured and unstructured electronic medical record data and clinical, computational, and statistical methods.

The **Multi-Ethnic Study of Atherosclerosis** (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA includes a diverse, population-based sample of 6,814 asymptomatic individuals of European- African- Hispanic- and Chinese American ancestry ascertained across six field centers across the United States.

The sample included in this study was composed of those 4,912 individuals with available genome-wide genetic data and no history of cardiovascular events. LDLc was calculated using the Friedewald equation. In MESA, incident diabetes was defined as a fasting plasma glucose $\geq$ 7.0mmol/L or treatment with either insulin or a hypoglycemic medication.

The **Rotterdam Study** is a prospective population-based cohort study in Ommoord, a suburb of Rotterdam, designed to investigate the prevalence and incidence of and risk factors for chronic diseases in the elderly. More than 15,000 subjects aged 45 years or over comprise the Rotterdam Study cohort.

For the current analysis, 7,686 adults were eligible as they had available DNA data, LDLc determinations, and outcome information. In RS, LDLc was calculated using the Friedewald equation. BMI was obtained from height and weight. T2D was defined according to WHO guidelines as a fasting glucose level >7mmol/l, non-fasting glucose level >11.1mmol/l or use of glucose-lowering medication.

The **Women's Genome Health Study** (WGHS) is a prospective cohort of initially healthy, female North American health care professionals at least 45 years old at baseline representing participants in the Women’s Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses. The WHS was a 2x2 trial beginning in 1992-1994 of vitamin E and low dose aspirin in prevention of cancer and cardiovascular disease with about 10 years of follow-up. Since the end of the trial, follow-up has continued in observational mode.

For the present analysis. we included 20,757 participants. In WGHS, LDLc was quantified using the Friedewald formula for individuals’ triglycerides < 4.5 mmol/L. T2D ascertainment was based on revised American Diabetes Association diagnostic criteria. Cases were confirmed if 1 or more of the following conditions were met: (1) presence of more than 1 classic symptom of hyperglycemia (i.e., polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision) plus either a fasting plasma glucose $\geq$7.0mmol/L or higher or random plasma glucose $\geq$11.1mmol/L; (2) in the absence of symptoms, 2 or more elevated plasma glucose concentrations (fasting plasma glucose $\geq$7.0mmol/L, random plasma glucose $\geq$11.1mmol/L, or 2-hour plasma glucose $\geq$11.1mmol/L during oral glucose tolerance testing); or (3) use of insulin or an oral hypoglycemic agent. The primary care physician's office was contacted for supporting documentation as necessary.

Appendix 2

Pre-specified analysis plan

1. General methodological considerations

Participating cohort studies that had agreed to collaborate in this effort are listed below.

Main exclusion: History of previous cardiovascular events, including individuals with coronary heart disease, cerebrovascular disease, or peripheral artery disease. We also excluded participants with missing T2D status and those with missing genotype data (It was considered missing genotype data if a particular participant does not have any genetic information).

1.1 Primary outcome and exposures

Outcome:

Prevalent T2D;

Definition: ≥7mmol/l (126mg/dl), random plasma glucose ≥11.1mmol/L (200mg/dl), being on diabetes medications or self-reported diagnosis.

Exposure definitions:

We will generate a predicted value for both LDLc and BMI. To generate these predicted values, we will use three different sets of genetic variants including: a) genetic variants associated with LDLc only, b) genetic variants associated with BMI only, and c) genetic variants associated with both LDLc and BMI.

Genetic instruments for LDLc were identified from the largest GWAS meta-analysis of lipid traits from UKB (Richardson TG, et al Plos Med 2020). The number of distinct genetic instruments for LDLc from this study is 232. Genetic instruments for BMI were identified from the largest GWAS meta-analysis of BMI for European ancestry participants that does not include UKB participants (Locke A, et al Nat 2015). The number of distinct genetic instruments for LDLc from this study is 75. Because several genetic variants from both datasets are overlapping, we pruned the list of 232 LDLc + 75 BMI genetic instruments based on physical distance (1MB) and pairwise LD (r^2<0.001). A total of 259 distinct genetic instruments remains for the prediction of LDLc and BMI from the list of variants associated with both phenotypes.

To predict LDLc and BMI we will use genotyped variants from each participating cohort with call rate higher than 0.95 and Hardy-Weinberg equilibrium p-value higher than 1×10^{-4}. When not directly genotyped, we will use imputed variant based on the criteria of imputation quality (INFO) > 0.7 and MACH r^2>0.8. If variants included in the provided SNP lists are missing in specific participating cohorts, we will use proxy variants based on available variants reaching r^2>0.8 with the variant included in the original list.

1.2 Covariates

Models will be adjusted for 1) age (years, continuous), 2) sex (male, female, categorical), 3 ancestry-derived principal components (5 or more if needed), and 4) Cohort-specific covariates such as recruitment center or family relatedness should be included based on each specific case. For multi-ancestry cohorts, we will stratify individual analyses by major ethnic groups including a) European descent, b) African American, and c) Asian

1.4 Unit of analysis

To facilitate these analyses, and to enable a uniform approach to analyses across the participating consortia/studies, the Coordinating Center will provide R software scripts for direct use (or adaptation as needed). For example. For obtaining predicted values we will need to add all the genetic instruments separately in a regression model rather than combining them into a polygenic score. Estimated effect sizes will be reported per 1SD change in main exposures of interest.

1.5 Subgroup analysis

For multi-ancestry cohorts, we will stratify individual analyses by major ethnic groups including a) European descent, b) African American, and c) Asian

2. Statistical analyses

1. Each cohort lists whether information on LDLc and BMI genetic instruments discovered to date are available either via direct genotyping or via imputation with a sufficient imputation quality. We acknowledge that not all studies have full information on these genetic variants. However, a table providing the specific variants available by each study will clarify the exclusions made in the main analyses.

2. Each cohort will provide basic descriptive statistics (mean (SD), min, max) of main exposures and outcome of interest.

3. The following cohort-level characteristics at baseline will be provided:

1. Total number of participants
2. Total number of T2D cases
3. Country and region (i.e., Europe, North America).
4. Mean (SD) of LDLc
5. Mean (SD) of BMI
6. Mean (SD) of age
7. Number (%) of sex
8. Number (%) of participants of European, African American, or Asian descent
9. Mean (SD) of fasting glucose
10. Number (%) of participants with dyslipidemia
11. Mean (SD) of total cholesterol
12. Mean (SD) of HDLc
13. Mean (SD) of triglycerides
14. Ascertainment methods for T2D adjudication (i.e., fasting/non-fasting glucose determinations, treatment with either insulin or a hypoglycemic drug at follow-up examinations, or by reviewing medical record).
15. Method of assessment of LDLc.
16. Method of assessment of BMI.
17. Method of genotyping imputation panels, and quality metrics

The analysis plan is divided in three steps to calculate the total effect, the indirect effect, and the direct effect.

Step 1. Total effect of LDLc on T2D:

<u>1.1 Generate predicted LDLc:</u>

- Fit a linear regression without the addition of any covariates to obtain a predicted value for LDLc (LDLc ~ β_1SNP1 + β_2SNP2 + β_3SNP3 + …. + β_{232}SNP232; script was used in FHS was provided).
- LDLc should be in mg/dl, so if your cohort has LDLc in mmol/L please transform this variable to mg/dl before predicting LDLc (multiply mmol/L by 38.67 to obtain mg/dl).
- The output is a new variable which includes the fitted values from this model (i.e., predicted values). We denote the value for each participant as LDLc.232.

<u>1.2 Obtain T2D estimates*:*</u>

- Fit a regression model for T2D with LDLc.232 and covariates (T2D ~ β_{LDL}LDLc.232 + β_{CovLDL}covariates). The output from this analysis is β_{LDL}LDLc.232. We will internally denote β_{LDL}LDLc.232 as T_1.
- *We will meta-analyze all T_1 to obtain the total effect of LDLc on T2D.*

Step 2. Indirect effect of LDLc on T2D:

<u>2.1 Obtain the effect of the exposure on the mediator:</u>

- Use the previously generated LDLc.232 variable to calculate the effect of LDLc on BMI. Regression model for BMI with LDLc.232 and covariates (BMI ~ β_{LDL}LDLc.232 + β_{CovLDL} covariates).
- The output from this analysis is β_{LDL}LDLc.232. We will internally denote β_{LDL}LDLc.232 from this model as α_1.
- *We will meta-analyze all α_1 to obtain the effect of LDLc on BMI.*

2.2 Obtain the effect of the mediator on the outcome:

2.2.1 Generate predicted BMI:

- Fit a linear regression without the addition of any covariates to obtain a predicted value for BMI (BMI ~ β_1SNP1 + β_2SNP2 + β_3SNP3 + …. + β_{75}SNP75).
- BMI should be in kg/m^2
- The output is a new variable which includes the fitted values from this model. We denote the value for each participant BMI.75.

2.2.1 Obtain T2D estimates:

- Fit a regression model for T2D with BMI.75 and covariates (T2D ~ β_{BMI}BMI.75 + β_{CovBMI} covariates).
- The output from this analysis is β_{BMI}BMI.75. We will internally denote β_{BMI}BMI.75 as β_2
- *We will meta-analyze all β_2 to obtain the effect of BMI on T2D.*
- *To obtain the indirect effect we will use the product of coefficients method (α_1 * β_2).*

Step 3. Direct effect of LDLc on T2D:

3.1 Obtain predicted LDLc:

- Fit a linear regression without the addition of any covariates to obtain a predicted value for LDLc. (LDLc~ β_1SNP1 + β_2SNP2 + β_3SNP3 + …. + β_{259}SNP259).
- The output is a new variable with the fitted values from this model. We denote the value for each participant LDLc.hat

3.2 Obtain predicted BMI:

- Fit a linear regression without the addition of any covariates to obtain a predicted value for BMI. (BMI~β_1SNP1 + β_2SNP2 + β_3SNP3 + ….+ β_{259}SNP259).
- The output is a new variable with the fitted values from this model. We denote the value for each participant as BMI.hat.

3.3 Obtain estimates effect sizes on T2D*:*

- Fit a regression model with both predictors and covariates: T2D ~ β_{LDLadj} LDLc.hat + β_{BMIajd} BMI.hat + β_{CovAdj} covariates
- The output from this model is β_{LDLadj} LDLc.hat. We will internally denote β_{LDLadj} LDLc.hat as β_1
- *We will meta-analyze all β_1 to obtain the direct effect of LDLc on T2D.*

3. List of cohorts that had agreed to collaborate in this effort

Coronary Artery Risk Development in Young Adults (CARDIA), USA. The Cardiovascular Health Study (CHS), USA. The Danish General Suburban Population Study (GESUS), Denmark. The European Prospective Investigation into Cancer and Nutrition-Potsdam (EPIC-Potsdam) study, Germany. The Family Heart Study (FHS), USA. The Framingham Heart Study (FHS), USA. The Hispanic Community Health Study / Study of Latinos (HCHS/SOL), USA. The Jackson Heart Study (JHS), USA. The Johns Hopkins Genetic Study of Atherosclerosis Risk (GeneSTAR), USA. The Malmö Diet and Cancer-Cardiovascular Cohort study (MDC-CC), Sweden. The Mass General Brigham Biobank (MGBB), USA. The Multi-Ethnic Study of Atherosclerosis (MESA), USA. the Rotterdam Study (RS) The Netherlands. The Women's Genome Health Study (WGHS), USA.

(List in alphabetical order, updated January 2021).

Appendix 3

Acknowledgement of sources of funding for participating cohort studies

The **Coronary Artery Risk Development in Young Adults** study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201800005I & HHSN268201800007I), Northwestern University (HHSN268201800003I), University of Minnesota (HHSN268201800006I), and Kaiser Foundation Research Institute (HHSN268201800004I).

The **Cardiovascular Health Study** research reported in this article was supported by NHLBI contracts 75N92021D00006, HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and U01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through R01AG023629 from the National Institute on Aging. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center grant DK063491 to the Southern California Diabetes Endocrinology Research Center. A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The **Danish General Suburban Population Study** GESUS was funded by the Region Zealand Foundation, Naestved Hospital Foundation. Edith and Henrik Henriksens Memorial Scholarship, Johan and Lise Boserup Foundation, TrygFonden, Johannes Fog's Foundation, Region Zealand, Naestved Hospital, The National Board of Health, and the Local Government Denmark Foundation.

The recruitment phase of the **EPIC-Potsdam** study was supported by the Federal Ministry of Science, Germany (01 EA 9401) and the European Union (SOC 95201408 05F02). The follow-up of the EPIC-Potsdam study was supported by German Cancer Aid (70-2488-Ha I) and the European Community (SOC 98200769 05F02). This work was supported by a grant from the German Ministry of Education and Research (BMBF) and the State of Brandenburg (DZD grant 82DZD00302).

The **Family Heart Study** is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) R01HL117078 and by NIDDK R01-DK-089256

The **Framingham Heart Study** was conducted using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278).

The Hispanic Community Health Study/Study of Latinos is a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (HHSN268201300001I / N01-HC-65233), University of Miami (HHSN268201300004I / N01-HC-65234), Albert Einstein College of Medicine (HHSN268201300002I / N01-HC-65235), University of Illinois at Chicago (HHSN268201300003I / N01-HC-65236 Northwestern Univ), and San Diego State University (HHSN268201300005I / N01-HC-65237). The following Institutes/Centers/Offices have contributed to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, NIH Institution-Office of Dietary Supplements. The Genetic Analysis Center at the University of Washington was supported by NHLBI and NIDCR contracts (HHSN268201300005C AM03 and MOD03).

The Jackson Heart Study is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

The **Johns Hopkins Genetic Study of Atherosclerosis Risk** was supported by grants from the National Institutes of Health/National Heart, Lung, and Blood Institute (U01 HL72518, HL087698, HL49762, HL59684, HL58625, HL071025, HL092165, HL099747, K23HL105897), by grants from the National Institutes of Health/National Institute of Nursing Research (NR0224103, NR008153), by a grant from the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NS062059), by a grant from the National Institutes of Health/National Center for Research Resources (M01-RR000052) to the Johns Hopkins General Clinical Research Center, and by a grant from the National Center for Advancing Translational Sciences, National Institutes of Health (UL1TR001079) to the Johns Hopkins Institute for Clinical & Translational Research.

The **Malmö Diet and Cancer-Cardiovascular Cohort study** was supported by the Swedish Research Council, the Swedish Heart and Lung Foundation, the Novo Nordic Foundation, the Swedish Diabetes Foundation, and the Påhlsson Foundation, and by equipment grants from the Knut and Alice Wallenberg Foundation, the Region Skåne, Skåne University Hospital, the Linneus Foundation for the Lund University Diabetes Center and the European Research Council.

The **Mass General Brigham Biobank** was supported by funds from Partners HealthCare which includes Massachusetts General Hospital and Brigham and Women's Hospital.

The **Multi-Ethnic Study of Atherosclerosis** study and the MESA SHARe projects are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001420. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. Also supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

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The **Women's Genome Health Study** is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467) and the National Cancer Institute (CA047988 and UM1CA182913), with collaborative scientific support and funding for genotyping provided by Amgen.