Supplementary Materials

Appendix A: subtracting the effects of a single cohort from the results of a fixed effects inverse variance meta-analysis.

The corrected effect size for *N*-1 cohorts ($\overline{\beta_{N-1}}$, i.e. indicated by the dash on top and index *N*-1) based on the meta-GWAS results of *N* cohorts (indicated by the dash on top of the variables and index *N*) and the results of the cohort to be left out (indicated by the index 1):

$$\overline{\beta_N} = \frac{\sum_{i=1}^{N} 1/SE_i^2 \cdot \beta_i}{\sum_{i=1}^{N} 1/SE_i^2} = \frac{1/SE_1^2 \cdot \beta_1 + \sum_{i=2}^{N} 1/SE_i^2 \cdot \beta_i}{1/\overline{SE_N}^2}$$

$$\begin{aligned}
\Leftrightarrow \quad 1/\overline{SE_N}^2 \cdot \overline{\beta_N} &= 1/SE_1^2 \cdot \beta_1 + \sum_{i=2}^{N} 1/SE_i^2 \cdot \beta_i \\
&= 1/SE_1^2 \cdot \beta_1 + \sum_{i=2}^{N} 1/SE_i^2 \cdot \frac{\sum_{i=2}^{N} 1/SE_i^2 \cdot \beta_i}{\sum_{i=2}^{N} 1/SE_i^2} \\
&= 1/SE_1^2 \cdot \beta_1 + \sum_{i=2}^{N} 1/SE_i^2 \cdot \overline{\beta_{N-1}} \\
&= 1/SE_1^2 \cdot \beta_1 + \left(\sum_{i=1}^{N} 1/SE_i^2 - 1/SE_1^2 \right) \cdot \overline{\beta_{N-1}}
\end{aligned}$$

$$\Leftrightarrow \quad \overline{\beta_{N-1}} = \frac{\left(1/SE_N^2 \cdot \overline{\beta_N} \right) - \left(1/SE_1^2 \cdot \beta_1 \right)}{\left(1/\overline{SE_N}^2 - 1/SE_1^2 \right)}.$$

The corrected SE size for *N*-1 cohorts:

$$\overline{SE_{N-1}} = \frac{1}{\sqrt{\sum_{i=2}^{N} 1/SE_i^2}} = \frac{1}{\sqrt{\sum_{i=1}^{N} 1/SE_i^2 - 1/SE_1^2}} = \frac{1}{\sqrt{1/\overline{SE_N}^2 - 1/SE_1^2}}.$$

The corrected effect allele frequency size for *N*-1 cohorts (the derivation is similar to that of the corrected effect size and hence not completely given):

$$\overline{EAF_N} = \frac{\sum_{i=1}^{N} 1/SE_i^2 \cdot EAF_i}{\sum_{i=1}^{N} 1/SE_i^2}$$

$$\Leftrightarrow \quad \overline{EAF_{N-1}} = \frac{\left(1/SE_N^2 \cdot \overline{EAF_N}\right) - \left(1/SE_1^2 \cdot EAF_1\right)}{\left(1/\overline{SE_N}^2 - 1/SE_1^2\right)}.$$

The corrected Q-statistic size for *N*-1 cohorts:

$$\begin{aligned}
\overline{Q_{N-1}} &= \sum_{i=2}^{N} 1/SE_i^2 \cdot \left(\beta_i - \overline{\beta_{N-1}}\right)^2 \\
&= \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\beta_i - \overline{\beta_{N-1}}\right)^2 - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2 \\
&= \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\beta_i - \overline{\beta_N} + \overline{\beta_N} - \overline{\beta_{N-1}}\right)^2 - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2 \\
&= \sum_{i=1}^{N} 1/SE_i^2 \cdot \Bigg[\left(\beta_i - \overline{\beta_N}\right)^2 + 2 \cdot \left(\beta_i - \overline{\beta_N}\right)\left(\overline{\beta_N} - \overline{\beta_{N-1}}\right) + \\
&\qquad + \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)^2\Bigg] - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2 \\
&= \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\beta_i - \overline{\beta_N}\right)^2 + 2 \cdot \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\beta_i - \overline{\beta_N}\right)\left(\overline{\beta_N} - \overline{\beta_{N-1}}\right) \\
&\qquad + \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)^2 - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2 \\
&= \overline{Q_N} + 2 \cdot \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)\left(\sum_{i=1}^{N} 1/SE_i^2 \cdot \beta_i - \sum_{i=1}^{N} 1/SE_i^2 \cdot \overline{\beta_N}\right) \\
&\qquad + \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)^2 - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2 \\
&= \overline{Q_N} + 2 \cdot \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)\left(\sum_{i=1}^{N} 1/SE_i^2 \cdot \overline{\beta_N} - \sum_{i=1}^{N} 1/SE_i^2 \cdot \overline{\beta_N}\right) \\
&\qquad + \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)^2 - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2 \\
&= \overline{Q_N} + \left(1/\overline{SE_N}^2 \cdot EAF_1\right) \cdot \left(\overline{\beta_N} - \overline{\beta_{N-1}}\right)^2 - 1/SE_1^2 \cdot \left(\beta_1 - \overline{\beta_{N-1}}\right)^2.
\end{aligned}$$

Appendix B: subtracting the effects of a single cohort from the results of a fixed effects sqrt(sample size) weighted meta-analysis of z-scores

The corrected z-score size for *N*-1 cohorts based on the meta-GWAS results of *N* cohorts (indicated by the dash on top of the variables and index *N*) and the results of the cohort to be left out (indicated by the index 1):

$$
\begin{aligned}
\overline{Z_{N-1}} &= \frac{\sum_{i=2}^{N} \sqrt{N_i} \cdot Z_i}{\sqrt{\sum_{i=2}^{N} N_i}} \\
&= \frac{\sum_{i=1}^{N} \sqrt{N_i} \cdot Z_i - \sqrt{N_1} \cdot Z_1}{\sqrt{\sum_{i=1}^{N} N_i - N_1}} \\
&= \frac{\sqrt{\sum_{i=1}^{N} N_i} \cdot \overline{Z_N} - \sqrt{N_1} \cdot Z_1}{\sqrt{\overline{N_N} - N_1}} \\
&= \frac{\sqrt{\overline{N_N}} \cdot \overline{Z_N} - \sqrt{N_1} \cdot Z_1}{\sqrt{\overline{N_N} - N_1}}.
\end{aligned}
$$

The corrected Q-statistic size for *N*-1 cohorts:

$$
\begin{aligned}
\overline{Q_{N-1}} &= \sum_{i=2}^{N} N_i \cdot \left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 \\
&= \sum_{i=1}^{N} N_i \cdot \left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 \\
&= \sum_{i=1}^{N} N_i \cdot \left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} + \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 \\
&= \sum_{i=1}^{N} N_i \cdot \left[\left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} \right)^2 + 2 \cdot \left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} \right) \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right) + \right. \\
&\qquad \left. + \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 \right] - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2
\end{aligned}
$$

$$= \sum_{i=1}^{N} N_i \cdot \left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} \right)^2 + 2 \cdot \sum_{i=1}^{N} N_i \cdot \left(\frac{Z_i}{\sqrt{N_i}} - \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} \right)\left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)$$

$$+ \sum_{i=1}^{N} 1/SE_i^2 \cdot \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2$$

$$= \overline{Q_N} + 2 \cdot \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)\left(\sum_{i=1}^{N} N_i \cdot \frac{Z_i}{\sqrt{N_i}} - \sum_{i=1}^{N} N_i \cdot \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)$$

$$+ \sum_{i=1}^{N} N_i \cdot \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2$$

$$= \overline{Q_N} + 2 \cdot \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)\left(\sum_{i=1}^{N} N_i \cdot \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \sum_{i=1}^{N} N_i \cdot \frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} \right)$$

$$+ \sum_{i=1}^{N} N_i \cdot \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2$$

$$= \overline{Q_N} + \sum_{i=1}^{N} N_i \cdot \left(\frac{\overline{Z_N}}{\sqrt{\overline{N_N}}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 - N_1 \cdot \left(\frac{Z_1}{\sqrt{N_1}} - \frac{\overline{Z_{N-1}}}{\sqrt{\overline{N_{N-1}}}} \right)^2 .$$

Supplementary Table 1: Sample sizes of the participating cohorts of the VgHRV consortium

Study acronym	**RMSSD**[a]		**HF/pvRSA**[b]	
	n	**%**[c]	**n**	**%**[c]
ARIC	8,262	67%	8,262	64%
CHS	759	64%	759	60%
FHS	1,944	57%	1,944	52%
FINGESTURE	n.a.		494	50%
FLEMENGHO-EPOGH	n.a.		196	49%
GenR	n.a.		392	47%
KORA S4	1,617	50%	1,617	40%
MESA	2,401	41%	n.a.	
NESDA	1,740	34%	1,740	33%
NTR	439	32%	439	31%
PIVUS	n.a.		766	27%
PREVEND	2,793	21%	2,793	15%
RS2	985	17%	n.a.	
RS1	972	13%	n.a.	
TRAILS-CC	307	12%	307	14%
TRAILS-Pop	1,222	7%	1,222	8%
ULSAM	n.a.		67	8%
YFS	1,827	0%	1,827	0%
TOTAL	25,268		22,825	

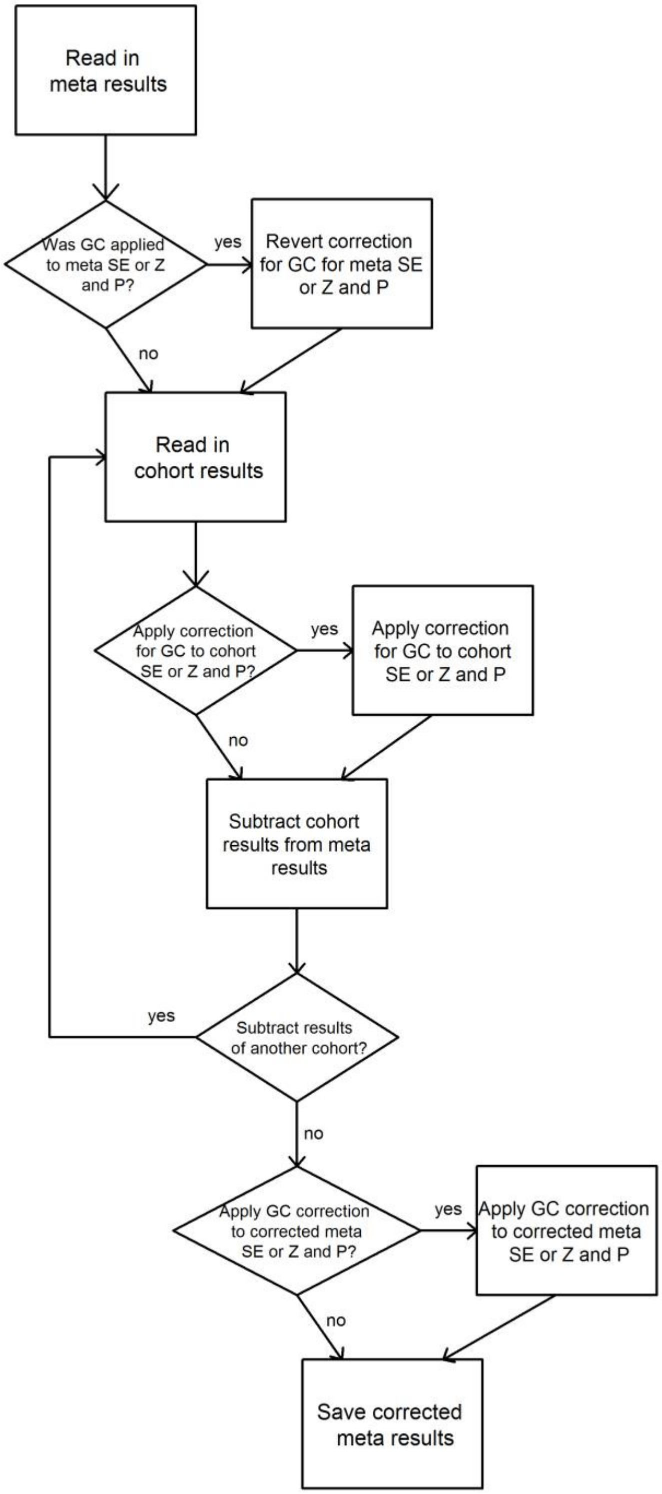
RMSSD: root mean square of successive differences; HF/pvRSA: high frequency power / respiratory sinus arrhythmia; n.a.:not available.

[a] RMSSD was analyzed using a fixed effect inverse variance meta-analysis.

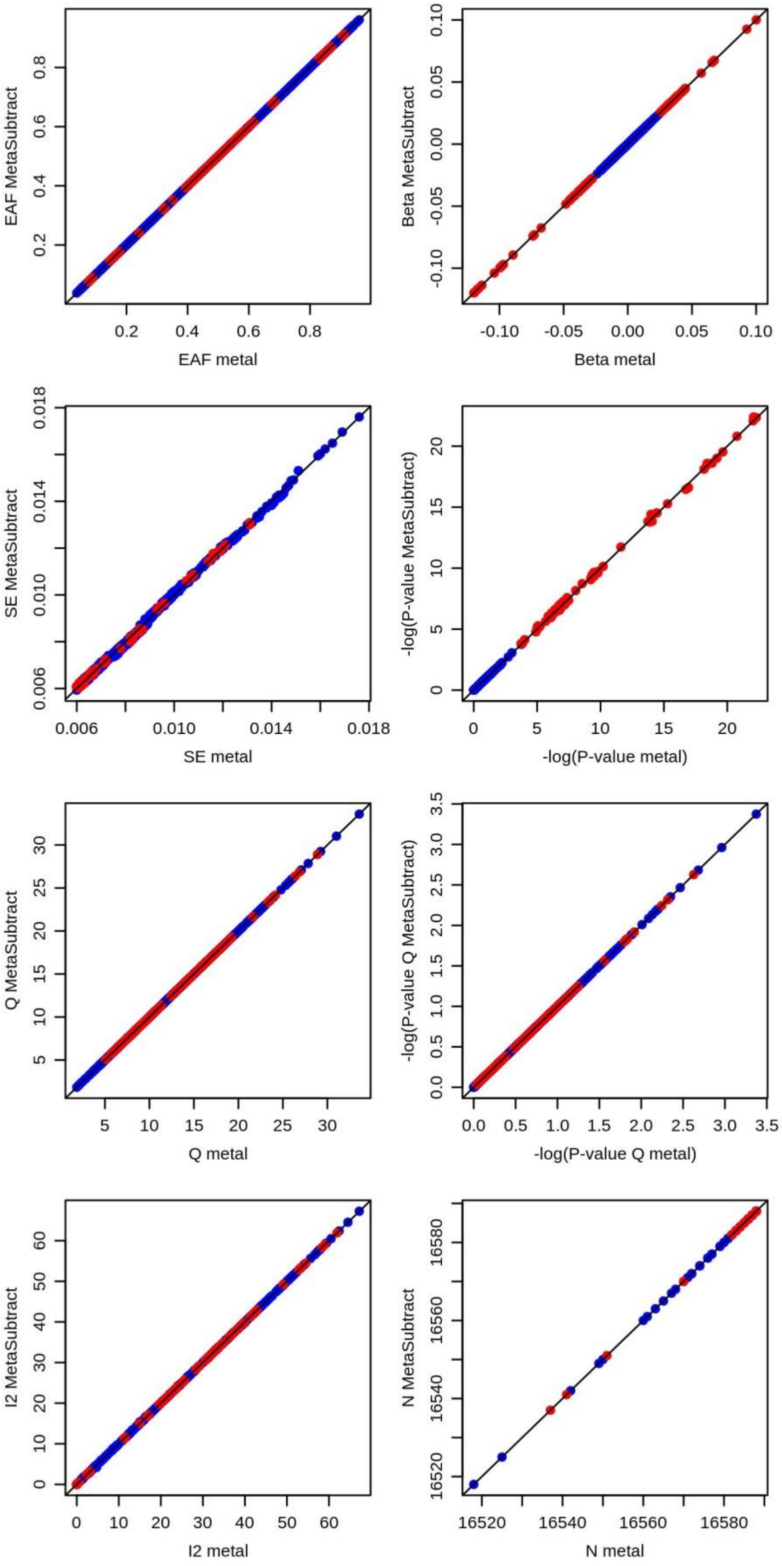
[b] HF and pvRSA was analyzed together using a fixed effect sqrt(sample size) weighted meta-analysis of z-scores.

[c] Percentage of remaining samples after exclusion if this and (alphabetically) preceding cohorts.

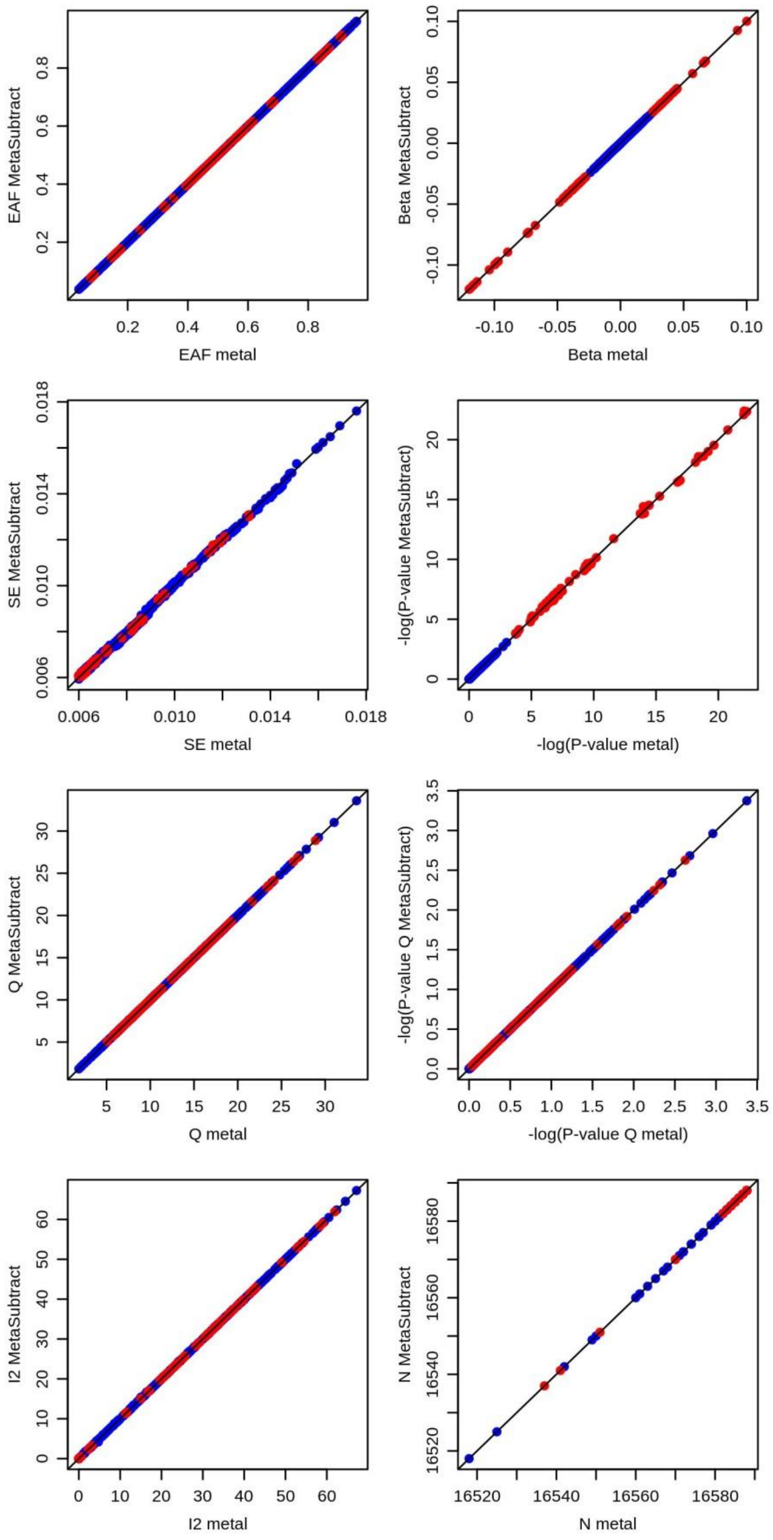
Supplementary Figure 1. Workflow diagram of MetaSubtract



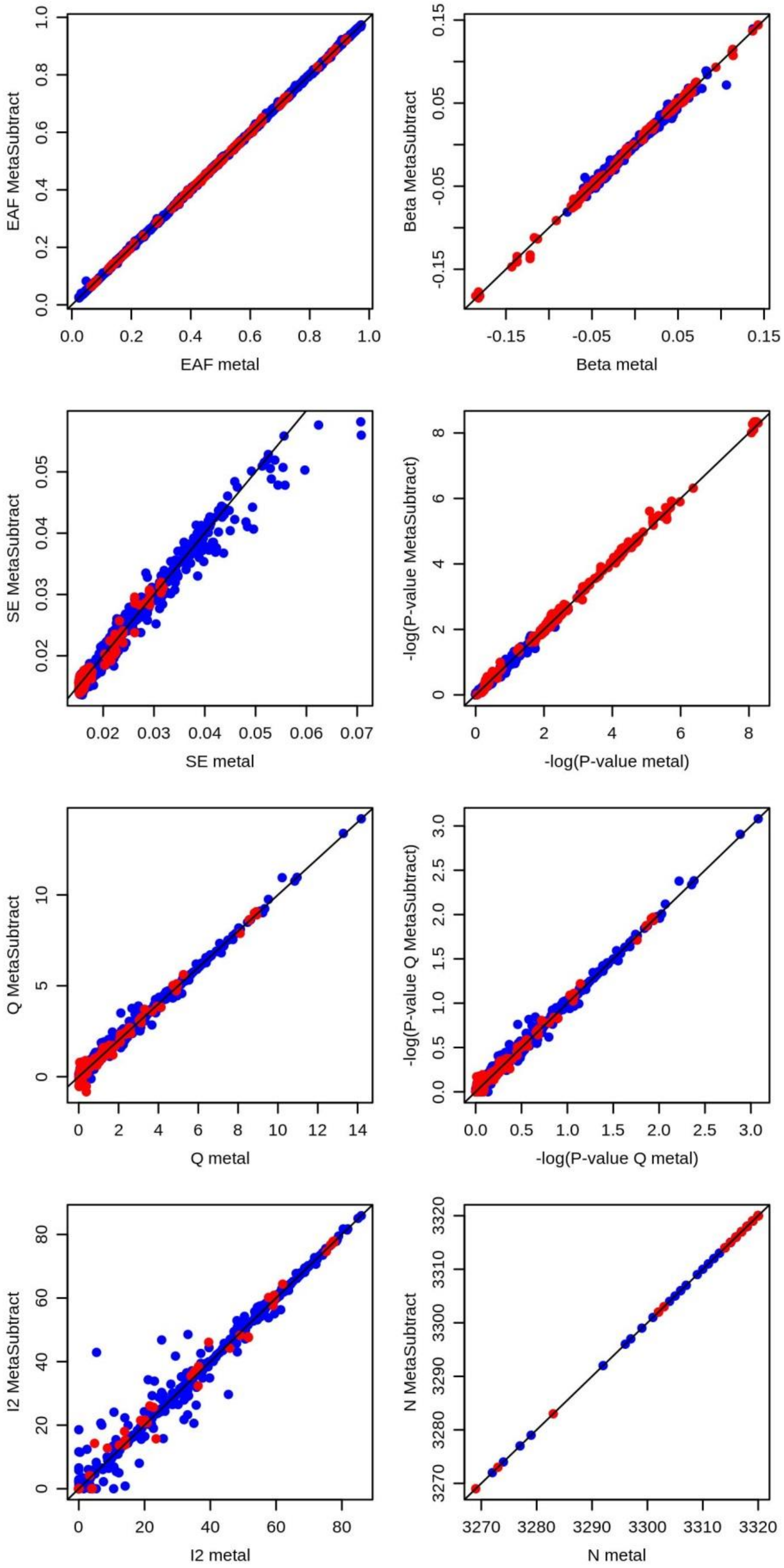
Supplementary Figure 2. Comparisons between the meta-GWAS results calculated with METAL (on the x-axis) and MetaSubtract (on the y-axis) for an inverse variance weighted meta-analysis using double genomic control correction when one (of 13) cohort was left out. The red dots represent variants that were initially genome-wide significant, the blue ones the non-significant ones. The line indication the diagonal y=x. EAF: effect allele frequency; SE: standard error of Beta.



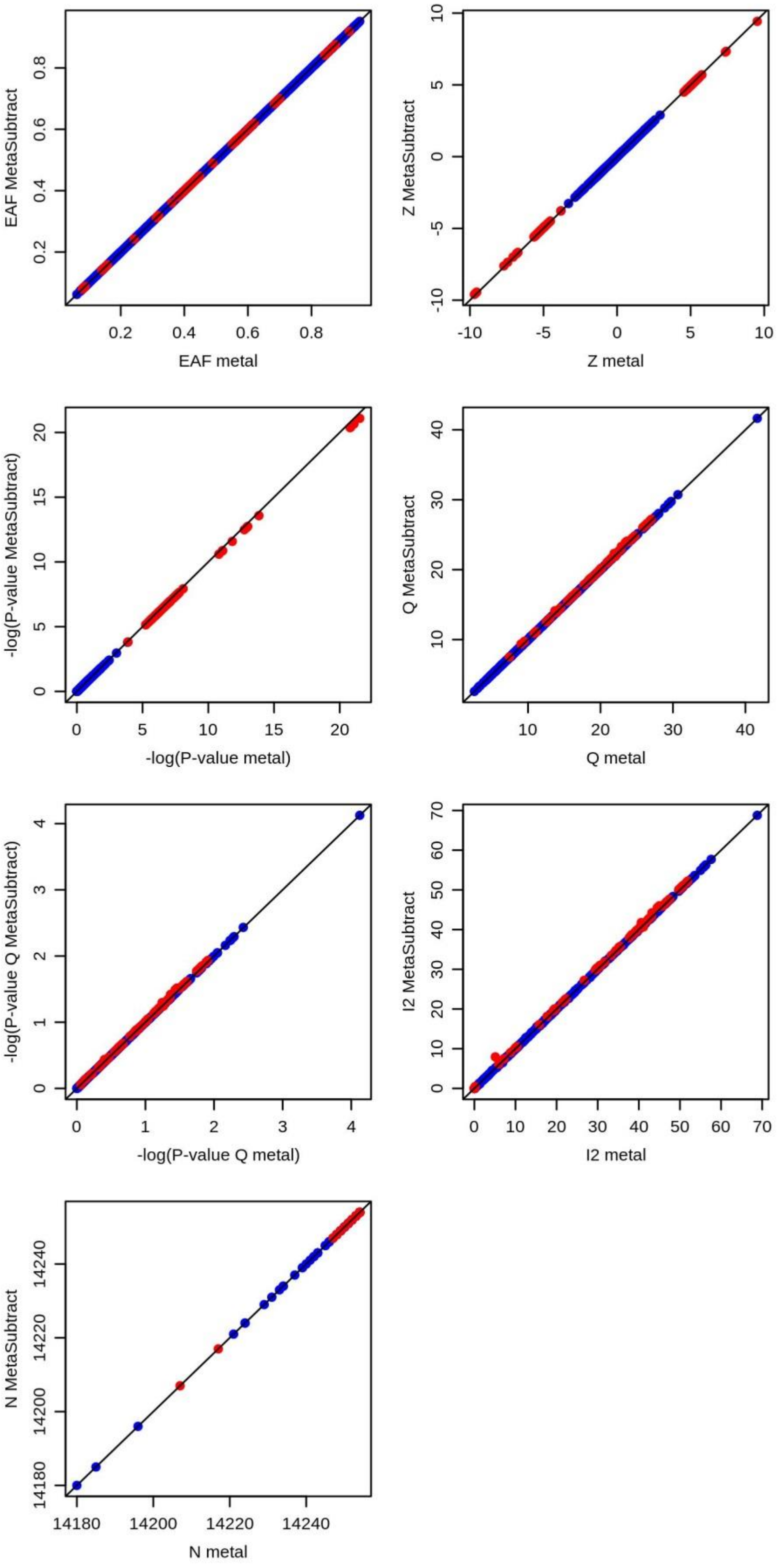
Supplementary Figure 3. Comparisons between the meta-GWAS results calculated with METAL (on the x-axis) and MetaSubtract (on the y-axis) for an inverse variance weighted meta-analysis using double genomic control correction when five (of 13) cohorts were left out. The red dots represent variants that were initially genome-wide significant, the blue ones the non-significant ones. The line indication the diagonal y=x. EAF: effect allele frequency; SE: standard error of Beta.



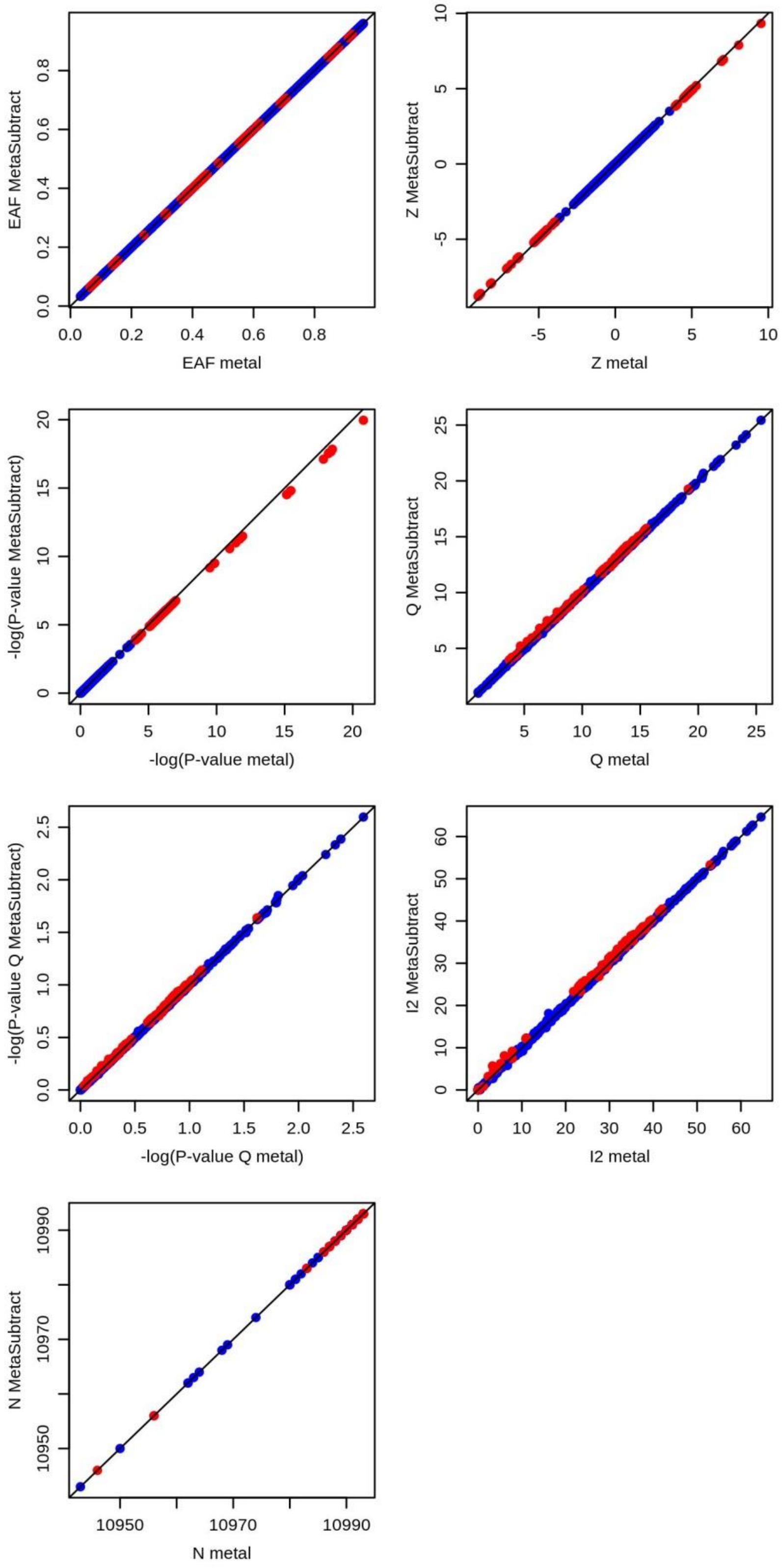
Supplementary Figure 4. Comparisons between the meta-GWAS results calculated with METAL (on the x-axis) and MetaSubtract (on the y-axis) for an inverse variance weighted meta-analysis using double genomic control correction when ten (of 13) cohorts were left out. The red dots represent variants that were initially genome-wide significant, the blue ones the non-significant ones. The line indication the diagonal y=x. EAF: effect allele frequency; SE: standard error of Beta.



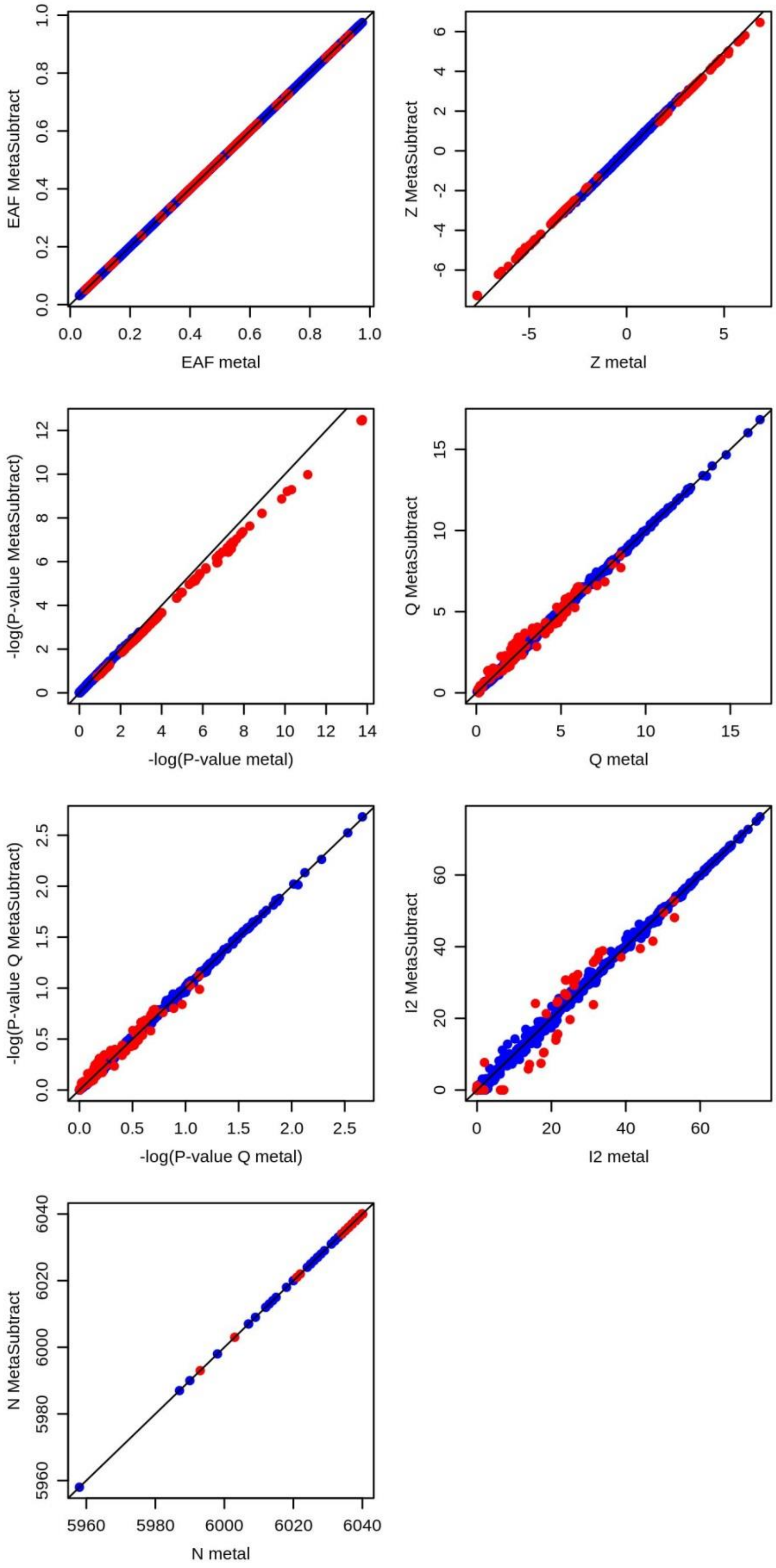
Supplementary Figure 5. Comparisons between the meta-GWAS results calculated with METAL (on the x-axis) and MetaSubtract (on the y-axis) for a sqrt(sample size) weighted meta-analysis of z-scores using double genomic control correction when one (of 15) cohort was left out. The red dots represent variants that were initially genome-wide significant, the blue ones the non-significant ones. The line indication the diagonal y=x. EAF: effect allele frequency.



Supplementary Figure 6. Comparisons between the meta-GWAS results calculated with METAL (on the x-axis) and MetaSubtract (on the y-axis) for a sqrt(sample size) weighted meta-analysis of z-scores using double genomic control correction when five (of 15) cohorts were left out. The red dots represent variants that were initially genome-wide significant, the blue ones the non-significant ones. The line indication the diagonal y=x. EAF: effect allele frequency.



Supplementary Figure 7. Comparisons between the meta-GWAS results calculated with METAL (on the x-axis) and MetaSubtract (on the y-axis) for a sqrt(sample size) weighted meta-analysis of z-scores using double genomic control correction when ten (of 15) cohorts were left out. The red dots represent variants that were initially genome-wide significant, the blue ones the non-significant ones. The line indication the diagonal y=x. EAF: effect allele frequency.



Supplementary Figure 8: Variance explained by PRSs for (a) RMSSD and (b) HF/pvRSA in the TRAILS cohort (n=1,179 and 1,182, respectively) derived using corrected effect sizes from the VgHRV consortium's calculated by METAL (blue line) and by MetaSubtract (red line). The genetic data were clumped (r^2=0.1; window=100kb) using the corresponding VgHRV meta-GWAS summary statistics. PLINK was used for clumping and PRS calculation. Age, sex, and the first five principle components were used as covariates in the linear regression analysis in R. The variance explained presented in the plots is the difference in R^2 between the model with and without the PRS.