Supplementary Online Content

White J, Swerdlow DL, Preiss D, et al. Association of lipid fractions with risks for coronary artery disease and diabetes. *JAMA Cardiol*. Published online August 3, 2016. doi:10.1001/jamacardio.2016.1884.

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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. LDL-C and CAD:
(A) plot to show proportion of variance of LDL-C explained, presence of directional pleiotropy and estimates derived from the three MR approaches; (B) scatter plot of LDL-C and CAD associations for SNPs and superimposed MR estimates

(A) (B)
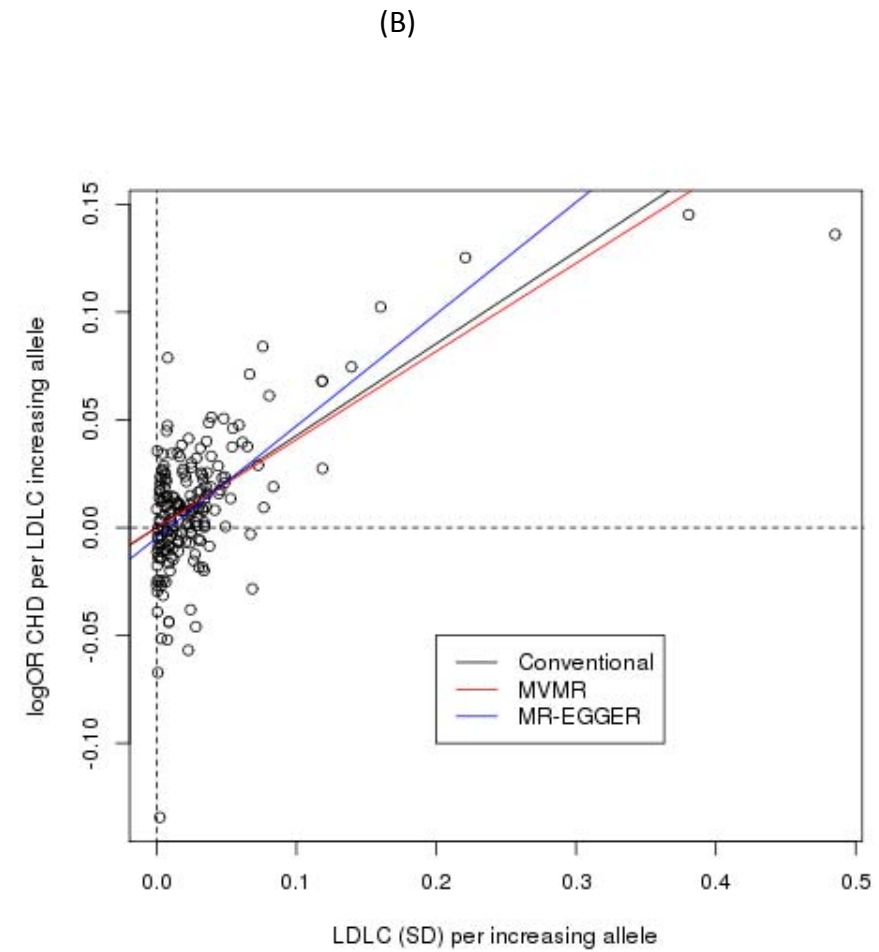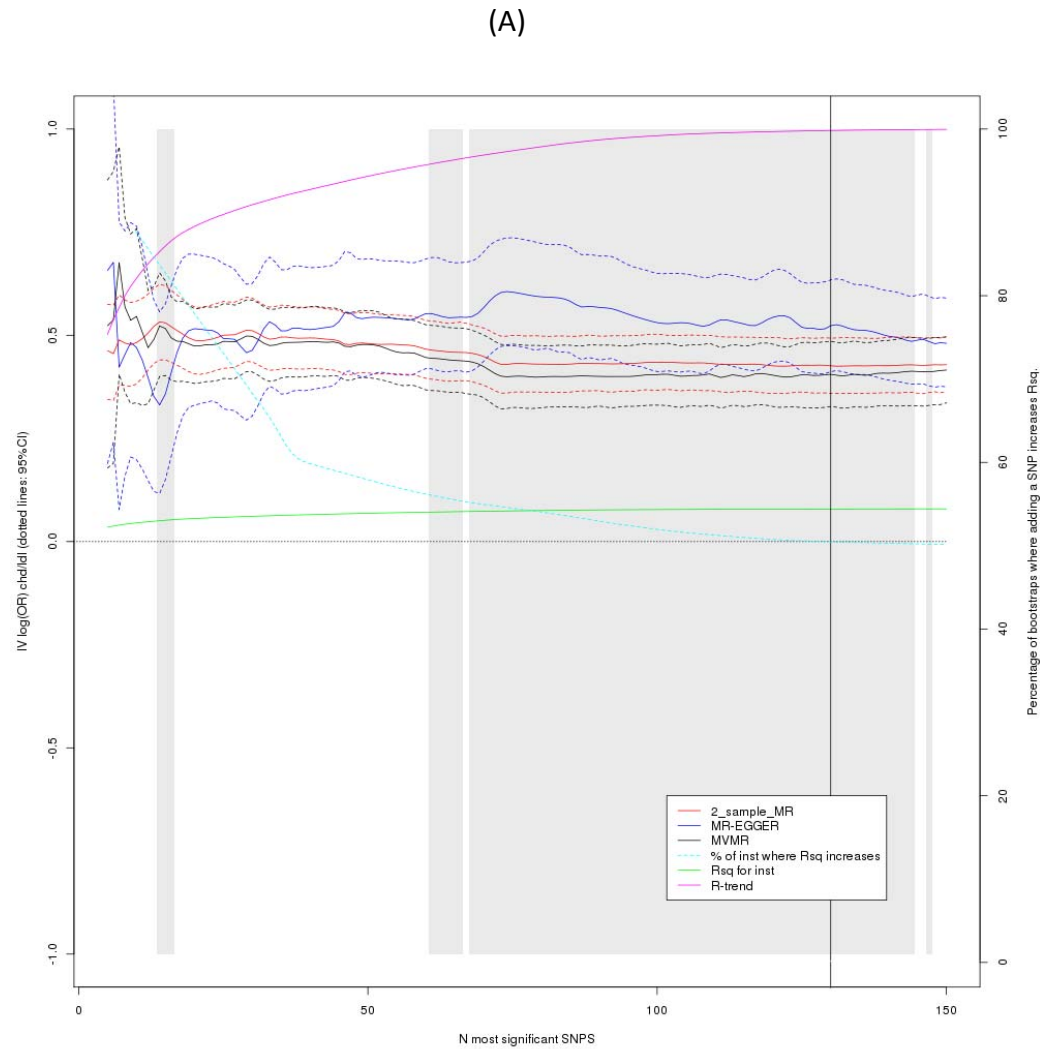
Orientation for eFigures 1 to 6

Panel A:
X-axis = SNPs contributing towards the genetic instrument, ordered by R^2 with lipid trait (highest first). Y-axis = Mendelian randomization estimate for disease (log odds scale).

Instrument properties: (a) proportion of variance of exposure
Green line: R^2 of the instrument
Purple line: R-trend = the ratio of R^2 for current instrument compared to R^2 for an instrument comprising 30 more SNPs; the beginning of the asymptotic phase marks where the instrument accounts for maximal variation in the trait while minimizing over-specification.
Turquoise dotted line: percentage of bootstraps where the current instrument has a higher R^2 with the exposure than the previous instrument.
Vertical black line: the position where the number of SNPs optimally explains variation in the trait (chosen for Mendelian randomization), selected based on (i) R-trend (purple line) and (ii) gain in R^2 compared to previous instrument (turquoise line)

Instrument properties: (b) directional pleiotropy of genetic instrument
Grey-shading = presence of pleiotropy, based on the intercept derived from MR-Egger. When directional pleiotropy is present, the most reliable estimate is derived from MR-Egger as conventional (2-sample) MR does not take into account directional pleiotropy and MVMR may not sufficiently remove the directional nature of the pleiotropy.

Mendelian randomization estimates: Solid lines and corresponding dotted lines represent point estimate and Bonferroni-adjusted 95%CI for the estimate derived from MR.
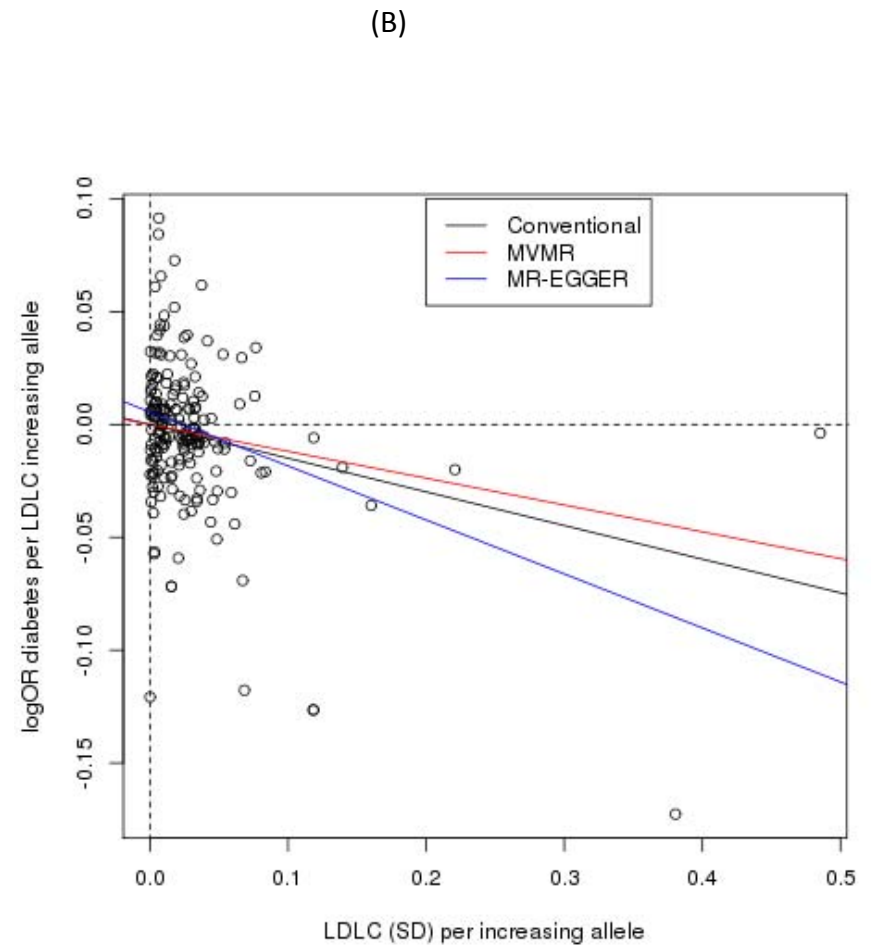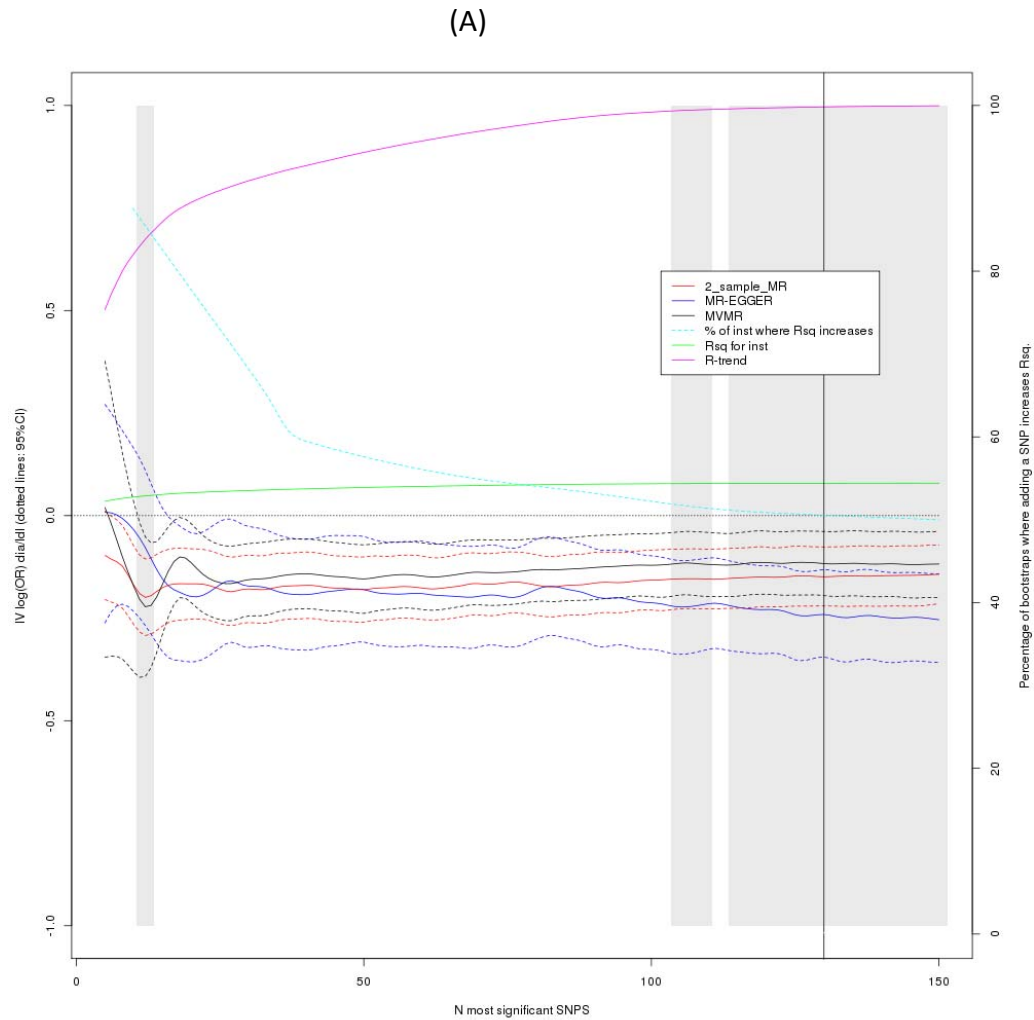Red line: conventional (2-sample) MR;
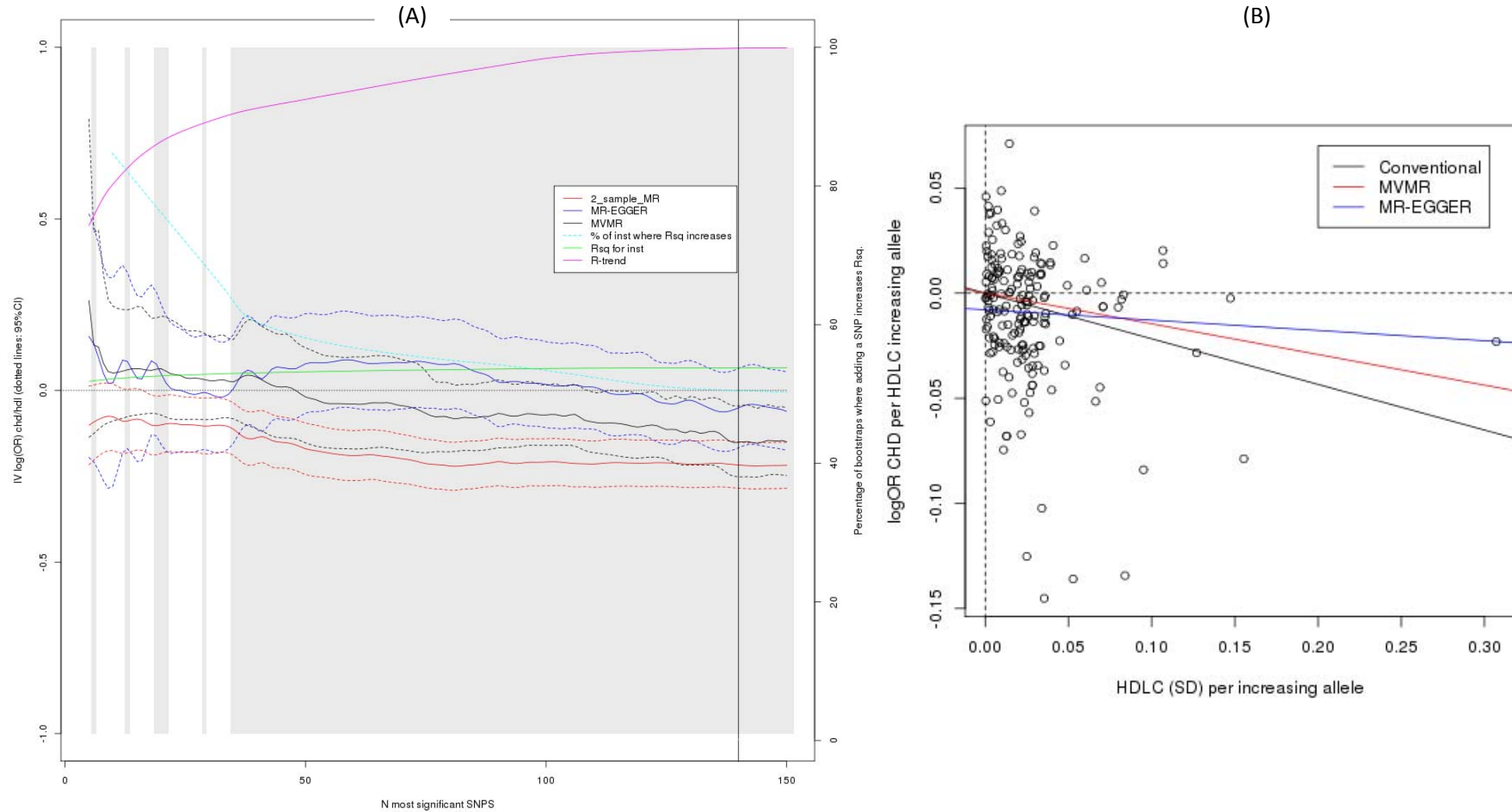Blue line: MR-Egger;
Black: multivariate MR (MVMR).

eFigure 2. LDL-C and T2D

(A) plot to show proportion of variance of LDL-C explained, presence of directional pleiotropy and estimates derived from the three MR approaches; (B) Scatter plot of LDL-C and T2D associations for SNPs and super-imposed MR estimates
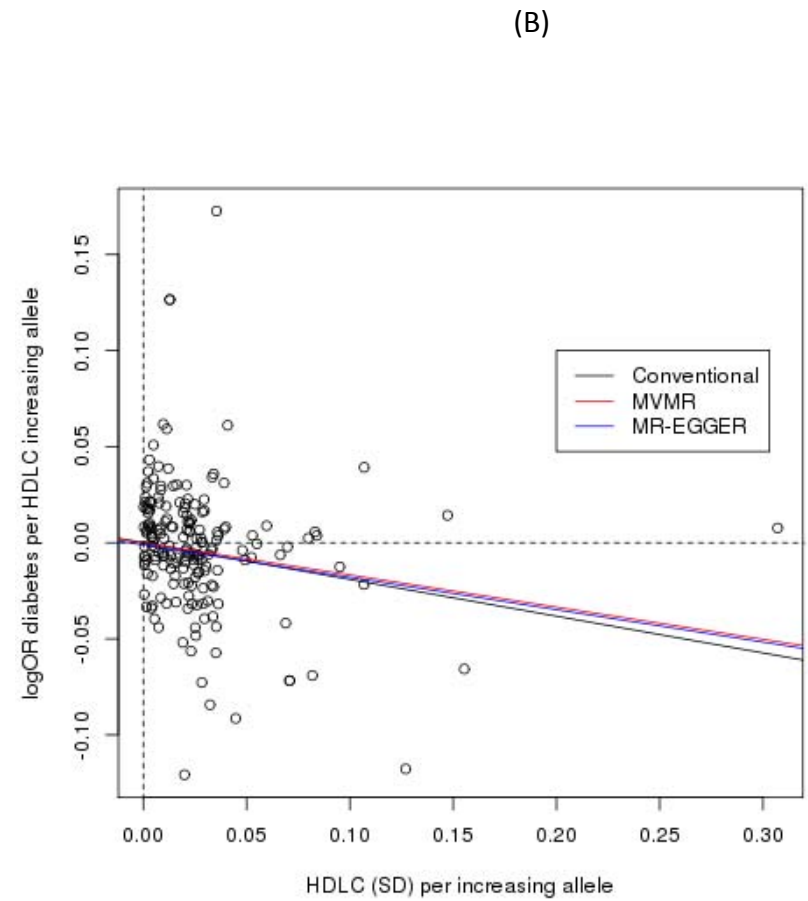
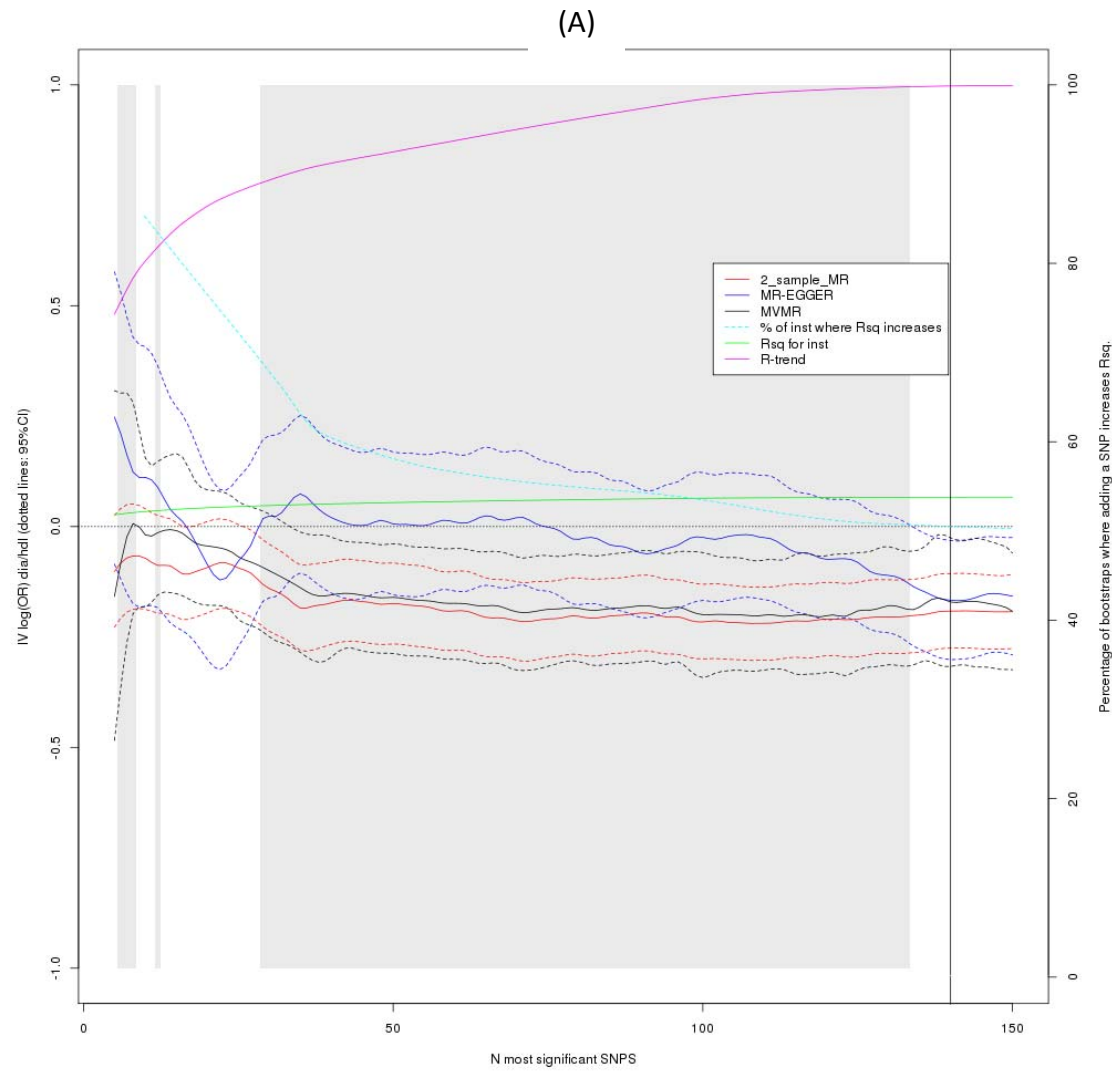Figure legend as for eFigure 1.

(A)

(B)

eFigure 3. HDL-C and CAD

(A) plot to show proportion of variance of HDL-C explained, presence of directional pleiotropy and estimates derived from the three MR approaches; (B) Scatter plot of HDL-C and CAD associations for SNPs and super-imposed MR estimates

Figure legend as for eFigure 1.

eFigure 4. HDL-C and T2D
(A) plot to show proportion of variance of HDL-C explained, presence of directional pleiotropy and estimates derived from the three MR approaches; (B) Scatter plot of HDL-C and T2D associations for SNPs and super-imposed MR estimates
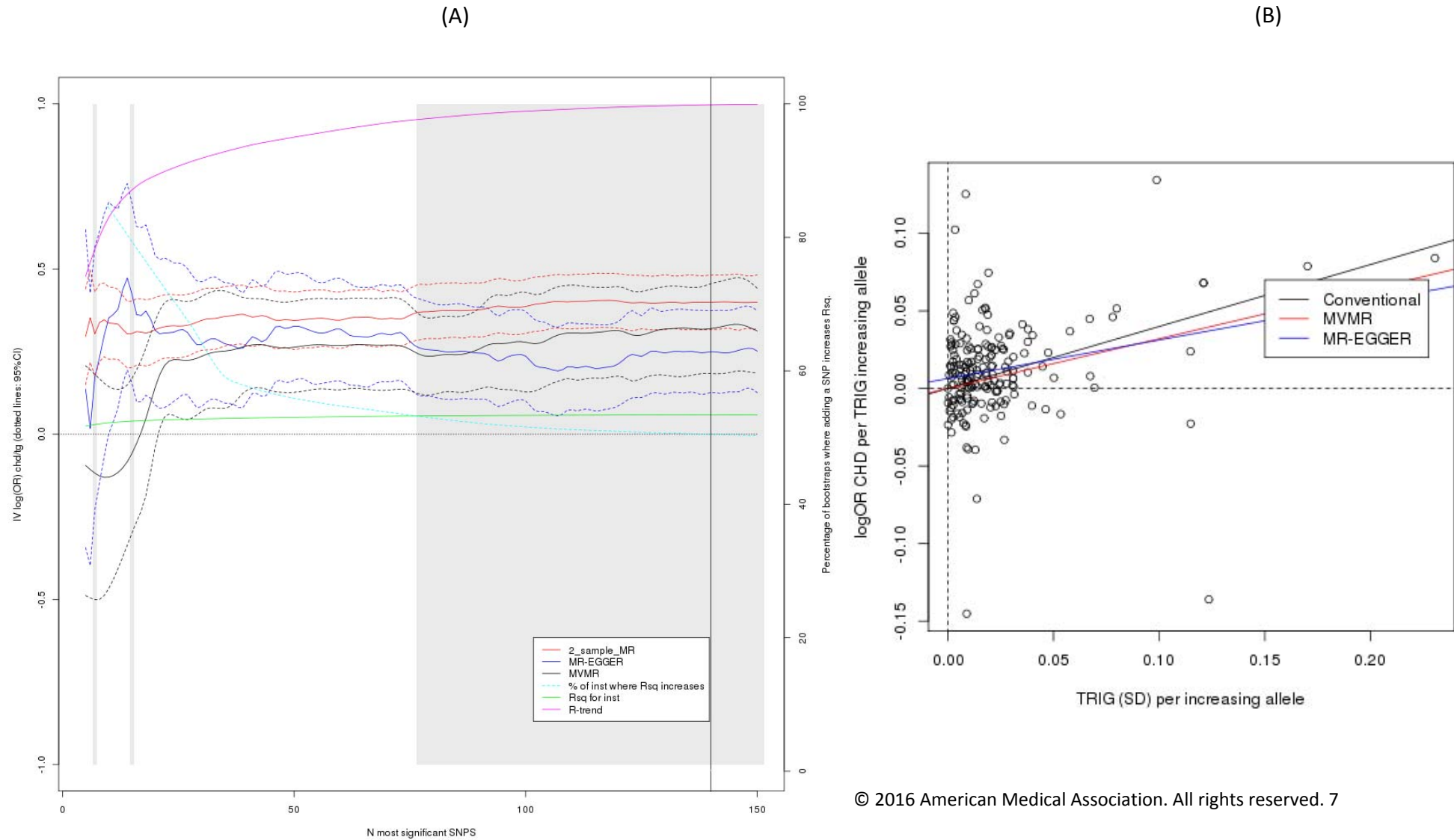Figure legend as for eFigure 1.

(A)

(B)

eFigure 5. TG and CAD

(A) plot to show proportion of variance of TG explained, presence of directional pleiotropy and estimates derived from the three MR approaches; (B) Scatter plot of TG and CAD associations for SNPs and super-imposed MR estimates

Figure legend as for eFigure 1.

(A)
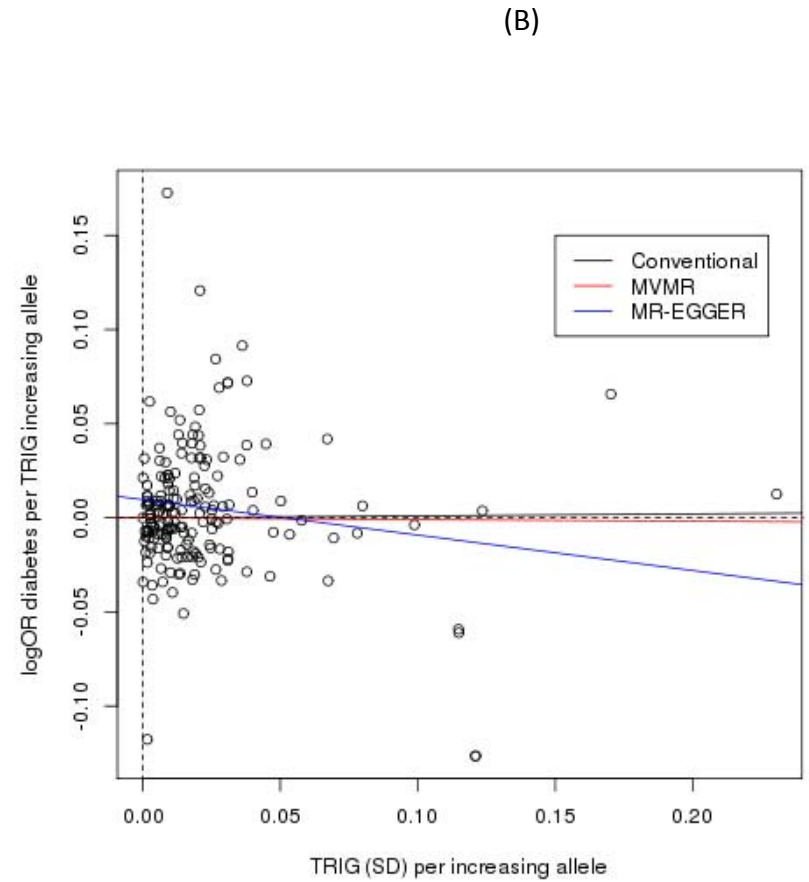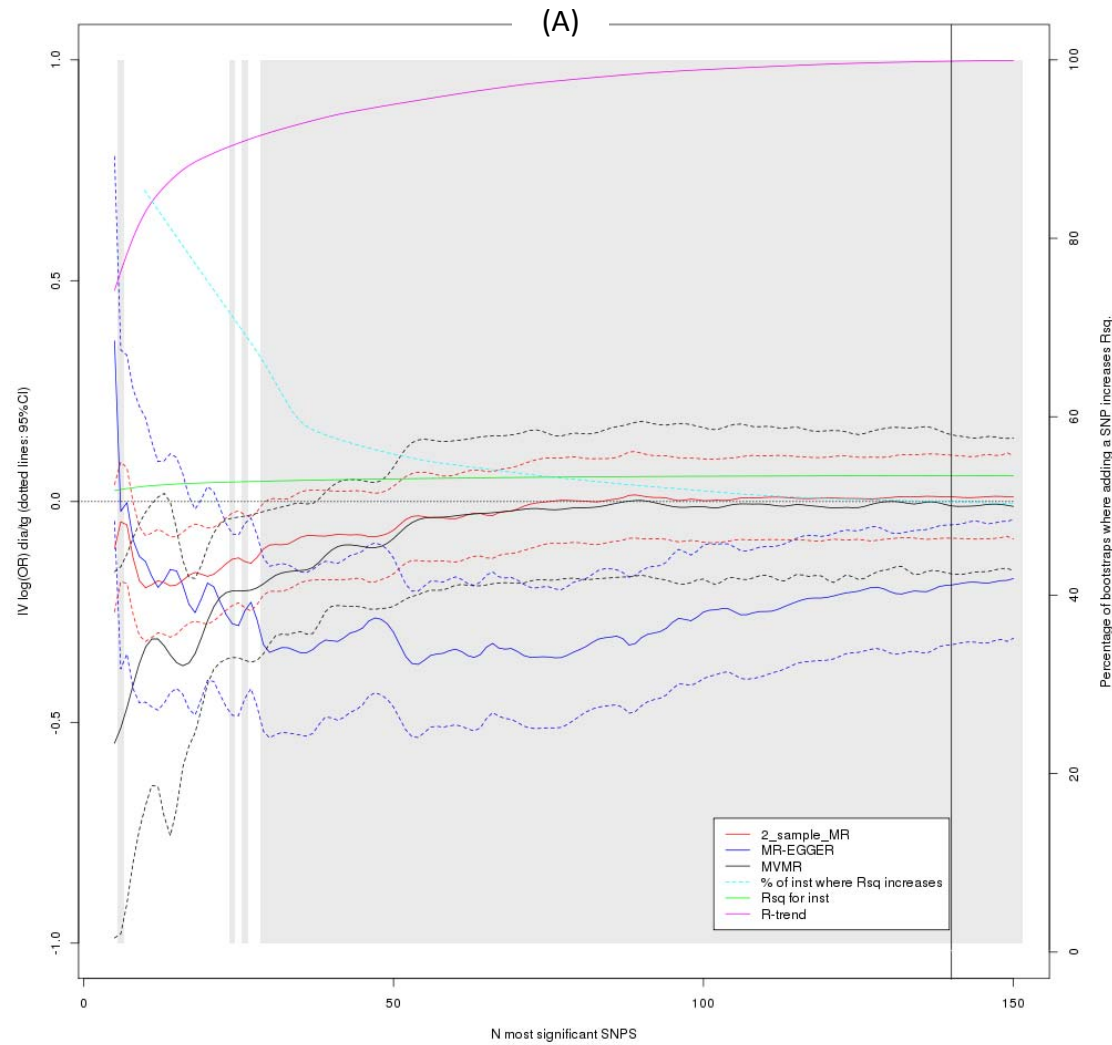
(B)

eFigure 6. TG and T2D

(A) plot to show proportion of variance of TG explained, presence of directional pleiotropy and estimates derived from the three MR approaches; (B) Scatter plot of TG and T2D associations for SNPs and super-imposed MR estimates

Figure legend as for eFigure 1.

(A)

(B)

eTable 1. The Correlation and (*P* Value) for an Association Test Between the Instrumental Variable Estimates and Exposure Estimates for the SNPs in the Chosen Instruments

Trait, #SNPs	CAD	T2D
LDL-C , 130 SNPs	0.081 (*0.274*)	-0.091 (*0.301*)
HDL-C, 140 SNPs	0.013 (*0.859*)	-0.038 (*0.659*)
TG, 140 SNPs	0.019 (*0.794*)	-0.115 (*0.179*)

Legend: A small P-value may indicate violation of the 'InSIDE rule'.

eTable 2. Magnitude of Associations That the Mendelian Randomization Analyses Had Sufficient Power (80%) to Detect (at a Bonferroni-Adjusted Alpha of 0.05/6)

Lipid	True effect (OR) which the experiment has 80% power to detect	
	CAD	T2D
LDL-C	1.056	0.923
HDL-C	0.945	0.926
TG	1.064	0.916

Legend: Values represent odds ratios for the association of a 1-SD genetically instrumented increase in LDL-C, HDL-C and TG and risk of CAD and T2D.