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Evaluation of GDF15 as a therapeutic target of cardiometabolic diseases in human: A Mendelian randomization study

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ABSTRACT

Background: Growth differentiation factor 15 (GDF15) is a key regulator of body weight in animals by regulating food intake. Its receptor, glial cell-derived neurotrophic factor receptor alpha-like (GFRAL), was identified recently. Pre-clinical studies showed that it is a promising therapeutic target for cardiometabolic diseases and anorexia/cachexia. Although many pharmaceutical companies are developing drugs targeting GFRAL, whether the findings from animal studies can be extrapolated to man is unknown. Mendelian randomization (MR) is useful in investigating the relationship between risk factors and disease outcomes. We aimed to use a two-sample MR approach to evaluate the clinical usefulness of targeting GDF15 for cardiometabolic diseases.

Methods: Genetic instruments and summary statistics for MR analyses were obtained from a large genome-wide association study (GWAS) of GDF15 and cardiometabolic outcomes (n = 27,394 to 644,875), including body mass index, waist-hip ratio, waist circumference, whole-body lean mass, fat percentage, Type 2 Diabetes, fasting glucose, glycated haemoglobin, fasting insulin, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglycerides, coronary artery disease, and estimated BMD (eBMD). Conventional inverse variance weighted (IVW) method was adopted to obtain the causal estimates of GDF-15 with different outcomes; weighted median and MR-egger were used for sensitivity analyses.

Findings: There was null association between GDF15 levels and anthropometric outcomes. One SD increase in genetically-determined GDF15 was significantly associated with reduced HDL-C (beta: -0.048SD; SE: 0.014; P = .001) but the result was not significant in sensitivity analyses. A consistent significant causal association was observed between GDF15 and eBMD in IVW (beta: 0.026 SD; SE: 0.005; P < .001) and subsequent sensitivity analyses.

Interpretation: This study sheds lights on the potential of drugs targeting the GDF15/GFRAL axis. It suggested that the effect of targeting GDF15/GFRAL axis for weight control in human may be different from the effects observed in animal studies. GDF15 treatment may improve BMD in humans.

Fund: No specific funding was received for this study.

1. Introduction

GDF15 has long been known to be involved in energy metabolism, body weight regulation, and cachexia [1,2]. However, there are no drugs in clinical use targeting GDF15, largely because its receptor has not been identified until recently. In 2017, four pharmaceutical companies simultaneously reported the identification of the receptor of GDF15, glial cell-derived neurotrophic factor receptor alpha-like (GFRAL) [3–6]. Stimulating GFRAL is believed to decrease food intake, and hence promote weight loss and improve metabolic parameters [1,2]. On the other hand, antagonising GFRAL is believed to increase food intake, which could be beneficial in people with anorexia and cancer cachexia [1]. Thus, agents targeting GDF15/GFRAL axis are actively under development [1].

All of the currently known biological effects of GDF15/GFRAL axis are derived from animal studies and human association studies. However, it is well documented that findings from animal studies may not be translated to human, while human association studies are prone to bias due to reverse causation and unmeasured confounders. For example, HDL-cholesterol was considered an excellent target for reducing cardiovascular diseases risk based on evidence from animal and human association studies [7]. However, none of the HDL-raising agents reduces risk of cardiovascular diseases in clinical trials. The costly failure of the cholesterol ester transfer protein (CETP) inhibitors that raise HDL

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Research in context

Evidence before this study

Growth differentiation factor 15 (GDF15) has long been known to be involved in energy metabolism, body weight regulation, and cachexia. In 2017, four pharmaceutical companies simultaneously reported the identification of the receptor of GDF15, glial cell-derived neurotrophic factor receptor alpha-like (GFRAL). Preclinical animal studies and human association studies on the biological effects of GDF15/GFRAL axis showed that it is a promising therapeutic target for cardiometabolic diseases and anorexia/cachexia. Thus, agents targeting GDF15/GFRAL axis are actively under development. However, it is well documented that findings from animal studies may not be translated to humans, while human association studies are prone to bias due to reverse causation and unmeasured confounders. One important example was HDL-raising drugs. Increasing HDL-C levels had long been considered as a therapeutic target for cardiovascular disease (CVD), based on evidence generated from animal and human association studies. However, subsequent RCTs since 2012 showed that HDL-raising drugs failed to reduce the risk of CVD. Indeed, Mendelian randomization (MR) analysis in 2012 showed that serum HDL-C levels are not associated with CVD events, suggesting that conducting MR study before RCT may be necessary and important clinically. Therefore, in the current study, we aimed to evaluate the causal relationship between serum GDF15 and cardiometabolic phenotypes in human using the MR approach.

Added value of this study

In this two-sample MR analysis, no causal effect of GDF15 was observed with any anthropometric measurements, including body mass index, waist-hip ratio, waist circumference, whole-body lean mass and fat percentage. These imply that physiological variations in GDF15 in humans has limited impact on body weight and fat metabolism. Our findings suggested that the effect of targeting GDF15/GFRAL axis for weight control in human may be different from the effects observed in animal studies.

Implications of all the available evidence

There are currently at least four pharmaceutical companies developing pharmacological agents targeting GDF15/GFRAL axis. Learning from previous experience on HDL-raising drugs, we realized that the costly failure of the cholesterol ester transfer protein (CETP) inhibitors that raise HDL could have been averted if MR data on the relationship between HDL and cardiovascular outcomes had been available earlier. It is extremely important at this stage to evaluate if GDF15 is causally related to cardiometabolic phenotypes in human before investing a tremendous amount of resources and initiating large randomised controlled clinical trials. Our study showed that the role of GDF15/GFRAL axis in weight regulation in humans may not be as important as previously thought, which is important and indicative for subsequent RCTs.

could have been averted if Mendelian randomization (MR) data on the relationship between HDL and cardiovascular outcomes had been available earlier. Thus, it is extremely important at this stage to evaluate if GDF15 is causally related to cardiometabolic phenotypes in human before investing a tremendous amount of resources and initiating large randomised controlled clinical trials. In the current study, we aimed to evaluate the causal relationship between serum GDF15 and cardiometabolic phenotypes in human using the MR approach.

2. Materials and methods

2.1. Genetic instruments of GDF15

The design of this MR study is illustrated in Supplementary Fig. 1. Three independent SNPs (rs888663, rs1054564, and rs749451) of GDF15 were identified in previous genome-wide association study (GWAS) of circulating GDF-15 levels [8] and used for MR study [9]. We updated the estimates of these SNPs using the data from the latest meta-analysis of GWAS of GDF-15 levels (Table 1) [10]. These SNPs explained ~7.9% of the variance of the circulating levels of GDF15; explained variance explained was calculated using the equation: $2 \times MAF \times (1\text{-}MAF) \times (\text{beta estimate})^2$.

2.2. Clinical outcomes and data sources for MR

The primary outcomes were anthropometric measurements, including body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), whole-body lean mass (WBLM) and fat percentage. Secondary outcomes were cardiometabolic phenotypes, which included glycemic traits (Type 2 diabetes (T2D), fasting glucose (FG), fasting insulin (FI), and glycated haemoglobin (A1c)), lipids (HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG)), coronary artery disease (CAD), and estimated bone mineral density (eBMD). The current MR study utilized summary statistics of the genetic instruments of GDF-15 from the GWAS or genome-wide meta-analysis of BMI [11], WHR [12], WC [12], WBLM [13], fat percentage [14], T2D [15], FG [16], FI [16], A1c [17], HDL-C [18], LDL-C [18], TC [18], TG [18], CAD [19] and eBMD [20]. The summary statistics for WBLM was in kg. To convert the unit into SD, we derived the average SD (~8.78 kg) in WBLM based on baseline characteristics of 53 studies included in the GWAS meta-analysis. The effect alleles were matched between the summary data of GDF-15 and the clinical outcomes.

2.3. Statistical analyses

MR analysis was conducted to infer causality of a risk factor on outcome using the R package "Mendelian Randomization" [21]. Primary analysis was done using the conventional inverse variance weighted (IVW) method [22]. Weighted Median [23] and MR-Egger [24] were used for sensitivity analysis. Although MR-PRESSO is an emerging approach to identify outliers [25], a minimum of 4 SNPs are required to run MR-PRESSO, thus we were not able to identify outliers using this approach.

For the genetic instruments of GDF15, the pairwise linkage disequilibrium (in terms of r^2) of these three SNPs were estimated to be 0.299 (rs888663-rs749451), 0.136 (rs1054564- rs749451), and 0.051 (rs888663-rs1054564) using the ensembl LD calculator (https://asia.ensembl.org/Homo_sapiens/Tools/LD), based on 1000GENOMES: phase_3:CEU population. Although the LDs were generally low, including rs749451 may still lead to over-estimation (which had a r^2 of 0.136 and 0.299 with two other SNPs). Therefore, we performed a sensitivity analysis by excluding rs749451 in the MR analysis. In the sensitivity analysis, only IVW was conducted since weighted median and MR-Egger methods require at least 3 SNPs in the analysis.

To correct for multiple testing, Bonferroni correction was applied and 2-sided *P*-value $<2.78 \times 10^{-3}$ (=0.05/18) was considered statistically significant. All analyses were conducted in R.

2.4. Power calculation

An online web tool, namely, mRnd (http://cnsgenomics.com/shiny/mRnd/) [26], was used to perform power calculation in this MR study. A conservative approach was adopted: for each outcome, in case the sample size differed among the three genetic instruments in the

Table 1
Summary statistics of the 3 genetic instruments of GDF15 with different phenotypes.

	Phenotypes	SNPs					
		rs749451 (C/T)		rs888663 (T/G)		rs1054564 (C/G)	
		Beta	SE	Beta	SE	Beta	SE
Anthropometry	GDF15	0.2129	0.0186	0.3012	0.0243	0.3083	0.0255
	BMI	0.0036	0.0018	−0.0031	0.0022	0.0006	0.0025
	WHR	0.0035	0.0046	0.0037	0.0059	0.0071	0.0063
	WC	0.0024	0.0047	−0.0006	0.006	0.003	0.0063
	WBLM	−0.0511	0.0382	−0.0935	0.0476	−0.0237	0.0443
	Fat percentage	−0.0037	0.0061	−0.0036	0.0077	−0.0038	0.0079
Glycaemic trait	T2D[a] (BMI adjusted)	0.0045	0.015	−0.0023	0.019	0.022	0.021
	T2D[a]	0.0044	0.013	−0.016	0.016	0.015	0.018
	FG (BMI adjusted)	−0.0017	0.0036	0.0037	0.0047	−0.0005	0.0049
	FG	0.0004	0.0035	0.0055	0.0046	0.0005	0.0047
	A1c	−0.0012	0.0019	0.0001	0.0024	0.0075	0.0026
	FI (BMI adjusted)	0.0055	0.0029	0.0028	0.0038	0.0022	0.0042
	FI	0.0084	0.0035	0.0051	0.0046	0.0032	0.0049
Lipids	LDL-C	−0.0062	0.0061	−0.0091	0.0078	0.0022	0.0079
	HDL-C	−0.006	0.0057	−0.0076	0.0075	−0.0258	0.0072
	TC	−0.0059	0.0059	−0.0108	0.0076	−0.0021	0.0077
	TG	0.011	0.0054	0.0012	0.0069	0.007	0.0071
	CAD[a]	−0.0109	0.0086	−0.0296	0.0108	0.0077	0.0121
	eBMD	0.0058	0.0019	0.013	0.0024	0.0013	0.0026

Body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), whole-body lean mass (WBLM), Type 2 Diabetes (T2D), fasting glucose (FG), glycated haemoglobin (A1c), fasting insulin (FI), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), coronary artery disease (CAD), and estimated bone mineral density (eBMD).
[a] Beta estimates are reported as ln(OR)s.

GWAS/meta-analysis of GWAS, the smallest sample size was applied in power calculation.

2.5. Role of the funding source

No specific funding was received for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

The beta-estimates of three independent SNPs included in the study with anthropometric measurements and cardiometabolic phenotypes are provided in Table 1.

For primary outcomes (Table 2), no significant association was observed with anthropometric measurements, although nominal association was observed between GDF15 and WBLM (beta-estimate: -0.022 SD; SE: 0.01; $P = .031$). A similar estimate was observed using the weighted median method but not MR-Egger. No significant pleiotropic effect was observed in the MR-Egger intercept. For secondary outcomes, one SD increase in genetically-determined GDF15 levels was significantly associated with reduced HDL-C after Bonferroni correction (beta-estimate: −0.048SD; SE: 0.014; $P = .001$); the association became insignificant in weighted median and MR-Egger analyses. Nominal significant association between GDF15 and CAD was observed (OR: 0.956; 95% CI: 0.916–0.999; $P = .043$); while the association became insignificant in weighted median and MR-Egger analyses. A significant association was also observed with eBMD upon Bonferroni correction (beta-estimate: 0.026 SD; SE: 0.005; $P < .001$); a similar

Table 2
Results from two-sample Mendelian randomization analysis using 3 genetic instruments of GDF15.

	Variables	IVW			Weighted median			MR-Egger				
		Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Intercept	P-value
Anthropometry	BMI	0.002	0.005	0.738	0.000	0.006	0.970	−0.054	0.033	0.101	0.015	0.087
	WHR	0.017	0.012	0.148	0.016	0.014	0.235	0.021	0.069	0.760	−0.001	0.955
	WC	0.006	0.012	0.620	0.009	0.014	0.534	−0.012	0.070	0.859	0.005	0.790
	WBLM	−0.022	0.010	0.031	−0.025	0.012	0.040	−0.002	0.067	0.973	−0.006	0.758
	Fat percentage	−0.014	0.015	0.373	−0.012	0.017	0.480	0.000	0.089	0.999	−0.004	0.878
Glycaemic trait	T2D[a] (BMI adjusted)	1.027	0.952–1.107	0.493	1.019	0.932–1.115	0.682	1.058	0.681–1.642	0.803	−0.008	0.894
	T2D[a]	1.001	0.938-1.068	0.974	1.013	0.937–1.096	0.737	0.943	0.575–1.545	0.815	0.016	0.808
	FG (BMI adjusted)	0.001	0.009	0.881	−0.001	0.011	0.959	0.035	0.054	0.516	−0.009	0.527
	FG	0.008	0.009	0.405	0.002	0.011	0.863	0.027	0.052	0.611	−0.005	0.711
	A1c	0.007	0.005	0.179	0.002	0.007	0.821	0.055	0.056	0.331	−0.013	0.385
	FI (BMI adjusted)	0.014	0.008	0.071	0.009	0.009	0.322	−0.033	0.044	0.460	0.012	0.285
	FI	0.022	0.009	0.018	0.017	0.012	0.147	−0.046	0.053	0.380	0.018	0.190
Lipids	LDL-C	−0.016	0.015	0.284	−0.029	0.019	0.129	0.034	0.090	0.702	−0.014	0.566
	HDL-C	−0.048	0.014	0.001	−0.032	0.019	0.084	−0.128	0.139	0.357	0.022	0.56
	TC	−0.023	0.015	0.122	−0.027	0.018	0.124	−0.003	0.087	0.976	−0.006	0.811
	TG	0.024	0.014	0.074	0.021	0.017	0.218	−0.073	0.080	0.358	0.026	0.214
	CAD[a]	0.956	0.916-0.999	0.043	0.946	0.890–1.005	0.073	0.993	0.554–1.779	0.981	−0.010	0.898
	eBMD	0.026	0.005	<0.001	0.029	0.008	<0.001	0.016	0.095	0.867	0.003	0.914

Body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), whole-body lean mass (WBLM), Type 2 Diabetes (T2D), fasting glucose (FG), glycated haemoglobin (A1c), fasting insulin (FI), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), coronary artery disease (CAD), and estimated bone mineral density (eBMD).
[a] Data are reported as OR and 95% CI.

Table 3
Sensitivity analysis using 2 genetic instruments of GDF15.

Variables	IVW (sensitivity analysis)		
	Estimate	SE	P-value
BMI	−0.005	0.005	0.375
WHR	0.017	0.014	0.218
WC	0.004	0.014	0.794
WBLM	−0.021	0.012	0.086
Fat percentage	−0.012	0.018	0.502
T2D[a] (BMI adjusted)	1.029	0.940–1.127	0.533
T2D[a]	0.993	0.919–1.073	0.858
FG (BMI adjusted)	0.005	0.011	0.624
FG	0.010	0.011	0.358
A1c	0.012	0.006	0.044
FI (BMI adjusted)	0.008	0.009	0.370
FI	0.014	0.011	0.211
LDL-C	−0.011	0.018	0.534
HDL-C	−0.056	0.017	0.001
TC	−0.021	0.018	0.233
TG	0.013	0.016	0.413
CAD[a]	0.959	0.910–1.010	0.112
eBMD	0.025	0.006	<0.001

Body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), whole-body lean mass (WBLM), Type 2 Diabetes (T2D), fasting glucose (FG), glycated haemoglobin (A1c), fasting insulin (FI), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), coronary artery disease (CAD), and estimated bone mineral density (eBMD).

[a] Data are reported as OR and 95% CI.

significant result was observed in weighted median analysis but not in MR-Egger analysis. No significant pleiotropic effect was observed in the MR-Egger intercept.

In sensitivity analysis using two independent SNPs (Table 3), significant associations were observed with HDL-C (beta-estimate: −0.056 SD; SE: 0.017; $P = .001$) and eBMD (beta-estimate: 0.025 SD; SE: 0.006; $P < .001$) after correcting for multiple testing. Nominal significant association was observed with A1c (beta-estimate: 0.012 SD; SE: 0.006; $P = .044$). Null association was observed for other outcomes.

4. Discussion

In this two-sample MR analysis, no causal effect of GDF15 was observed with any anthropometric measurements. The only consistent causal effect of GDF15 was observed with eBMD, while the effect on HDL-C was inconsistent. These findings suggested that the effect of targeting GDF15/GFRAL axis for weight control in human may be different from the effects observed in animal studies.

In this study, we used three common SNPs affecting circulating levels of GDF15 to conduct the MR analysis, but failed to demonstrate association between GDF15 and major cardiometabolic traits, except BMD. The null association could be due to the fact that GFRAL, known as a receptor for GDF15, is only localized in the area postrema of the brain in rodents [6]. Deficiency of the GFRAL in peripheral tissues may explain the results of this study, which have shown that GDF15 has no effect on improvement of anthropometric and glycemic traits. On the other hand, the null association may be explained by the SNP representing circulating levels of GDF15. Among the three SNPs, two of them may be functionally relevant to the gene expression of GDF15. Both rs888663 and rs749451 are located upstream of the GDF15 gene locus, while rs1054564 is located at the 3' UTR of the GDF15 gene locus. Notably, rs888663 (the most associated SNP of GDF15) is located at the DNase hypersensitivity peak that is highly enriched with H3K27ac based on the data from the ENCODE project. On the other hand, using regulomeDB, it was reported that rs1054564 had a RegulomeDB score of 1f, and bound by the proteins of CREBBP, EGR1, GATA1, HDAC2, POLR2A, RCOR1, SMARCC1, and Zinc Finger Protein 143, 263 and 274 as illustrated by the ChIP-seq experiment (http://www.regulomedb.org/snp/chr19/18499814). Thus, both rs888663 and rs1054564 may play a regulatory role in gene expression of GDF15. Although rs749451 is not associated with any specific genomic feature associating with gene expression, the conclusion was essentially unchanged by excluding rs749451 (Table 3).

Recombinant GDF15 treatment reduced body weight in mice, rats, and obese cynomolgus monkeys [27], but this effect has not been tested in humans. Several similar studies focusing on the GDF15/GFRAL axis showed that deletion of GFRAL per se had limited effect on body weight and cardiometabolic phenotypes [3–6], but it abolished the GDF15-induced weight loss. These findings suggested that high levels of GDF15 is the key determinant of weight loss in the GDF15/GFRAL axis, while low GDF15 levels may have limited impact on body weight. In the current study, no association between GDF15 and anthropometric measurements was observed. These imply that physiological variation of GDF15 in humans has limited impact on body weight and fat metabolism. This should not be surprising since human body weight is determined by multiple factors besides appetite. Moreover, we also performed power calculation (Supplementary Table 1); the current study has at least 80% power in detecting the effect size from 0.013 SD (BMI) to 0.06 SD (WBLM) per 1 SD change in GDF15. Therefore, the effect size of GDF15 on cardiometabolic traits is expected to be very small, even if there is a real causal effect.

In additional to anthropometric measurements, there are substantial differences observed between animal studies and our human MR study. There are two studies showing the effect of GDF15 on bone metabolism. Hinoi et al. [28] showed that GDF15 promotes osteoclastogenesis under hypoxia in vivo; while Westhrin et al. [29] showed that GDF15 inhibited osteoblast differentiation (from bone marrow derived mesenchymal stem cells) but increased osteoclast differentiation (from peripheral mononuclear cells or pre-osteoclast cells). These two studies therefore suggest that GDF15 may play a negative role on bone metabolism. However, a recent study [27] showed that recombinant GDF15 treatment did not alter BMD in mice. These studies are indeed contradictory. These inconsistent results might be due to differences in experimental conditions like the exposure to hypoxia, the use of cell cultures versus animal study, and in the dosages and duration of GDF15 treatment. GDF15 has a short half-life of 3 h [27]. Hence, the study conducted by both Hinoi and Westhrin et al. mainly reflect the short-term effect of GDF15 treatment. On the other hand, Xiong et al. used an engineered GDF15 with extended half-life and greater efficacy, which eventually resulted in an null observation. This may highlight the effect of GDF15 on bone may be time- and condition-dependent. Although no significant association was observed between GDF15 and eBMD in MR-Egger analysis, this method is well documented to be low in power. On the other hand, improved glucose metabolism and better lipid profiles were observed in mice receiving recombinant GDF15 treatment [27], but this effect was not observed for serum LDL-C, TC, TG, FG, FI, and A1c in humans (Table 2). Instead, GDF15 was found to have a negative impact on HDL-C in IVW analysis (Table 2). It is therefore not surprisingly that null association was observed between GDF15, T2D, and CAD (Table 2).

Circulating GDF15 levels have been reported to be associated with multiple diseases, e.g. Alzheimer's disease [30] and cancers. We conducted a MR analysis and found that there was a nominally significant association of GDF15 with an increased risk of Alzheimer's disease (IVW: OR: 1.12; 95% CI: 1.027–1.220; $P = .01$). On the other hand, no significant association was observed with breast cancer and prostate cancer (data not shown). These findings suggest that targeting GDF15/GFRAL axis in human may have little effect on cancer risk, while its potential impact on increased risk of Alzheimer's disease requires further study.

There are at least four pharmaceutical companies developing pharmacological agents targeting GDF15/GFRAL axis. The current study sheds light on the relationship between GDF15 and cardiometabolic phenotypes in humans, which is important and indicative for subsequent RCTs. In the literature, there are important examples

demonstrating the importance of MR study in drug development. For example, increasing HDL-C levels had long been considered as a therapeutic target for cardiovascular disease (CVD), based on evidence generated from animal and human association studies. However, subsequent RCTs since 2012 showed that HDL-raising drugs failed to reduce the risk of CVD [31,32]. Indeed, MR analysis in 2012 showed that serum HDL-C levels are not associated with CVD events [16], suggesting that conducting MR study before RCT may be necessary and important clinically. On the other hand, two MR studies showed that loss of function mutation in APOC3 was associated with lower triglycerides levels and lower risk of CVD [33,34]. Volanesorsen, which is an antisense oligonucleotide selectively inhibiting APOC3, has been proven to reduce triglycerides level [35]. It is now in phase 3 development and if the findings in the MR studies are correct, it may reduce the risk of CVD. Therefore, our study showed that the role of GDF15/GFRAL axis in weight regulation in man may not be as important as previously thought. On the other hand, recombinant GDF15 treatment may improve BMD in man.

There are several strengths in the current study. To the best of our knowledge, this is the first MR study to evaluate of the causal role of GDF15 in 15 cardiometabolic phenotypes. We have ample power to detect small causal effects (Supplementary Table 1), given that the genetic instruments explained 7.9% (3 SNPs) and 5.74% (2 SNPs) of the variance of GDF15, and the summary statistics of all cardiometabolic phenotypes were retrieved from GWAS or genome-wide meta-analysis with huge sample size (Supplementary Table 1). Multiple sensitivity analyses were conducted. Moreover, these SNPs were not significantly associated with any other traits in the GWAS catalog, suggesting that the current null association is unlikely to be confounded by the association between the GDF15-associated SNPs and other related phenotypes.

There are also limitations. No food intake data is available, thus whether GDF15 affects food intake in humans is unknown. The genetically determined GDF15 may only reflect the effect of GDF15 within the physiological range, therefore the effects of GDF15 in the supraphysiological range is unknown. The current MR study addresses the effects of GDF15 on various clinical outcomes in a largely normal population. The role of GDF15 may change in disease states. For example, a recent study showed that GDF15 is among the best biomarkers predicting all-cause and cause-specific mortality in people with acute coronary syndrome [36]. Therefore the role of GDF15 in different diseases still needs to be explored. The mean levels of circulating GDF-15 are not available, despite it would not affect the validity of the current findings.

In conclusion, life-long GDF15 levels is not causally associated with body weight, glycemic phenotypes, lipids, and CAD in humans. It may be associated with higher bone mass in humans. This study provides important insights into the potential of drugs targeting the GDF15/GFRAL axis. Whether supraphysiological concentration is useful in reducing food intake and improving cardiometabolic phenotypes remains an open question for further study.

Author contributions

CLC conceived the study design, data extraction, data analysis, and drafted the manuscript. PCA and GHL did the data checking and analysis. All authors critically reviewed the manuscript.

Declaration of interests

All authors declare that we have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2019.02.021.

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