

Supplementary Materials

Table S1. Format and details of source data from the 8 studies included in the meta-analysis.

Study (year)	Original unit of estimated HR for GDF-15 concentration	Expression of average GDF-15 levels	Measurement of dispersion of GDF-15 levels (pg/ml)		GDF-15 quantification assay	Ref.
Carlsson et al. (2020)	Per SD of \log_2 (GDF-15)	N/A	N/A		Multiplex CVD I 96x96 kit (Olink Proseek)	[14]
Cavusoglu et al. (2015)	Per SD of \log (GDF-15)	Median (25 th , 75 th)	PLTP <17.44: 1134 (855, 1557)	PLTP \geq 17.44: 1365 (961, 2050)	ELISA (R&D Systems)	[24]
Frimodt-Møller et al. (2018)	Per SD of \log_2 (GDF-15)	Median (IQR)	1533 (1132–2236)		Elecsys 2010 (Roche)	[13]
Gerstein et al. (2015)	Per SD of \log (GDF-15)	N/A	N/A		Human DiscoveryMAP (Rules-Based Medicine)	[25]
Pavo et al. (2016)	Per IQR of \log (GDF-15)	Median (IQR)	1391 (881–2176)		ELISA (Roche)	[26]
Resl et al. (2016)	Per \log (GDF-15)	Median (IQR)	1474 (906–2178)		ELISA (Roche)	[27]
Sen et al. (2021)	Per doubling \log (GDF-15)	Median (IQR)	1774 (1242–2514)		Elecsys (Roche)	[20]
Sharma et al. (2020)	Per \log_2 (GDF-15)	Median	1246		ELISA (Roche)	[28]

ELISA, enzyme-linked immunosorbent assay; GDF-15, growth differentiation factor-15; HR, hazard ratio; IQR, interquartile range; \log , logarithmic transformations; N/A, not applicable or available; P, plasma; PLTP, phospholipid protein; S, serum; SD, standard deviation.

Table S2. Summary table of included studies with harmonized hazard ratios and the harmonization methodology used (see text for details)

Study (year)	Original unit of estimated HR for GDF-15 concentration	Expression of average GDF-15 levels	Original estimate of CVD outcomes*	Harmonized estimate of CVD outcomes*	Original estimate of all-cause mortality*	Harmonized estimate of all-cause mortality*	Harmonization methodology	[Ref.]
Carlsson et al. (2020)	Per SD of log ₂ (GDF-15)	N/A	1.34 (0.96–1.87)	1.34 (0.97–1.86)	N/A	N/A	N/A	[14]
Cavusoglu et al. (2015)	Per SD of log(GDF-15)	Median (25 th , 75 th)	N/A	N/A	1.91 (1.47–2.49)	1.57 (1.31–1.88)	Eqn. (1)	[24]
Frimodt-Møller et al. (2018)	Per SD of log ₂ (GDF-15)	Median (IQR)	1.25 (0.85–1.84)	1.25 (0.85–1.84)	1.90 (1.24–2.89)	1.90 (1.24–2.91)	N/A	[13]
Gerstein et al. (2015)	Per SD of log(GDF-15)	N/A	1.18 (1.12–1.24)	1.12 (1.08–1.16)	1.29 (1.20–1.38)	1.19 (1.13–1.25)	Eqn. (1)	[25]
Pavo et al. (2016)	Per IQR of log(GDF-15)	Median (IQR)	2.23 (1.79–2.78)	1.74 (1.50–2.03)	3.55 (2.60–4.84)	2.41 (1.94–2.99)	Eqn. (1), (2) & (3)	[26]
Resl et al. (2016)	Per log(GDF-15)	Median (IQR)	1.37 (1.12–1.68)	1.24 (1.08–1.43)	N/A	N/A	Eqn. (1), (2) & (3)	[27]
Sen et al. (2021)	Per doubling log(GDF-15)	Median (IQR)	1.20 (1.04–1.38)	1.05 (1.01–1.09)	1.32 (1.14–1.54)	1.08 (1.03–1.12)	Eqn. (1), (2) & (3)	[20]
Sharma et al. (2020)	Per log ₂ (GDF-15)	Median	1.15 (1.04–1.27)	1.13 (1.03–1.23)	N/A	N/A	Eqn. (2) & (3)	[28]

Eqn., equation; HR, hazard ratio; IQR, interquartile range; log, logarithmic transformations; N/A, not applicable/available, ref., reference number, SD, standard deviation.

*effect size estimates were expressed in adjusted hazard ratios (95% confident interval).

Table S3. Assessment of quality of studies using the Newcastle-Ottawa scale.

		Study [Ref. no.]							
		Carlsson et al. [14]	Cavusoglu et al.[24]	Frimodt-Møller et al. [13]	Gerstein et al. [25]	Pavo et al. [26]	Resl et al. [27]	Sen et al. [20]	Sharma et al. [28]
Components									
Selection	Representative of the exposed cohort	★	★	★	★	★	★	★	★
	Selection of external cohort	★	★	–	–	–	–	★	★
	Ascertainment of exposure ^a	★	★	★	★	★	★	★	★
	Outcome of interest not present at the start of the study ^b	★	–	★	★	★	★	★	★
Comparability	Comparability of cohorts ^c : main factor	★	★	★	★	–	★	★	★
	Comparability of cohorts ^d : additional factor	★	★	★	★	–	★	★	★
Outcome	Assessment of outcome	★	★	★	★	★	★	★	★
	Sufficient follow-up time ^e	–	★	★	★	★	★	★	★
	Adequacy of follow-up	★	★	★	★	★	★	★	★
Total score (out of 9)		8	8	8	8	8	6	8	9

A total score of ≥6 points indicates good quality.

^aOne star was assigned if details about measurement of blood GDF-15 concentration were provided.

^bOne star was assigned if a CVD outcome(s) of interest was not available at the start of study.

^cOne star was assigned for a study that controlled for age.

^dOne star was assigned to a study that controlled for additional factors apart from age.

^eOne star was assigned for mean or median follow-up duration of ≥5 years. –, not applicable

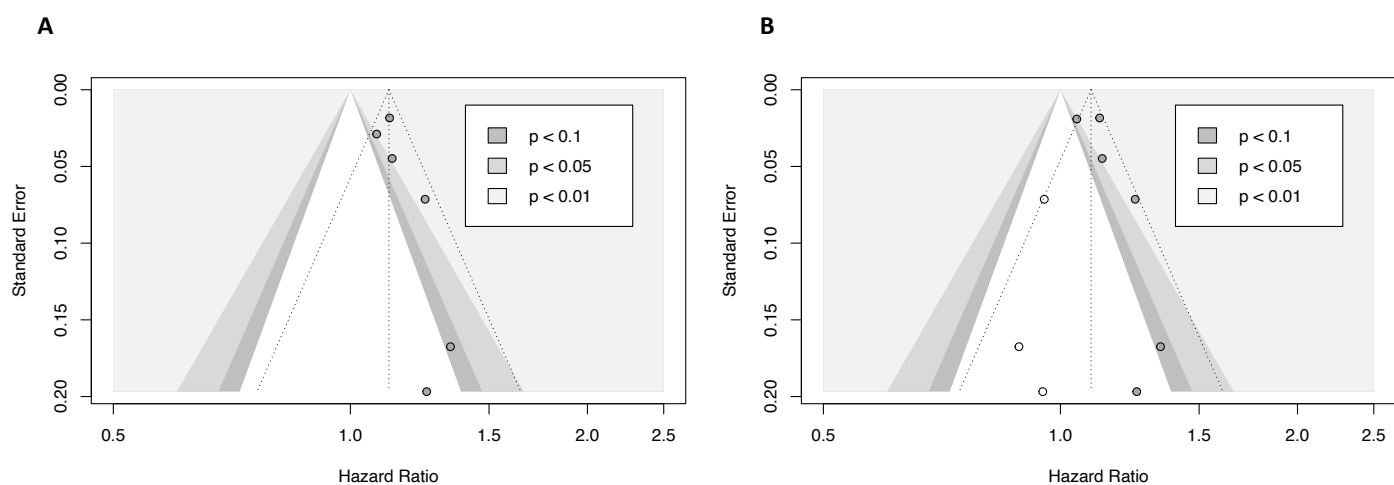


Figure S1. Funnel plots assessing publication bias in the meta-analysis of A) MACE. Effect corrected by small-study bias by Duval and Tweedie's trim and fill test B) shared similar size as pooled effect size A).