

Title: Evaluating the cardiovascular safety of sclerostin inhibition using evidence from meta-analysis of clinical trials and human genetics

One sentence summary: Genetic variants in *SOST* (encoding sclerostin) associated with higher bone mineral density and lower fracture risk also associate with increased risk of cardiovascular disease in large-scale biobanks, corroborating evidence of adverse cardiovascular effects reported in clinical trials of romosozumab, a first-in-class sclerostin inhibitor for treatment of osteoporosis.

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Abstract: Inhibition of sclerostin is a novel therapeutic approach to lowering fracture risk in patients with osteoporosis. However, data from phase III randomized controlled trials (RCTs) of romosozumab, a first-in-class monoclonal antibody that inhibits sclerostin, suggest an imbalance of serious cardiovascular events, and regulatory agencies have recently issued disparate verdicts on applications for marketing authorization. Here we meta-analyse published and unpublished cardiovascular outcome trial data of romosozumab, and investigate whether genetic variants that mimic therapeutic inhibition of sclerostin are associated with higher risk of cardiovascular disease. Meta-analysis of up to three RCTs indicated a higher risk of cardiovascular events with romosozumab. Scaled to the equivalent dose of romosozumab (210mg/month; 0.09 g/cm² higher bone mineral density), the *SOST* genetic variants were associated with lower risk of fracture and osteoporosis (commensurate with the therapeutic effect of romosozumab), and with a higher risk of myocardial infarction and/or coronary revascularization and major adverse cardiovascular

events. The same variants were also associated with increased risk of type 2 diabetes and higher systolic blood pressure and central adiposity. Taken together, our findings indicate that inhibition of sclerostin may elevate cardiovascular risk, warranting a rigorous evaluation of the cardiovascular safety of romosozumab and other sclerostin inhibitors.

Introduction

Osteoporosis, a disorder characterized by low bone mass, is a common condition associated with considerable morbidity and mortality, particularly among postmenopausal women and the elderly (1). A range of therapeutics for osteoporosis is currently available, though these agents are plagued by poor adherence (fewer than 40% of patients prescribed oral bisphosphonates still take these medications after one year (2)), occurrence of rare but serious adverse events (e.g., osteonecrosis of the jaw), high cost, and uncertainty regarding long-term efficacy (3). There is therefore a substantial demand for effective, safe and well-tolerated anti-osteoporotic therapies (4).

Sclerostin, a glycoprotein encoded by the *SOST* gene, is a negative regulator of bone formation that is secreted by osteocytes. It inhibits Wnt signaling, which leads to down-regulation of osteoblast development and function (5). Loss-of-function mutations in *SOST* lead to sclerosteosis, a rare autosomal recessive condition characterized by bone overgrowth (6). Similarly, van Buchem's disease, another rare autosomal recessive condition with a clinical picture similar to sclerosteosis (albeit generally milder), is caused by a deletion of a *SOST*-specific regulatory element (7). The discovery of functional variants in *SOST* as the underlying cause of these rare conditions of bone overgrowth nearly 2 decades ago, led to the development of sclerostin inhibitors as a treatment for osteoporosis (8).

Three anti-sclerostin monoclonal antibodies have been, or are, currently in clinical development (5), including romosozumab (Amgen, UCB) and blosozumab (Eli Lilly and Company) for osteoporosis and setrusumab (Mereo BioPharma), currently in phase IIb for osteogenesis imperfecta and previously also studied in adults with hypophosphatasia (9). Despite phase II results showing increases in bone mineral density (BMD) (10), a biomarker used to evaluate the effect of anti-osteoporotic treatments, clinical development for blosozumab was halted in 2015, reportedly due to injection site reactions (11). Phase II and III randomized controlled trials (RCTs) have shown that romosozumab is effective at increasing BMD in both men and women, whilst also reducing vertebral and non-vertebral fracture risk in women (12–15). However, adverse event data reported in the phase III BRIDGE and ARCH trials (in men and postmenopausal women, respectively) have suggested that romosozumab may be associated with an excess

risk of cardiovascular events (14, 15). Concerns about the cardiovascular safety of romosozumab, and sclerostin-inhibition more generally, have previously been raised (8, 16–18), and in 2017, the US Food and Drug Administration (FDA) rejected an initial Biologics Licence Application for romosozumab due to concerns regarding cardiovascular adverse effects seen in the ARCH trial (19). Further licencing submissions were subsequently made to various regulatory agencies, including a resubmission to the FDA (20, 21). On 9 April 2019, the FDA approved romosozumab for the treatment of osteoporosis in postmenopausal women at high risk of fracture, with a boxed warning highlighting the risk of cardiovascular adverse events, and a post-marketing requirement to assess the cardiovascular safety of romosozumab (22). Further approvals have since been issued in Canada, Japan and South Korea (including for both men and women in the latter two countries, and with no specific warning label in Japan). The European Medicines Agency (EMA) issued a refusal of marketing authorization for romosozumab in June 2019, citing “an increased risk of serious effects on the heart or circulatory system” (23). In October 2019, following a re-examination procedure, the EMA recommended granting of market authorisation, (24) leading to approval by the European Commission in December 2019, with a special warning relating to the risk of myocardial infarction and stroke (25).

A detailed appraisal of the cardiovascular effects of sclerostin inhibition by exploiting randomized data from orthogonal sources is therefore both timely and warranted, particularly given the discrepancy in opinions issued by regulatory agencies, and may assist in the evaluation of whether this class of drugs represents a rational and safe therapeutic strategy for the prevention of fracture. Naturally-occurring human genetic variation can serve as a proxy for therapeutic stimulation or inhibition of a drug target, presenting a valuable opportunity to assess the likely consequences of modifying a therapeutic target on both the intended therapeutic effects and target-mediated adverse drug reactions (25, 26). The application of this approach in a Mendelian randomization framework has previously shown to recapitulate known clinical effects of drug target modulation (27–31). In this study, we used this genetic approach to examine the effect of BMD-increasing alleles in the *SOST* locus (as a proxy for sclerostin inhibition) on the risk of bone fracture, osteoporosis, cardiovascular risk factors and disease, and complemented this with meta-analysis of cardiovascular data from RCTs of sclerostin inhibitors, to shed

light on whether treatment with this novel class of drugs is likely to adversely impact on cardiovascular disease.

Results

Risk of cardiovascular events in phase III RCTs of sclerostin inhibitors

Romosozumab was the only sclerostin inhibitor with data from phase III RCTs. Four published phase III RCTs of romosozumab, including 11,954 individuals were identified (**Table S1**), of which three trials (BRIDGE (15), ARCH (14) and FRAME (13)) reported cardiovascular adverse event data (**Table S2**). Only the BRIDGE (15) and ARCH (14) trials reported data on 'cardiac ischemic events' and 'cerebrovascular events' in their respective peer-reviewed publications. Unpublished data from the FRAME trial pertaining to these outcomes and data pertaining to major adverse cardiovascular events (MACE; a composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) were extracted from US FDA Drugs Advisory Committee briefing documentation (32).

Meta-analysis (using the Mantel-Haenszel method without continuity correction) of 25 events in 4,298 individuals, from two RCTs (BRIDGE (15) and ARCH (14)) identified that 210mg romosozumab monthly, as compared to the comparator, led to a higher risk of cardiac ischemic events (odds ratio [OR], 2.98; 95% confidence interval (CI), 1.18-7.55; P=0.02; **Fig. 1a**). Addition of the unpublished (and non-peer reviewed) FRAME data made available to the US FDA Drugs Advisory Committee, brought the total number of cardiac ischemic events to 57 in 11,455 individuals, and resulted in a pooled OR of 1.54 (95% CI, 0.90-2.64; P=0.12; **Fig. 1a**). Corresponding estimates for cerebrovascular events were 27 events; OR 2.15 (95% CI, 0.94-4.92; P=0.07) prior to US FDA meeting and 48 events; OR, 1.44 (95% CI, 0.80-2.58; P=0.22) afterwards. Estimates for MACE (130 events; OR 1.39; 95%, 0.98-1.98; P=0.07) and serious cardiovascular events (183 events; OR 1.21; 95% CI, 0.90-1.63; P=0.20) were directionally concordant with increased vascular risk arising from romosozumab treatment (**Fig. 1b**). Sensitivity analyses using the Peto-method showed similar results (**Fig. S1A** and **Table S3**), as did inclusion of an alternative number of serious cardiovascular events in the FRAME trial, using FDA-sourced data (Fig S1B).

Expression of *SOST* mRNA

We identified two conditionally independent genetic variants in the *SOST* locus associated with BMD, rs7209826 (A>G, G-allele frequency in UKBB = 40%) and rs188810925 (G>A, A-allele frequency = 8%), from a recent large-scale GWAS for estimated heel-bone BMD (eBMD) (33). Expression of *SOST* across 53 human tissue types in the Genotype-Tissue Expression consortium was highest in arterial tissue (**Fig. S2**; bone expression data not available). The minor alleles of rs7209826 (G-allele) and rs188810925 (A-allele) were both associated with lower expression of *SOST* mRNA in various human tissues, with the strongest associations with *SOST* expression for each variant identified in tibial artery (rs7209826: $P=1.4\times10^{-8}$; 388 samples) and aorta (rs188810925: $P=7.6\times10^{-6}$; 267 samples; **Fig. S3** and **Table S4**). Colocalization analyses showed evidence (34–37) of a shared causal variant driving the association with eBMD and *SOST* gene expression in tibial artery tissue (posterior probability of a shared causal variant of 74% in tibial artery for the rs7209826 signal, after adjusting for other independent signals in the region; **Table S5** and **Fig. S4**), with other arterial tissues underpowered to provide a reliable probability of colocalization. No valid sclerostin protein quantitative trait loci (pQTLs) could be identified (**Note S1**).

Association of rs7209826 and rs188810925 with BMD

The minor alleles of both SNPs were associated with higher estimated heel-bone BMD (eBMD) in UKBB (33) (rs7209826: 0.04 g/cm² [95% CI, 0.04-0.05; $P=2.3\times10^{-36}$] per G allele and rs188810925: 0.07 g/cm² [95% CI, 0.05-0.08; $P=1.3\times10^{-26}$] per A allele, **Fig. S5**), and with higher lumbar spine BMD (LS-BMD) (38) (rs7209826: 0.008 g/cm² [95% CI, 0.005-0.01; $P=5.4\times10^{-07}$] per G allele; rs188810925: 0.016 g/cm² [95% CI, 0.01-0.022; $P=4.3\times10^{-07}$] per A allele, **Fig. S5**). We subsequently scaled all further genetic estimates to the increase in lumbar spine BMD seen with 12 months of 210mg romosozumab monthly (equivalent to a 0.09 g/cm² higher BMD) (39).

Association with osteoporosis and fracture risk

Scaled to match the effect of 12 months of 210mg romosozumab monthly on lumbar spine BMD, meta-analysis of rs7209826 and rs188810925 yielded a 57% lower risk of osteoporosis (OR, 0.43; 95% CI,

0.36-0.52; $P=2.4\times 10^{-18}$) and a 41% lower risk of sustaining a bone fracture (OR, 0.59; 95% CI, 0.54-0.66; $P=1.4\times 10^{-24}$; **Fig. 2** and **Fig. S6**). Associations were consistent across fracture sites (**Fig. S7**).

Association with cardiovascular events

Next, we investigated the associations of the *SOST* variants with cardiovascular outcomes comparable to those used in the RCTs of romosozumab. In meta-analysis of scaled genetic estimates, the BMD-increasing *SOST* variants associated with an 18% higher risk of myocardial infarction and/or coronary revascularization (69,649 cases; OR, 1.18; 95% CI, 1.06-1.32; $P=0.003$) and a 12% higher risk of major adverse cardiovascular events (MACE; 119,032 cases; OR 1.12, 95% CI 1.03-1.21, $p=0.007$; **Fig. 3** and **Fig. S8**). Using a broader and less specific definition of CHD, which included self-reported angina and chronic stable ischemic heart disease (up to 106,329 cases), the *SOST* variants associated with a 10% increased risk of disease (OR, 1.10; 95% CI, 1.00-1.20; $P=0.04$; **Fig. 3** and **Fig. S8**).

Association with additional cardiometabolic risk factors and diseases

Evaluation of cardiometabolic risk factors and diseases revealed that the BMD-increasing *SOST* variants associated with higher risks of hypertension (OR, 1.12; 95% CI, 1.05-1.20; $P=8.9\times 10^{-4}$) and T2D (OR, 1.15; 95% CI, 1.05-1.27; $P=0.003$; **Fig. 4A**).

Consistent with the effect on hypertension, we found the *SOST* variants to be associated with 1.3 mmHg higher systolic blood pressure (SBP; 95% CI, 0.8-1.9; $P=5.9\times 10^{-6}$), but observed no effect on diastolic blood pressure (DBP; **Fig. 4B**). In addition, the *SOST* variants associated with 0.05 standard deviation (SD) units higher WHR adjusted for BMI (95% CI, 0.02-0.08; $P=8.5\times 10^{-4}$), and, nominally, with higher serum triglycerides (9.6 mg/dl higher; 95% CI, 1.3-18.8 mg/dl; $P=0.02$). We found no further associations (**Figs. S9-S12** and **Tables S6-S7**). Sex-stratified analyses revealed that on average the point estimates for cardiometabolic risk factors and disease appeared stronger in women than men, however there was little statistical evidence of heterogeneity (**Table S8**). Colocalization analyses of SBP and WHR adjusted for BMI with eBMD were inconclusive due to low power (**Table S9**), and a sensitivity analysis utilising conditionally independent *SOST* variants from a more recent GWAS of eBMD (40) yielded comparable

results (Figs. S13-S14). An exploratory phenome-wide association analysis of 1,074 binary outcomes in UKBB did not reveal any further suggestive associations (**Fig. S15**).

Triangulation of randomized controlled trials and human genetics

Triangulation refers to the integration of results from orthogonal approaches to study design (where each such approach has different sources of potential bias) to arrive at more reliable answers (41, 42). If the results from such approaches all support the same conclusion, this bolsters our confidence in the finding. To this end, we first performed fixed-effect meta-analysis of 337 clinical fractures in 11,273 individuals from two RCTs with fracture outcome data (FRAME (13) and ARCH (14), **Table S10**), and identified that 210mg romosozumab monthly, as compared to comparator, led to a 32% lower risk of clinical fracture (hazard ratio 0.68; 95% CI, 0.55-0.85; $P=6.0\times 10^{-4}$; **Fig. 5** and **Fig. S16**) at 12 months. This compared well to the scaled genetic estimate, using the two *SOST* variants, of a 41% lower risk of fracture (**Fig. 5**). Evidence from treatment trials (up to three romosozumab phase III RCTs (14, 15)) and human genetics (two *SOST* variants) demonstrated an increased risk of coronary events (**Fig. 5**), indicating that this adverse effect is likely real and target-mediated.

Finally, we compared the estimates of our *SOST*-specific instrument with those of a recent MR study evaluating the causal effect of genetically-predicted eBMD on risk of T2D and CHD (43). Scaling to the same difference in eBMD (an increase of 0.14g/cm² in eBMD), we found that estimates for the *SOST*-specific instrument were very similar to those of the eBMD-instrument for both T2D and CHD (**Fig. S17**). This suggests that the associations of our instrument with risk of T2D and CHD are consistent with the overall effect of BMD on these cardiometabolic outcomes (which reduces the likelihood of them arising due to pleiotropy).

Discussion

Using data from human genetics and randomized interventional trials, we have shown that sclerostin inhibition leads to higher BMD and lower risk of osteoporosis and fractures, but also a higher risk of CHD. While prior phase III RCTs of sclerostin inhibition by romosozumab suggested an increased risk of

adverse cardiac events (14, 15), it remained possible that the finding was due to chance owing to the low number of events. With the addition of data that had not undergone peer review, made available by the sponsors of romosozumab to the US FDA in January 2019, the cumulative estimate for cardiac ischemic events attenuated but remained consistent with romosozumab leading to a higher risk of cardiac disease. Our genetic analysis which includes up to 106,329 CHD cases, shows that the excess risk of CHD from sclerostin inhibition is likely to be real, and supports the FDA's and EMA's addition of a warning for cardiovascular events to romosozumab's label. Our findings also suggest that the excess risk of coronary events is driven, at least in part, by an increase in cardiovascular risk factors with an established etiological role in CHD, including adiposity, blood pressure, and T2D. Given the high short-term mortality associated with some types of fragility fracture (e.g., up to 25% mortality in the 12 months following a hip fracture (44)), a careful assessment of the potential risks vs benefits is warranted, weighing the merits of lower fracture (and fracture-related morbidity and mortality) against the potential harm from higher risk of metabolic and vascular disease. Whilst clinical trials of romosozumab suggest that the reduction in relative risk of fracture (32%) is greater than the increased risk of coronary events (18%), such estimates relate to relative risks versus absolute risks (with absolute risks being more clinically meaningful), and furthermore, they do not take into account the differential impact that each disease has on an individual's quality of life (as may be necessary to estimate the "benefit-risk" of a therapeutic). Furthermore, the use of human genetics may pose a translational challenge in estimating the expected effects of a therapy (in both relative and absolute terms), owing to, for example, genotype approximating prolonged (i.e. lifetime) exposure whereas in contrast, a clinical trial is typically of considerably shorter duration (45).

We did not observe statistical evidence of heterogeneity according to sex in our analyses, a finding which is supported by romosozumab's comparable effect on BMD in men and women (15). It is however notable that the genetic estimates for CHD, blood pressure and T2D tended to be of greater magnitude in women than men (**Table S8**). These findings emphasize that, despite limiting romosozumab's label in the U.S. to only women, it is likely to lead to higher vascular risk in this group of patients.

There are several additional lines of evidence supporting the findings of our study. Sclerostin is expressed in cardiovascular tissues (46, 47), supporting a potential biological role for this protein in these tissue types. In observational studies, higher levels of circulating sclerostin are associated with a higher risk of cardiovascular disease together with higher levels of cardiometabolic risk factors such as hypertension, T2D and central adiposity (48–53). In contrast to our genetic findings, these data suggest that lowering of sclerostin may confer protection from cardiovascular disease; however, observational studies also show that osteoporosis and lower BMD are associated with lower levels of sclerostin (54, 55) — suggesting that increasing sclerostin would lead to higher BMD. We know this to be spurious given the well-established effects of therapeutic sclerostin inhibition on BMD. Furthermore, recent investigations of BMD show that the observational association with risk of CHD and the corresponding estimate from Mendelian randomization are directionally opposite (43), making observational associations of bone density and vascular disease unreliable. More recent evidence has suggested that sclerostin may be up-regulated in the vasculature in response to vascular calcification, as part of a regulatory process aimed at counteracting such calcification (18), whereas murine studies have implicated sclerostin in adipocyte metabolism (56) and the development of atherosclerosis, aortic aneurysm and hemopericardium (57, 58). Whilst these human and animal data serve as evidence for the biological plausibility of sclerostin inhibition altering cardiovascular risk, it is important to note that extrapolating findings from animal models of disease to humans is plagued by failures of translation (59, 60), and that observational studies of humans can be influenced by sources of error. This is why studies employing a randomized design in humans provide more reliable evidence on causation (42).

Elucidation of whether adverse effects are on- or off-target is critical (8) as on-target effects would mean that any drug under development in the same class (i.e., a sclerostin inhibitor), would be expected to share a similar adverse effect profile (i.e. higher risk of vascular events). Our genetic data provide strong evidence in support of target-mediated adverse effects of sclerostin inhibition on coronary events. Sclerostin exerts its effects on bone as an inhibitor of the Wnt-signaling pathway (a pathway also previously linked to vascular calcification(61–63)) by binding to the Wnt co-receptor low density lipoprotein receptor-related protein (LRP) 5 and 6 (64). Protein-coding mutations in both *LRP5* and *LRP6*

have been linked to alterations in BMD and cardiometabolic risk profiles, including insulin resistance, dyslipidemia, hypertension and CHD (65, 66), which supports our findings of altered cardiometabolic disease in carriers of *SOST* variants.

Concerns of cardiovascular safety have also plagued other anti-osteoporotic agents. Odanacatib, a cathepsin K inhibitor developed by Merck for the treatment of osteoporosis, while shown to reduce fracture risk in phase III trials, was not developed further owing to an increased risk of stroke (67). While we did not identify strong associations of *SOST* variants with risk of stroke subtypes in our analyses, the point estimates for both ischemic and hemorrhagic stroke were OR > 1. With genetic lowering of sclerostin leading to elevations in systolic blood pressure and WHR adjusted for BMI (each of which plays a causal role in stroke (68, 69)), it is plausible that additional stroke cases would identify such an association. More broadly, genetically elevated BMD may exert a modest causal effect on risk of T2D and CHD (43). Interestingly, other BMD-raising therapies, e.g., denosumab or bisphosphonates, have not shown an association with increased risk of cardiovascular events in clinical trials (70–72). Importantly, some reports (32), using network meta-analysis, have suggested that the increased cardiovascular risk seen in the romosozumab-arm of the ARCH trial (14) may have been due to a cardioprotective effect of alendronate, a bisphosphonate used in the ARCH control arm. However, meta-analyses of RCTs of bisphosphonates have shown that the effect of bisphosphonates (as compared to placebo or standard of care) on risk of cardiovascular events is null (71, 72), arguing against such an effect. In addition, this would not explain the imbalance seen in the placebo-controlled BRIDGE trial (15), nor would it account for our genetic findings.

The approach to exploiting human genetics to validate target-mediated effects is well-established (27–31). In our study, we selected variants associated with reduced expression of *SOST* and increased BMD as proxies for the effect of sclerostin inhibition. We validated the effects of the *SOST* genetic variants on risk of osteoporosis and bone fracture (including fracture across several sites), and leveraged a large number of CHD cases (a more than 1,800-fold increase over the number of cases reported in phase III trials of romosozumab (14, 15)). Our approach also facilitated identification of potential mechanisms and

mediators that may drive this excess coronary risk. For example, the association of *SOST* variants with central adiposity, SBP and T2D has not been previously reported and if not measured in a clinical trial, such associations cannot be readily explored.

Our study is subject to several limitations. Firstly, we examined life-long effects of genetic variants, which are not necessarily representative of the effects seen with pharmacological perturbation of shorter duration later in life. Second, the common, non-coding variants that we use in this study have not been conclusively linked to altered sclerostin protein levels or function. A recent GWAS of circulating serum levels of sclerostin (73) reported three trans-pQTLs but found that SNPs in the *SOST* locus were only nominally associated with sclerostin serum levels. The authors speculated that this finding may suggest that *SOST* SNPs influence BMD and fracture risk by altering local sclerostin activity in bone, independently of serum sclerostin levels. Further studies of larger sample size will however be needed to explore the effect of genetic variants in the *SOST* locus on circulating sclerostin levels. We attempted to investigate the effects of the trans-pQTLs, but found that they were unlikely to be reliable instruments (**Note S1**). Nonetheless, the validity of our variants as suitable genetic instruments to mimic treatment with an inhibitor of sclerostin is supported by their association and colocalization with *SOST* mRNA expression across various tissue types, and more importantly with relevant therapeutic outcomes including BMD, fracture risk and osteoporosis. Thirdly, whilst rare mutations in *SOST* have been linked to an extreme BMD phenotype (i.e. indicating the presence of an allelic series of common and rare trait-associated alleles (74)), we were not able to evaluate the effect of loss-of-function coding variants in *SOST*, primarily due to the relative scarcity of such variants in the general population (e.g. the most common predicted loss-of-function *SOST* variant in the gnomAD database (75) has a minor allele frequency of 9.2×10^{-6} , with no homozygotes reported). Increased cardiovascular risk has not been reported in individuals with Mendelian disorders of absent or low sclerostin expression (e.g. van Buchem disease or sclerosteosis). Reasons for this may include a shortened life-expectancy observed in some of these patients (for non-cardiovascular reasons, e.g. due to raised intracranial pressure) (76) and having not been examined for cardiovascular disease specifically. Deep phenotyping, including comprehensive cardiovascular evaluation, of individuals with loss-of-function variants in *SOST* would likely be of value

(77, 78). Fourth, in scaling the allelic estimates to match the effect of pharmacologic inhibition of sclerostin, we assumed that the effect of the variants on BMD and the outcomes of interest is linear in nature. Observational evidence suggests that the association between BMD and cardiovascular risk is inversely linear (with lower BMD and osteoporosis associated with higher cardiovascular risk (43, 79, 80)); however, this is directionally opposite to the evidence from MR studies, which suggests that higher BMD is causally associated with higher cardiovascular risk (43), and therefore poses challenges in testing the assumption of linearity in the genetic associations. Nevertheless, the same approach to scaling allelic estimates has also been applied in studies similar to ours, and is an established approach in Mendelian randomization (29, 31, 81). Finally, we note that the effect estimates derived from the meta-analysis of RCTs of sclerostin inhibition provide only weak evidence of an adverse effect on cardiac disease. At the time of initiating this study, prior to the FDA meeting of January 2019, the unpublished data from the FRAME trial had not been made available. Our meta-cumulative plot shows the evolving nature of the vascular disease effects of sclerostin (**Fig. 1a**): prior to the FDA hearing, the OR of cardiac ischemic events was 2.98 (95% CI, 1.18-7.55) with 25 events. Addition of non-peer-reviewed vascular disease events, which more than doubled the number of cases, led to a halving of the effect estimate (OR 1.54) with the 95% CI including the null (95% CI, 0.90, 2.64). While we note that network meta-analysis may suggest that the excess risk from romosozumab could have arisen due to a protective effect of alendronate (32), this is not supported by large-scale meta-analyses of bisphosphonates. Irrespective, our genetic estimates are consistent with an excess risk of cardiac events being real and target-mediated. Further, the pattern of associations of *SOST* variants not only with CHD, but also with risk factors with an established causal role in CHD including adiposity, blood pressure and T2D make it implausible that these genetic findings have arisen by chance.

Our findings support the FDA's addition of a boxed warning for cardiovascular risk to romosozumab's label (22), and indicate that other therapies inhibiting sclerostin are also very likely to exert similar cardiovascular effects. Importantly, our analyses could have identified the increased cardiovascular risk prior to initiating clinical development of romosozumab (and other sclerostin inhibitors). This may have enabled better trial design, particularly for directly evaluating the effect of romosozumab on

cardiovascular outcomes and risk factors in adequately-powered RCTs. The post-marketing surveillance mandated by the FDA (consisting initially of a five-year observational feasibility study (22)), whilst important, is subject to numerous sources of bias (82, 83). Our results therefore emphasise the utility of large-scale human genetic data in preclinical drug target validation (26, 74, 84).

In conclusion, our results warrant a rigorous assessment of the effect of romosozumab (and other sclerostin inhibitors in clinical development) on cardiovascular disease and cardiometabolic risk factors. This adds valuable information as to whether pharmacological inhibition of sclerostin should be pursued as a therapeutic strategy for the prevention of fracture.

Materials and Methods

Study design. We performed two major analyses to investigate whether treatment with sclerostin inhibitors is likely to adversely impact on cardiovascular disease. Firstly, we meta-analysed cardiovascular outcomes data from randomized controlled trials (RCTs) of sclerostin inhibitors. Secondly, we examined the effect of bone mineral density (BMD)-increasing alleles in the SOST gene (encoding sclerostin) on the risk of therapeutic and cardiovascular outcomes. An overview of the genetic analysis is shown in **Fig. S18**.

Study population. We examined individual-level genotypic and phenotypic data for 502,617 subjects in UK Biobank (UKBB), a population-based cohort based in the United Kingdom. In addition, we included data from a further two European-ancestry cohorts: Partners HealthCare Biobank (PHB; up to 19,132 subjects) and Estonian Biobank (EGCUT; up to 36,074 subjects). Trans-ethnic replication was attempted in China Kadoorie Biobank (CKB; up to 81,546 subjects). Further detail pertaining to each cohort is described below.

UK Biobank (UKBB). UKBB is a prospective study of more than 500,000 British individuals recruited from 2006 to 2010 and aged between 45 and 69 (85). Phenotypic information available includes self-reported medical history as ascertained by verbal interview with a medical professional at enrolment, hospital-derived electronic health record (EHR) data, including International Classification of Diseases, ninth and tenth revision (ICD-9 and ICD-10) codes and Office of Population and Censuses Surveys (OPCS-4) procedure codes, and an extensive set of physical measurements. Genotypic data (see below for detail) is available for 488,377 individuals, of whom 487,409 have imputed genotype data. For the purposes of this study, we excluded all samples indicated to have poor quality genotypes by UKBB (on the basis of high sample heterozygosity and missingness), and further excluded individuals that had: reported non-white or mixed ethnicity at any point during follow-up; withdrawn their consent for participation; >10 third degree relatives; putative sex chromosome aneuploidy; sex mismatches (comparing genetically determined vs. self-reported sex, and comparing between assessments); ethnicity mismatches (mismatches between genetically determined and self-reported ethnicity for white British

individuals, and any ethnicity mismatches between assessments). We reviewed pairwise genetic relatedness between individuals and excluded one individual per pair of individuals with an estimated 2nd degree or closer relatedness (equivalent to a kinship coefficient of greater than 0.0884 (86)). After applying these filters, 423,766 subjects remained. Baseline characteristics of participants in UKBB are shown in **Table S11**.

Genotyping in UKBB. Genotyping, quality control and imputation were performed centrally by UKBB, and details are fully described elsewhere (85). Briefly, genotype data is available for 488,377 individuals, 49,950 of whom were genotyped using the Applied Biosystems™ UK BiLEVE Axiom™ Array by Affymetrix (containing 807,411 markers(87)). The remaining 438,427 individuals were genotyped using the Applied Biosystems™ UK Biobank Axiom™ Array by Affymetrix (containing 825,927 markers). Both of these arrays were specifically designed for use in the UKBB project and share ~95% of marker content. Phasing was done using SHAPEIT3, and imputation was conducted using IMPUTE4. For imputation, the Haplotype Reference Consortium (HRC) panel(88) was used wherever possible, and for single nucleotide polymorphisms (SNPs) not in that reference panel, a merged UK10K + 1000 Genomes reference panel was used. SNPs were imputed from both panels, but the HRC imputation was preferentially used for SNPs present in both panels.

Both SNPs selected as instruments in this study demonstrated high imputation quality in UKBB (info scores of 0.98 and 0.95 for rs7209826 and rs188810925, respectively).

Study outcomes and definitions in UKBB. Fracture status was based on an affirmative answer to the question “Have you fractured/broken any bones in the last 5 years?” at either baseline or at follow-up. Individuals were designated as missing if they answered “Do not know” or “Prefer not to answer” at baseline and at all follow-up occasions. All remaining individuals were designated as controls. An identical definition has been used in recent GWAS of BMD and fracture (33, 89), and the use of self-reported fracture has previously been validated (90). Individuals who reported having sustained a fracture were asked “Which bone(s) did you fracture/break?”, and given a list of options to choose from (including

ankle, leg, hip, spine, wrist, arm and other bones). For the purposes of our analysis, we grouped these into upper limb (wrist, arm), lower limb (ankle, leg, hip), vertebral (spine) and other fractures.

Individual values for systolic and diastolic blood pressure and the definition of hypertension were derived using the same method as in a recent GWAS for blood pressure performed in UKBB (91). We derived the mean SBP and DBP for each subject from two blood pressure measurements performed at baseline. For subjects with only a single measurement available, we used this single value. We then adjusted these values for blood pressure-lowering medication use by addition of 10 and 15 mmHg to DBP and SBP, respectively, for subjects who had reported taking blood pressure medication at baseline (92). Individuals were coded as having hypertension if they had an adjusted SBP of 140 mmHg or higher, DBP of 90 mmHg or higher, or reported use of antihypertensive medication.

To create phenotypes for body mass index (BMI) and waist-to-hip ratio (WHR) adjusted for BMI (WHRadjBMI), we followed steps consistent with those followed in the GIANT consortium (93–95).

Baselines measures of BMI, waist circumference and hip circumference were used. We first divided waist circumference by hip circumference to calculate the WHR, and then regressed WHR on BMI, sex, age at time of assessment and (age at time of assessment)², whereas BMI was regressed on sex, age at time of assessment and (age at time of assessment)². Next we performed rank inverse normalization on the resulting residuals from the regressions. These normalized residuals (for BMI and WHRadjBMI) were used for performing allelic association testing.

We included two definitions for coronary heart disease (CHD): an inclusive CHD phenotype including angina and other forms of chronic CHD, and a more specific phenotype of myocardial infarction and/or coronary revascularization only. Both of these definitions were derived from those used in a recent GWAS of CHD conducted in UKBB by the CARDIoGRAMplusC4D consortium (96).

Detailed definitions for all binary outcomes analyzed in UKBB (and not specifically defined above) are given in **Table S12**.

Ethical considerations. The UKBB project was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate. This research has been conducted under UKBB application number 11867.

Partners HealthCare Biobank (PHB). We identified patients with relevant phenotype information and genotype data from the Partners HealthCare Biobank (97, 98), a biorepository of consented patient samples at Partners HealthCare hospitals in the Boston area of Massachusetts. The Partners HealthCare Biobank maintains blood and DNA samples, clinical records and genotype data from consented patients. Patients are recruited in the context of clinical care appointments and electronically. All patients who participate in the Partners Biobank are consented for their samples to be linked to their clinical information for the use in broad-based research.

A total of 19,136 patients of European ancestry were genome-wide genotyped in Partners Biobank, including 8,868 males and 10,268 females with age at recruitment ranged from 19 to 102 (mean=59.4, median=62, SD=16.61). For these patients, electronic health records were available for extracting the following phenotypes: fracture, osteoporosis, coronary heart disease, myocardial infarction and/or coronary revascularization, type 2 diabetes, body mass index, HDL-cholesterol, LDL-cholesterol, triglycerides, and hypertension. We subset these patients according to the phenotype information availability for each genetic association analysis (See *Study outcomes and definitions in PHB* below).

Genotyping in PHB. DNA samples from whole blood and genome-wide genotyping were done for 25,582 patients. Genotyping were done with Illumina Multi-Ethnic Genotyping Array (first batch), Expanded Multi-Ethnic Genotyping Array (second batch), and Multi-Ethnic Global BeadChip (third batch), all of which were designed to capture the global diversity of genetic backgrounds (N of genotyped variants: 1,416,020 – 1,778,953).

Pre-imputation QC was performed on each genotyping batch separately as follows: we removed single nucleotide polymorphisms (SNPs) with genotype missing rate > 0.05 before sample-based QC; excluded samples with genotype missing rate > 0.02, absolute value of heterozygosity > 0.2, or failed sex checks; removed SNPs with missing rate > 0.02 after sample-based QC. To merge genotyping batches for imputation and analyses, we performed batch QC by removing SNPs with significant batch association ($p\text{-value} < 1.0 \times 10^{-6}$ between different batches).

Since the Partners Biobank samples have diverse population backgrounds, we performed Hardy-Weinberg equilibrium test ($p\text{-value} < 1.0 \times 10^{-6}$) for SNP-based QC after extracting samples of European ancestry (see below). We also performed relatedness tests by identifying pairs of samples with $\pi > 0.2$ and excluding one sample from each related sample pair (560 samples excluded). All QC were conducted using PLINK v1.9 and R software.

We extracted samples with European ancestry based on principal component analysis (PCA) with 1000 Genomes Project reference samples. To identify patients of European ancestry, we first performed PCA on LD-pruned dataset merged with 1000 Genomes Project reference samples labeled with 5 distinct super-populations (European [EUR], African [AFR], East Asian [EAS], admixed American [AMR], and South Asian [SAS]). Then, we used the top 4 PCs to build a random forest classifier trained on 1000 Genomes Project reference samples with super-population labels. Finally, we applied the trained random forest classifier to identify patients of European ancestry from Partners Biobank (with predicted probability of European ancestry > 0.9).

Genotype imputation was performed on the QCed patients of European ancestry with a 2-step pre-phasing/imputation approach. We used Eagle2 for the pre-phasing and minimac3 for imputation, with a reference panel from 1000 Genomes Project phase 3.

Study outcomes and definitions in PHB. We extracted relevant phenotype information from electronic health records for the patients with imputed genome-wide genotype data. The phenotype definition and number of samples are described in **Table S13**.

Ethical considerations in PHB. The Partners HealthCare Biobank maintains blood and DNA samples from consented patients seen at Partners HealthCare hospitals in the Boston area of Massachusetts. Patients are recruited in the context of clinical care appointments, and also electronically. Biobank subjects provide consent for the use of their samples and data in broad-based research.

Estonian Biobank (EGCUT). The Estonian Biobank is the population-based biobank containing longitudinal data and biological samples, including DNA, for 5% of the adult population of Estonia. The broad informed consent form signed by the participants of the biobank allows the Estonian Genome Center to continuously update their records through periodical linking to central electronic health record databases and registries. We studied the genotypic and phenotypic data of 51881 individuals and after removing relatives ($PiHat > 0.2$), 36073 individuals (65% women, 35% men) with average age of 45 years were included for further analysis. For the CHD analyses in EGCUT, we only included participants not previously included in the CARDIoGRAMplusC4D consortium.

Genotyping in EGCUT. Of all the studied biobank participants 33,155 have been genotyped using the Global Screening Array, 8137 HumanOmniExpress beadchip, 2640 HumanCNV370-Duo BeadChips and 6861 Infinium CoreExome-24 BeadChips from Illumina. Furthermore, of 2056 individuals' whole genomes have been sequenced at the Genomics Platform of the Broad Institute.

Sequenced reads were aligned against the GRCh37/hg19 version of the human genome reference using BWA-MEM1 v0.7.7; PCR duplicates were marked using Picard (<http://broadinstitute.github.io/picard>) v1.136, and the Genome Analysis Toolkit (GATK) v3.4-46 applied for further processing of BAM files and genotype calling. All insertion-deletions (indels) in the Variant Call Format (VCF) were normalized and multiallelic sites split using bcftools (<https://samtools.github.io/bcftools/bcftools.html>). The following genotypes were set to missing: genotype quality < 20 , read depth > 200 , allele balance < 0.2 or > 0.8 for heterozygous calls. The GATK's Variant Quality Score Recalibration (VQSR) metric was used to filter variants with a truth sensitivity of 99.8% for SNVs and of 99.9% for indels. Furthermore, variants with inbreeding coefficient < -0.3 , quality by depth < 2 for SNVs and < 3 for indels, call rate $< 95\%$, or Hardy-Weinberg equilibrium (HWE) P -value $< 1 \times 10^{-6}$ were excluded.

The genotype calling for the Illumina microarrays was performed using Illumina's GenomeStudio V2010.3 software. The genotype calls for rare variants on the GSA array were corrected using the zCall software (version May 8th, 2012). After variant calling, the data was filtered using PLINK (v.1.90) by sample (call rate $> 95\%$, no sex mismatches between phenotype and genotype data, heterozygosity $< \text{mean} \pm 3 \text{ SE}$) and marker-wise (HWE p -value $> 1 \times 10^{-6}$, call rate $> 95\%$, and for the GSA array additionally by Illumina

GenomeStudio GenTrain score >0.6, Cluster Separation Score >0.4). Before the imputation, variants with MAF <1% and C/G or T/A polymorphisms as well as indels were removed, as these genotype calls do not allow precise phasing and imputation. The genotype data obtained on all of the arrays were separately phased using Eagle2 (v. 2.3) and imputed using the BEAGLE (v. 4.1) software implementing a joint Estonian and Finnish reference panel (99).

Study outcomes and definitions in EGCUT. We tested the associations of rs7209826 and rs188810925 with fracture (ICD-10 codes S52.5, S82.6, S22.3, S42.2, S52.6, S22.4, S42.0, S82.8, S72.0, S71.1, S52.1, S32.0, S52.0, S82.4, S82.3, S72.1, S82.5, S22.0, S82.1, S82.7, S82.2, S82.0, S32.5, S32.2, S42.3, S52.2, S52.3, S42.4, S72.3, S52.8, S22.2, S52.4, S42.1, S72.2, S72.4, S32.1, S22.1, S12.2, S32.7, S32.8, S32.4, S82.9, S32.3, S52.9, S12.1, S42.8, S12.7, S72.8, S42.7, S72.9, S22.5, S72.7, S12.0, S42.9), osteoporosis (ICD-10 codes M80 and M81), the prevalent coronary artery disease (ICD-10 codes I20, I21, I22, I23, I24, I25), infarction (ICD-10 codes I21, I22, I25.2) and systolic blood pressure (measured at participant recruitment). For all of the outcome variables with an exception of cardiovascular disease we considered prevalent case statuses reported at recruitment and individuals with records of diagnosis codes reported in the electronic registries before the recruitment. For the outcome of cardiovascular disease, we considered only prevalent cases reported at recruitment.

Ethical considerations in EGCUT. Analyses in EGCUT were approved by the Ethics Review Committee of the University of Tartu (243T-12).

China Kadoorie Biobank (CKB). The China Kadoorie Biobank is a prospective cohort of 512,713 adults aged 30-79 years. Individuals were recruited between the years of 2004-2008 from 5 urban and 5 rural regions across China, as previously described (100). Baseline information was collected via detailed questionnaire (including demographic/ lifestyle factors and medical history) and physical measurements (which included anthropometry, blood pressure and spirometry). A non-fasting blood sample was taken and separated into plasma and buffy-coat fractions for long-term storage. Long-term follow up is through electronic linkage of each participant's unique national identification number to the Chinese national

health insurance system, and established regional registries for death and disease. Health insurance reports include detailed information (e.g. disease description, International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] code, and procedure or examination codes) about each hospital admission. Vascular disease events have been reviewed and standardized by clinicians.

Genotyping in CKB. 102,783 CKB participants were genotyped using 2 custom-designed Affymetrix Axiom arrays including up to 800K variants, optimized for genome-wide coverage in Chinese populations. Stringent quality control included SNP call rate >0.98, plate effect $p > 10^{-6}$, batch effect $p > 10^{-6}$, HWE $p > 10^{-6}$ (combined 10df Chi-Sq test from 10 regions), biallelic, MAF difference from 1KGP EAS < 0.2, sample call rate >0.95, heterozygosity < mean + 3SD, no chrXY aneuploidy, genetically-determined sex concordant with database, and exclusion of recent immigrants to each study area as identified by region-specific principal component analysis, resulting in genotypes for 532,415 variants present on both array versions in 94,592 individuals. Imputation into the 1,000 Genomes Phase 3 reference (EAS MAF > 0) using SHAPEIT version 3 and IMPUTE version 4 yielded genotypes for 10,276,634 variants with MAF > 0.005 and info > 0.3. rs188810925 was not imputed (1KGP EAS MAF = 0), rs7209826 was imputed with info = 0.986, MAF = 0.30.

Study outcomes and definitions in CKB. Outcomes, phenotypes and transformations are defined in **Table S14**. Disease endpoints are for hospitalisations, from electronic linkage to the national health insurance system. Phenotypes were measured either at baseline or in a subset of individuals at the second resurvey of ~5% of the CKB cohort.

Ethical considerations in CKB. Ethical approval for CKB was obtained jointly from the University of Oxford, the Chinese Centre for Disease Control and Prevention (CCDC) and the regional CCDC from the 10 study areas.

Results. Results pertaining to CKB are reported in **Note S2**.

Genome-wide association study (GWAS) consortia. We supplemented data from UKBB with summary-level data from 9 genome-wide association study (GWAS) consortia, including data for BMD (both ultrasound-derived estimated heel-bone BMD (33) (eBMD) and dual-energy x-ray absorptiometry (DXA)-derived BMD measured at various anatomical sites (38)), coronary heart disease (CHD) and myocardial infarction (101), stroke (102), atrial fibrillation (103), type 2 diabetes mellitus (104) and glycaemic traits (105, 106), serum lipid fractions (107), anthropometric traits (94, 95), and chronic kidney disease (108, 109). Where available, we selected data pertaining to analyses conducted in European-ancestry individuals. Further details on each consortium are provided in **Table S15**.

GEFOS consortium. Detailed descriptions pertaining to measurement of eBMD and BMD are provided elsewhere (33, 38). Estimates for eBMD were provided in g/cm² units (33). Estimates for DXA-derived BMD across three anatomical sites (lumbar spine (LS-BMD), femoral neck (FN-BMD) and forearm (FA-BMD)) were provided in standard deviation (SD) units (38). We standardized these estimates to g/cm² units using an estimate of the pooled population SD for each of these three measures (0.18 g/cm², 0.14 g/cm² and 0.07 g/cm² for LS-BMD, FN-BMD and FA-BMD, respectively) in the GEFOS consortium (38).

Genetic instrument selection and validation. A recent large-scale GWAS for eBMD, conducted in 142,487 individuals (33), identified two conditionally independent ($r^2=0.13$ among European ancestry individuals in UKBB) genetic variants in the *SOST* locus associated with eBMD: rs7209826 (A>G, G-allele frequency in UKBB = 40%) and rs188810925 (G>A, A-allele frequency = 8%). Both SNPs are located ~35kb downstream from *SOST* and fall within or near a 52kb area that contains the van Buchem disease deletion (**Fig. S19**), a region previously shown to affect *SOST* expression in human bone (7). Recent functional evidence has also shown that SNPs in this area (one of which, rs7220711, is in high LD [$r^2=0.99$] with rs7209826) regulate *SOST* expression via differential transcription factor binding (110). Previous Mendelian randomization studies have also made use of non-coding variants with an effect on gene expression as proxies for pharmacologic modulation of the same target-gene (27, 31, 111, 112). We extracted estimates for these two SNPs (rs7209826 and rs188810925) from GWAS consortia listed in **Table S15**. For GWAS datasets that did not include these variants, we selected proxy variants in high LD

($r^2 > 0.9$) with our selected SNPs using HaploReg (113). We set an r^2 threshold of > 0.9 (in European ancestry individuals) for selection of suitable proxies. We identified 14 SNPs to be in high LD ($r^2 = 0.99$) with rs7209826. Of these 14, we selected rs7220711 as a proxy for rs7209826 based on high LD ($r^2 = 0.99$ in European ancestry populations), availability across most consortia, and prior functional evidence linking rs7220711 to *SOST* expression (110). In addition, we validated the effect of rs7220711 on various measures of BMD as being comparable to that of rs7209826 (**Fig. S20**). There were no suitable proxies ($r^2 > 0.9$) for rs188810925.

We examined the associations of rs7209826 and rs188810925 (and their selected proxies) on DXA-derived measures of BMD measured at specific body sites (lumbar spine, femoral neck, and forearm), using data from the largest GWAS to date for these phenotypes (38).

We next examined the effect of these variants on *SOST* mRNA expression levels in various human tissues in the Genotype-Tissue Expression (GTEx) project dataset (114).

Study outcomes. Specific definitions used in each cohort are specified above. We first tested the association of rs7209826 and rs188810925 with key efficacy outcomes, i.e., fracture risk and risk of osteoporosis (both defined as a combination of self-reported outcomes and International Classification of Diseases, ninth and tenth revision (ICD-9 and ICD-10) codes).

We selected coronary heart disease (CHD) as the primary outcome of interest, given the statistically significant association with cardiac ischemic events reported in a previous RCT of romosozumab (14). We examined the association of the BMD-increasing alleles of rs7209826 and rs188810925 with risk of myocardial infarction and/or coronary revascularization (including self-reported and ICD-9/ICD-10 codes for myocardial infarction, coronary artery bypass graft surgery and/or percutaneous transluminal coronary angioplasty) and a broader composite of all CHD (including all codes for myocardial infarction [MI] and/or coronary revascularization, plus self-reported and ICD-9/ICD-10 codes for angina and chronic stable ischemic heart disease; see **Tables S12-S14** for specific codes included).

Next, we investigated the association of the *SOST* variants with further outcomes and traits in two tiers: firstly, we examined risk of major adverse cardiovascular events (a composite of myocardial infarction and/or coronary revascularization, stroke, or death from either) and all stroke (analogous to the 'major

adverse cardiovascular events (MACE)' and 'cerebrovascular events' outcomes studied in RCTs of romosozumab) and association with cardiovascular risk factors previously shown to play a causal role in CHD (including hypertension, T2D, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), waist-hip ratio (WHR) adjusted for BMI, low-density lipoprotein (LDL) cholesterol, triglycerides, fasting insulin and HbA1c). Secondly, we evaluated an exploratory group of outcomes and traits to identify further putative associations (including ischemic stroke, hemorrhagic stroke, peripheral vascular disease, atrial fibrillation, heart failure, chronic kidney disease, aortic aneurysm, aortic stenosis, high-density lipoprotein (HDL) cholesterol, fasting glucose and serum creatinine-estimated glomerular filtration rate (eGFR)).

Statistical Analyses. We derived cohort-specific SNP effect estimates from participants in the 4 prospective cohorts. Estimates (log(OR) and the standard error of log(OR) for binary outcomes and beta and the standard error of beta for quantitative traits) for the per-allele effect of these variants on disease outcomes and quantitative traits were aligned to the BMD-increasing alleles (as per the effect of therapeutic sclerostin inhibition), and scaled to an increase in BMD equivalent to that reported with romosozumab treatment (see below). Estimates in each cohort were derived as described below.

UKBB. The genotype-outcome association analyses in UKBB were performed using SNPTTEST v2.5.4. We used an additive frequentist model (using “*-frequentist 1*”) and included sex, age at baseline, genotyping array (a binary variable), and the first 15 principal components as covariates in all analyses. We accounted for genotype uncertainty by using “*-method expected*”.

PHB. Linear (for continuous phenotype) or logistic regression (for case-control binary phenotype) was used to test associations between SNPs rs188810925 and rs7209826 and phenotypes of interest using PLINK 1.9. For phenotypes without residual inverse rank normalization, we adjusted for sex, age at assessment, age squared, genotype batches and 15 principal components in the regression model. For phenotypes with residual inverse rank normalization, we did not adjust for any covariates in the regression model.

EGCUT. We calculated the effect estimates for the two SNPs using logistic regression and adjusting for age, sex and 15 principal components. All associations were tested under an additive model using glm function with R software (3.3.2).

CKB. To avoid ascertainment biases, unless otherwise specified, controls for binary endpoints were restricted to a 72,795 subset who had been randomly-selected for genotyping (~28k of genotyped samples were selected on the basis of incident CVD or COPD disease events). Covariates were as specified in **Table S14**. All analyses used release version 15 of the CKB database and were performed using SAS software (version 9.3; SAS Institute, Inc).

Scaling of allelic estimates. Similar to other studies utilising genetic variants to estimate the effects of drug target modulation (29, 81), we scaled allelic estimates pertaining to risk of osteoporosis, fractures, cardiometabolic outcomes and quantitative traits to an increase in BMD equivalent to that reported in a phase II RCT of 12 months of 210mg romosozumab monthly (39). This corresponds to the dose evaluated in phase III RCTs of romosozumab, and represents a 0.09 g/cm² increase in lumbar spine BMD (LS-BMD) in postmenopausal women (39). We selected lumbar spine BMD as the reference phenotype as this was the only BMD phenotype for which we had genetic data (38) and clinical trial data (39) in the same units of measurements (i.e. g/cm²). To do this, we derived the allelic effect estimates (in SD units) for the association of rs7209826 and rs188810925 with LS-BMD from a previous large-scale GWAS of LS-BMD(38) (0.046 and 0.09 SD units, respectively). Since these estimates were reported in SD units, we first standardized these to g/cm² units. To standardize to g/cm² units, we used the pooled (median) SD of LS-BMD as reported in the same study (one SD = 0.18 g/cm²). We then multiplied the SD-units effect estimates by this value, to derive estimates in g/cm² units (rs188810925: 0.016 g/cm²; rs7209826: 0.008 g/cm²). Next, we derived a scaling factor for each SNP by dividing the increase in LS-BMD arising from treatment with 210mg romosozumab monthly for 12 months (0.09 g/cm²) by the allelic effect estimate for LS-BMD (scaling factors: rs188810925 = 5.52; rs7209826 = 10.84)). All per-allele effect estimates (log(OR) and the standard error of log(OR) for binary outcomes; beta and the standard error of beta for

quantitative traits) were subsequently multiplied by these scaling factors to estimate the effects expected with 12 months of 210mg romosozumab monthly.

Meta-analysis of scaled allelic estimates. We meta-analysed scaled estimates from the prospective cohorts with (scaled) estimates from GWAS consortia for equivalent outcomes using inverse-variance weighted fixed-effect meta-analysis. We predefined a p-value threshold of <0.05 for the association with CHD given the association of sclerostin inhibition with cardiac ischemic events in prior RCTs (14, 15). For the first tier of outcomes and traits, we used a Bonferroni adjusted p-value threshold of < 0.004 (adjusting for a cumulative 13 tests), and for the second tier, an adjusted p-value threshold of < 0.002 (adjusting for a cumulative 24 tests). The R-package METAFOR was used for performing all meta-analyses of scaled allelic estimates (115). Fixed-effect meta-analyses were used in all instances. Cochran's Q test and the I^2 statistic were used to evaluate heterogeneity for all meta-analyses performed (see **Table S7**).

Sex-specific analyses. In light of the proposed indication for romosozumab in the US (i.e. in women only), we performed additional sex-specific sensitivity analyses for all associated outcomes from the combined sexes analysis. Sexual heterogeneity was evaluated using Cochran's Q test and the I^2 statistic.

Colocalization analyses. We used *coloc*, a Bayesian modelling approach (116), to estimate the posterior probability of shared causal variant(s) driving associations in pairs of traits (i.e. colocalization). We assessed colocalization of eBMD and tissue-specific *SOST* mRNA expression between conditionally independent eBMD signals in the *SOST* locus (i.e. those pertaining to rs7209826 and rs188810925) by first applying conditional analysis using the *GCTA-COJO* statistical suite (117), using genotype data from UKBB as an LD reference panel. We conditioned all datasets on rs2523161 (an independent eBMD-associated variant ~600Kb from *SOST*), on either rs7209826 or rs188810925, and on any further independent eQTLs identified in specific tissues. We ran *coloc* on 400-kb and 2Mb regions centred on each independent lead eBMD-associated SNP, and used the default priors. We investigated colocalization between eBMD and *SOST* gene expression in various tissues, systolic blood pressure, and waist-hip ratio adjusted for BMI. Colocalization analyses where $PP3 + PP4 < 0.8$ were considered to be

underpowered to detect colocalization (118, 119). Visual assessment of colocalization was performed using the LocusCompareR R library (120). For adequately powered colocalization analyses, we considered a $PP4 > 0.8$ as evidence of colocalization between the two traits.

Protein quantitative trait loci analysis. We sought to investigate whether lower levels of circulating sclerostin protein were also associated with an increased risk of cardiometabolic diseases. For this analysis, we used genetic variants associated with circulating sclerostin protein as reported in a recent GWAS of this trait (73). Three trans-pQTLs (and no cis-pQTLs) were reported (two, rs215226 and rs7241221, meeting genome-wide significance of $p < 5 \times 10^{-8}$, and one (rs1485303) suggestive at $p = 7.70 \times 10^{-8}$). We first evaluated the effect of these variants on various measures of BMD to confirm that the variants had a robust and appropriate effect on these biomarkers, before investigating their effects on clinical outcomes of interest. Results pertaining to this investigation are reported in **Note S1**.

Phenome-wide association analysis. We extracted estimates relating to the association of rs188810925 and rs7209826 with 1,074 binary outcomes (those with more than 200 cases available) from publicly available summary statistics generated by the Lee lab (available from: <https://www.leelabsg.org/resources>). All estimates were scaled to match the effect of 210mg romosozumab monthly for 12 months on lumbar spine bone mineral density (0.09 g/cm²) and aligned to the BMD-increasing alleles.

Meta-analysis of RCTs of sclerostin-inhibitors. We searched for all phase III RCTs performed for sclerostin inhibitors (romosozumab, blosozumab and setrusumab). We collected a record of trials conducted for sclerostin inhibitors from the websites of the agents' developers (<http://www.amgentrials.com/amgen/study.aspx>; <https://www.mereobiopharma.com/pipeline/bps-804-setrusumab/>), and supplemented this with further searches on clinical trials registries (ClinicalTrials.gov, EU Clinical Trials Register and International Clinical Trials Registry Platform) and PubMed (1966-present), using the key-words ("sclerostin" OR "romosozumab" OR "AMG-785" OR "setrusumab" OR "blosozumab") AND ("trial" OR "randomized controlled trial" OR "RCT" OR "randomised controlled trial")

for PubMed. One of the authors (J.B.) screened the titles and abstracts of all identified studies for eligibility; where doubt arose as to eligibility, the full paper was evaluated. Potentially eligible studies were reviewed with two senior authors (C.M.L. and M.V.H.). All published studies with available cardiovascular outcome data pertaining to a double-blind, comparator-controlled phase III RCT were eligible for inclusion. Our search strategy and results are summarised in **Table S17**, with last search performed on 08 November 2019. Seven phase III trials were identified (**Table S18**), of which three trials met our criteria for inclusion in the meta-analysis. Assessment of risk of bias for each eligible trial was completed using the Cochrane Risk of Bias tool (121), and is presented in **Fig. S23**. We extracted each trial's duration, blinding status, nature of the control intervention, and data pertaining to risk of 'clinical fracture' (a composite of nonvertebral fracture and symptomatic vertebral fracture) and risk of four cardiovascular outcomes ('cardiac ischemic events', 'cerebrovascular events', 'major adverse cardiovascular events', and 'serious cardiovascular events') from the peer-reviewed publications of the trials. Where trials reported data pertaining to multiple phases (e.g. an initial blinded phase, followed by an open-label phase), only data pertaining to the blinded phase was extracted. We also incorporated unpublished data pertaining to the cardiovascular outcomes newly released by the sponsors of romosozumab for the US FDA Drugs Advisory Committee meeting in January 2019 (122), with the caveat that some of these data have not undergone peer-review (albeit adjudicated by two independent bodies — the Duke Clinical Research Institute [DCRI] and the Thrombolysis in Myocardial Infarction [TIMI] Study Group). Inclusion of these data in our analyses is indicated where appropriate. Data extracted from trial publications were cross-checked with the FDA-reported data, where possible. If data for the same trial and outcome differed between the original publication and the FDA-reported data, we included data from the original publication in our primary analysis and performed further sensitivity analyses with inclusion of the FDA-reported data. The risk of bias arising from selective publication of trials was deemed to be low - of the seven phase III trials of romosozumab we identified (**Table S18**), three were unpublished. The largest unpublished trial included 294 participants (compared to the two largest, published phase III trials, ARCH and FRAME, totalling 4,093 and 7,180 participants, respectively).

We then performed meta-analyses of cardiovascular outcome data at 12 months (corresponding to the duration of the blinded phase) from phase III RCTs using 210mg romosozumab monthly for 12 months

(since this was the only agent for which eligible RCTs were available, and also the standard dose and duration used across the eligible phase III trials), with 'cardiac ischemic events' as the primary outcome of interest, given the association with this outcome observed in a previous RCT of romosozumab (14).

Further meta-analyses were performed for 'cerebrovascular events' and two composite outcomes: 'serious cardiovascular events' (including cardiac ischemic events, cerebrovascular events, heart failure, cardiovascular death, non-coronary revascularization and peripheral vascular ischemic events not requiring revascularization) and 'major adverse cardiovascular events' (a composite of myocardial infarction, stroke, or cardiovascular death). Meta-analyses were performed by computing odds ratios and 95% confidence intervals for each cardiovascular outcome, using fixed-effects models. Cochran's Q test was used to evaluate heterogeneity between trials. We set a prespecified p-value threshold of <0.05 for meta-analyses of the RCTs given the prior evidence for ischemic cardiovascular events seen in individual RCTs of romosozumab (14, 15)).

All meta-analyses of RCT cardiovascular outcomes were performed according to the Mantel-Haenszel method without continuity correction. This method has been shown to perform relatively well when events are rare, and is also the default fixed-effect meta-analysis method recommended by the Cochrane collaboration (123–125). We performed additional sensitivity analyses using the Peto method, a fixed-effect method shown to provide relatively unbiased results if within-trial intervention and control groups are of approximately equal size and if the effect size is modest (123, 124). Meta-analysis of fracture data was performed using inverse variance weighted fixed-effect meta-analysis of fracture risk at 12 months in the FRAME (13) and ARCH (14) trials (**Table S10**). All meta-analyses of trial data were performed using the R-package METAFOR. We completed the PRISMA checklist (126) (see Supplementary Materials).

Supplementary Materials

Note S1. Evaluation of genetic variants associated with circulating sclerostin level.

Note S2. Trans-ethnic replication in China Kadoorie Biobank.

Figure S1A. Meta-analysis of romosozumab and risk of cardiovascular events from phase III randomized controlled trials, using Peto Method.

Figure S1B. Meta-analysis of romosozumab and risk of serious cardiovascular events from phase III randomized controlled trials, using FDA meeting data.

Figure S2. *SOST* expression is highest in arterial tissues.

Figure S3. *SOST* mRNA expression by rs7209826 and rs188810925 genotype.

Figure S4. Colocalization of *SOST* mRNA expression in tibial artery tissue and eBMD.

Figure S5. Per-allele associations of rs7209826 and rs188810925 with various bone mineral density (BMD) measures.

Figure S6. Study-specific scaled estimates and meta-analysis of BMD-increasing *SOST* variants with risk of osteoporosis and fracture.

Figure S7. Scaled estimates and meta-analysis of BMD-increasing *SOST* variants with risk of fracture in the preceding 5 years, at different anatomical sites, in UKBB.

Figure S8. Study-specific scaled estimates and meta-analysis of BMD-increasing *SOST* variants with risk of myocardial infarction and/or coronary revascularization, coronary heart disease and major adverse cardiovascular events.

Figure S9. Study-specific scaled estimates and meta-analysis of BMD-increasing *SOST* variants with risk of 11 cardiometabolic outcomes.

Figure S10. Study-specific scaled estimates and meta-analysis of BMD-increasing *SOST* variants with systolic and diastolic blood pressure.

Figure S11. Study-specific scaled estimates and meta-analysis of BMD-increasing *SOST* variants with waist to hip ratio (WHR; adjusted for body mass index), body mass index (BMI), LDL cholesterol, HDL cholesterol and triglycerides.

Figure S12. Scaled estimates and meta-analysis of BMD-increasing *SOST* variants with glomerular filtration rate estimated from serum creatinine (eGFR) in the CKDGEN consortium.

Figure S13. Per-allele associations of *SOST* variants identified by different eBMD GWAS with various BMD measures.

Figure S14. Comparison of associations of *SOST* variants identified by different eBMD GWAS with major outcomes of interest.

Figure S15. Phenome-wide association analysis of *SOST* variants with 1,074 binary outcomes in UK Biobank.

Figure S16. Meta-analysis of romosozumab and risk of clinical fracture from phase III randomized controlled trials.

Figure S17. Scaled estimates of *SOST*-specific instrument and all eBMD-associated SNPs with T2D and CHD.

Figure S18. Overview of genetic analysis.

Figure S19. Regional association plots of *SOST* locus in GWAS of heel-bone estimated bone mineral density in UKBB (n = 142,487).

Figure S20. Per-allele associations of rs7209826 and selected proxy (rs7220711; $r^2 = 0.99$) with various bone mineral density (BMD) measures.

Figure S21. Per-allele association of rs7209826 with estimated heel-bone bone mineral density (eBMD) in UKBB and China Kadoorie Biobank.

Figure S22. Regional association plot of *SOST* locus in GWAS of heel-bone estimated bone mineral density in China Kadoorie Biobank (n = 21,547).

Figure S23. Assessment of risk of bias in phase III randomized controlled trials of romosozumab included in meta-analysis.

Table S1. Published phase III randomized controlled trials of romosozumab.

Table S2. Reported cardiovascular outcomes at 12 months from published phase III randomized controlled trials of romosozumab.

Table S3. Summary statistics of meta-analyses of cardiovascular events in randomized controlled trials of romosozumab.

Table S4. Effect of rs7209826 and rs188810925 on *SOST* gene expression in arterial tissues.

Table S5. Colocalization analysis of *SOST* mRNA expression in various tissues and eBMD.

Table S6. Scaled estimates for glycaemic traits from MAGIC consortium.

Table S7. Summary statistics of meta-analyses of scaled allelic estimates.

Table S8. Sex-specific summary statistics.

Table S9. Colocalization analysis of eBMD with systolic blood pressure and waist-hip ratio adjusted for BMI.

Table S10. Reported fracture outcomes at 12 and 24 months from published phase III randomized controlled trials of romosozumab.

Table S11. Baseline characteristics in UK Biobank.

Table S12. Definitions of outcomes analyzed in UK Biobank.

Table S13. Definitions of outcomes analyzed in Partners HealthCare Biobank.

Table S14. Definitions of outcomes analyzed in China Kadoorie Biobank.

Table S15. Genome-wide association studies and consortia included in present study.

Table S16. Per-allele estimates for rs7209826 in China Kadoorie Biobank.

Table S17. Search strategy and results for identifying phase III randomized controlled trials of sclerostin inhibitors.

Table S18. Phase III randomized controlled trials conducted for romosozumab.

Supplementary references (1-8).

References

1. J. E. Compston, M. R. McClung, W. D. Leslie, Osteoporosis, *Lancet* **393**, 364–376 (2019).
2. D. M. Black, C. J. Rosen, Clinical Practice. Postmenopausal Osteoporosis, *N. Engl. J. Med.* **374**, 254–262 (2016).
3. S. Khosla, L. C. Hofbauer, Osteoporosis treatment: recent developments and ongoing challenges, *Lancet Diabetes Endocrinol* **5**, 898–907 (2017).
4. T. J. de Villiers, The quest for new drugs to prevent osteoporosis-related fractures, *Climacteric* **20**, 103–106 (2017).
5. M. R. McClung, Clinical utility of anti-sclerostin antibodies, *Bone* **96**, 3–7 (2017).
6. M. E. Brunkow, J. C. Gardner, J. Van Ness, B. W. Paeper, B. R. Kovacevich, S. Proll, J. E. Skonier, L. Zhao, P. J. Sabo, Y.-H. Fu, R. S. Alisch, L. Gillett, T. Colbert, P. Tacconi, D. Galas, H. Hamersma, P. Beighton, J. T. Mulligan, Bone Dysplasia Sclerosteosis Results from Loss of the SOST Gene Product, a Novel Cystine Knot-Containing Protein, *Am. J. Hum. Genet.* **68**, 577–589 (2001).
7. G. G. Loots, M. Kneissel, H. Keller, M. Baptist, J. Chang, N. M. Collette, D. Ovcharenko, I. Plajzer-Frick, E. M. Rubin, Genomic deletion of a long-range bone enhancer misregulates sclerostin in Van Buchem disease, *Genome Res.* **15**, 928–935 (2005).
8. C. J. Rosen, Romosozumab - Promising or Practice Changing?, *N. Engl. J. Med.* **377**, 1479–1480 (2017).
9. L. Seefried, J. Baumann, S. Hemsley, C. Hofmann, E. Kunstmann, B. Kiese, Y. Huang, S. Chivers, M.-A. Valentin, B. Borah, R. Roubenoff, U. Junker, F. Jakob, Efficacy of anti-sclerostin monoclonal antibody BPS804 in adult patients with hypophosphatasia, *J. Clin. Invest.* **127**, 2148–2158 (2017).
10. R. R. Recker, C. T. Benson, T. Matsumoto, M. A. Bolognese, D. A. Robins, J. Alam, A. Y. Chiang, L. Hu, J. H. Krege, H. Sowa, B. H. Mitlak, S. L. Myers, A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density, *J. Bone Miner. Res.* **30**, 216–224 (2015).
11. I. R. Reid, Targeting Sclerostin in Postmenopausal Osteoporosis: Focus on Romosozumab and Blosozumab, *BioDrugs* **31**, 289–297 (2017).
12. M. R. McClung, A. Grauer, S. Boonen, M. A. Bolognese, J. P. Brown, A. Diez-Perez, B. L. Langdahl, J.-Y. Reginster, J. R. Zanchetta, S. M. Wasserman, L. Katz, J. Maddox, Y.-C. Yang, C. Libanati, H. G. Bone, Romosozumab in Postmenopausal Women with Low Bone Mineral Density, *N. Engl. J. Med.* **370**, 412–420 (2014).
13. F. Cosman, D. B. Crittenden, J. D. Adachi, N. Binkley, E. Czerwinski, S. Ferrari, L. C. Hofbauer, E. Lau, E. M. Lewiecki, A. Miyauchi, C. A. F. Zerbini, C. E. Milmont, L. Chen, J. Maddox, P. D. Meisner, C. Libanati, A. Grauer, Romosozumab Treatment in Postmenopausal Women with Osteoporosis, *N. Engl. J. Med.* **375**, 1532–1543 (2016).
14. K. G. Saag, J. Petersen, M. L. Brandi, A. C. Karaplis, M. Lorentzon, T. Thomas, J. Maddox, M. Fan, P. D. Meisner, A. Grauer, Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis, *N. Engl. J. Med.* **377**, 1417–1427 (2017).
15. E. M. Lewiecki, T. Blicharski, S. Goemaere, K. Lippuner, P. D. Meisner, P. D. Miller, A. Miyauchi, J. Maddox, L. Chen, S. Horlait, A Phase 3 Randomized Placebo-controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis, *J. Clin. Endocrinol. Metab.* **103**, 3183–3193 (2018).

16. P. Evenepoel, P. D'Haese, V. Brandenburg, Romosozumab in postmenopausal women with osteopenia *N. Engl. J. Med.* **370**, 1664 (2014).
17. E. Tsourdi, T. D. Rachner, L. C. Hofbauer, Romosozumab versus Alendronate and Fracture Risk in Women with Osteoporosis *N. Engl. J. Med.* **378**, 195 (2018).
18. V. M. Brandenburg, A. Verhulst, A. Babler, P. C. D'Haese, P. Evenepoel, N. Kaesler, Sclerostin in chronic kidney disease-mineral bone disorder think first before you block it!, *Nephrol. Dial. Transplant* **34**, 408–414 (2018).
19. A. Mullard, FDA rejects first-in-class osteoporosis drug, *Nat. Rev. Drug Discov.* **16**, 593 (2017).
20. European Medicines Agency Accepts Filing For EVENITY (Romosozumab) (2018) (available at <https://www.amgen.com/en-au/media/news-releases/2018/01/european-medicines-agency-accepts-filing-for-evenity-romosozumab/>).
21. Amgen And UCB Resubmit Biologics License Application BLA For EVENITY (romosozumab) To The US FDA (2018) (available at <https://www.amgen.com/media/news-releases/2018/07/amgen-and-ucb-resubmit-biologics-license-application-bla-for-evenity-romosozumab-to-the-us-fda/>).
22. Amgen, FDA Approves EVENITY™ (romosozumab) For The Treatment Of Osteoporosis In Postmenopausal Women At High Risk For Fracture *PR Newswire* (2019) (available at <https://www.prnewswire.com/news-releases/fda-approves-evenity-romosozumab-aqqg-for-the-treatment-of-osteoporosis-in-postmenopausal-women-at-high-risk-for-fracture-300828376.html>).
23. E. M. Francisco, Evenity: Pending EC decision - European Medicines Agency *European Medicines Agency* (2019) (available at <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/evenity>).
24. EVENITY® (romosozumab) Receives Positive CHMP Opinion for the Treatment of Severe Osteoporosis in Postmenopausal Women at High Risk of Fracture (available at <https://www.ucb.com/stories-media/Press-Releases/article/EVENITY-romosozumab-Receives-Positive-CHMP-Opinion-for-the-Treatment-of-Severe-Osteoporosis-in-Postmenopausal-Women-at-High-Risk-of-Fracture>).
25. V. M. Walker, G. Davey Smith, N. M. Davies, R. M. Martin, Mendelian randomization: a novel approach for the prediction of adverse drug events and drug repurposing opportunities, *Int. J. Epidemiol.* **46**, 2078–2089 (2017).
26. M. V. Holmes, Human Genetics and Drug Development, *N. Engl. J. Med.* **380**, 1076–1079 (2019).
27. M. V. Holmes, T. Simon, H. J. Exeter, L. Folkersen, F. W. Asselbergs, M. Guardiola, J. A. Cooper, J. Palmen, J. A. Hubacek, K. F. Carruthers, B. D. Horne, K. D. Brunisholz, J. L. Mega, E. P. A. van Iperen, M. Li, M. Leusink, S. Trompet, J. J. W. Verschuren, G. K. Hovingh, A. Dehghan, C. P. Nelson, S. Kotti, N. Danchin, M. Scholz, C. L. Haase, D. Rothenbacher, D. I. Swerdlow, K. B. Kuchenbaecker, E. Staines-Urias, A. Goel, F. van 't Hooft, K. Gertow, U. de Faire, A. G. Panayiotou, E. Tremoli, D. Baldassarre, F. Veglia, L. M. Holdt, F. Beutner, R. T. Gansevoort, G. J. Navis, I. Mateo Leach, L. P. Breitling, H. Brenner, J. Thiery, D. Dallmeier, A. Franco-Cereceda, J. M. A. Boer, J. W. Stephens, M. H. Hofker, A. Tedgui, A. Hofman, A. G. Uitterlinden, V. Adamkova, J. Pitha, N. C. Onland-Moret, M. J. Cramer, H. M. Nathoe, W. Spiering, O. H. Klungel, M. Kumari, P. H. Whincup, D. A. Morrow, P. S. Braund, A. S. Hall, A. G. Olsson, P. A. Doevendans, M. D. Trip, M. D. Tobin, A. Hamsten, H. Watkins, W. Koenig, A. N. Nicolaides, D. Teupser, I. N. M. Day, J. F. Carlquist, T. R. Gaunt, I. Ford, N. Sattar, S. Tsimikas, G. G. Schwartz, D. A. Lawlor, R. W. Morris, M. S. Sandhu, R. Poledne, A. H. Maitland-van der Zee, K.-T. Khaw, B. J. Keating, P. van der Harst, J. F. Price, S. R. Mehta, S. Yusuf, J. C. M. Witteman, O. H. Franco, J. W. Jukema, P. de Krijff, A. Tybjaerg-Hansen, D. J. Rader, M. Farrall, N. J. Samani, M. Kivimaki, K. A. A. Fox, S. E. Humphries, J. L. Anderson, S. M. Boekholdt, T. M. Palmer, P. Eriksson, G. Paré, A. D. Hingorani, M. S. Sabatine, Z. Mallat, J. P. Casas, P. J. Talmud, Secretory phospholipase A(2)-IIA and cardiovascular

disease: a mendelian randomization study, *J. Am. Coll. Cardiol.* **62**, 1966–1976 (2013).

28. Myocardial Infarction Genetics Consortium Investigators, N. O. Stitziel, H.-H. Won, A. C. Morrison, G. M. Peloso, R. Do, L. A. Lange, P. Fontanillas, N. Gupta, S. Duga, A. Goel, M. Farrall, D. Saleheen, P. Ferrario, I. König, R. Asselta, P. A. Merlini, N. Marziliano, M. F. Notarangelo, U. Schick, P. Auer, T. L. Assimes, M. Reilly, R. Wilensky, D. J. Rader, G. K. Hovingh, T. Meitinger, T. Kessler, A. Kastrati, K.-L. Laugwitz, D. Siscovick, J. I. Rotter, S. L. Hazen, R. Tracy, S. Cresci, J. Spertus, R. Jackson, S. M. Schwartz, P. Natarajan, J. Crosby, D. Muzny, C. Ballantyne, S. S. Rich, C. J. O'Donnell, G. Abecasis, S. Sunaev, D. A. Nickerson, J. E. Buring, P. M. Ridker, D. I. Chasman, E. Austin, I. J. Kullo, P. E. Weeke, C. M. Shaffer, L. A. Bastarache, J. C. Denny, D. M. Roden, C. Palmer, P. Deloukas, D.-Y. Lin, Z.-Z. Tang, J. Erdmann, H. Schunkert, J. Danesh, J. Marrugat, R. Elosua, D. Ardissino, R. McPherson, H. Watkins, A. P. Reiner, J. G. Wilson, D. Altshuler, R. A. Gibbs, E. S. Lander, E. Boerwinkle, S. Gabriel, S. Kathiresan, Inactivating mutations in NPC1L1 and protection from coronary heart disease, *N. Engl. J. Med.* **371**, 2072–2082 (2014).

29. R. A. Scott, D. F. Freitag, L. Li, A. Y. Chu, P. Surendran, R. Young, N. Grarup, A. Stancáková, Y. Chen, T. V. Varga, H. Yaghootkar, J. 'an Luan, J. H. Zhao, S. M. Willems, J. Wessel, S. Wang, N. Maruthur, K. Michailidou, A. Pirie, S. J. van der Lee, C. Gillson, A. A. Al Olama, P. Amouyel, L. Arriola, D. Arveiler, I. Aviles-Olmos, B. Balkau, A. Barricarte, I. Barroso, S. B. Garcia, J. C. Bis, S. Blankenberg, M. Boehnke, H. Boeing, E. Boerwinkle, I. B. Borecki, J. Bork-Jensen, S. Bowden, C. Caldas, M. Caslake, CVD50 consortium, L. A. Cupples, C. Cruchaga, J. Czajkowski, M. den Hoed, J. A. Dunn, H. M. Earl, G. B. Ehret, E. Ferrannini, J. Ferrieres, T. Foltynie, I. Ford, N. G. Forouhi, F. Gianfagna, C. Gonzalez, S. Grioni, L. Hiller, J.-H. Jansson, M. E. Jørgensen, J. W. Jukema, R. Kaaks, F. Kee, N. D. Kerrison, T. J. Key, J. Kontto, Z. Kote-Jarai, A. T. Kraja, K. Kuulasmaa, J. Kuusisto, A. Linneberg, C. Liu, G. Marenne, K. L. Mohlke, A. P. Morris, K. Muir, M. Müller-Nurasyid, P. B. Munroe, C. Navarro, S. F. Nielsen, P. M. Nilsson, B. G. Nordestgaard, C. J. Packard, D. Palli, S. Panico, G. M. Peloso, M. Perola, A. Peters, C. J. Poole, J. R. Quirós, O. Rolandsson, C. Sacerdote, V. Salomaa, M.-J. Sánchez, N. Sattar, S. J. Sharp, R. Sims, N. Slimani, J. A. Smith, D. J. Thompson, S. Trompet, R. Tumino, D. L. van der A, Y. T. van der Schouw, J. Virtamo, M. Walker, K. Walter, GERAD_EC Consortium, Neurology Working Group of the Cohorts for Heart, Aging Research in Genomic Epidemiology (CHARGE), Alzheimer's Disease Genetics Consortium, Pancreatic Cancer Cohort Consortium, European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD), EPIC-InterAct, J. E. Abraham, L. T. Amundadottir, J. L. Aponte, A. S. Butterworth, J. Dupuis, D. F. Easton, R. A. Eeles, J. Erdmann, P. W. Franks, T. M. Frayling, T. Hansen, J. M. M. Howson, T. Jørgensen, J. Kooner, M. Laakso, C. Langenberg, M. I. McCarthy, J. S. Pankow, O. Pedersen, E. Riboli, J. I. Rotter, D. Saleheen, N. J. Samani, H. Schunkert, P. Vollenweider, S. O'Rahilly, CHARGE consortium, CHD Exome+ Consortium, CARDIOGRAM Exome Consortium, P. Deloukas, J. Danesh, M. O. Goodarzi, S. Kathiresan, J. B. Meigs, M. G. Ehm, N. J. Wareham, D. M. Waterworth, A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease, *Sci. Transl. Med.* **8**, 341ra76 (2016).

30. B. A. Ference, J. G. Robinson, R. D. Brook, A. L. Catapano, M. J. Chapman, D. R. Neff, S. Voros, R. P. Giugliano, G. Davey Smith, S. Fazio, M. S. Sabatine, Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes, *N. Engl. J. Med.* **375**, 2144–2153 (2016).

31. I. Y. Millwood, D. A. Bennett, M. V. Holmes, R. Boxall, Y. Guo, Z. Bian, L. Yang, S. Sansome, Y. Chen, H. Du, C. Yu, A. Hacker, D. F. Reilly, Y. Tan, M. R. Hill, J. Chen, R. Peto, H. Shen, R. Collins, R. Clarke, L. Li, R. G. Walters, Z. Chen, China Kadoorie Biobank Collaborative Group, Association of CETP Gene Variants With Risk for Vascular and Nonvascular Diseases Among Chinese Adults, *JAMA Cardiol* **3**, 34–43 (2017).

32. FDA, *FDA Briefing Document for Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee* (FDA, 2019; <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM629456.pdf>).

33. J. P. Kemp, J. A. Morris, C. Medina-Gomez, V. Forgetta, N. M. Warrington, S. E. Youtten, J. Zheng, C. L. Gregson, E. Grundberg, K. Trajanoska, J. G. Logan, A. S. Pollard, P. C. Sparkes, E. J. Ghirardello,

R. Allen, V. D. Leitch, N. C. Butterfield, D. Komla-Ebri, A.-T. Adoum, K. F. Curry, J. K. White, F. Kussy, K. M. Greenlaw, C. Xu, N. C. Harvey, C. Cooper, D. J. Adams, C. M. T. Greenwood, M. T. Maurano, S. Kaptoge, F. Rivadeneira, J. H. Tobias, P. I. Croucher, C. L. Ackert-Bicknell, J. H. D. Bassett, G. R. Williams, J. B. Richards, D. M. Evans, Identification of 153 new loci associated with heel bone mineral density and functional involvement of GPC6 in osteoporosis, *Nat. Genet.* **49**, 1468–1475 (2017).

34. K. M. Siewert, B. F. Voight, Bivariate Genome-Wide Association Scan Identifies 6 Novel Loci Associated With Lipid Levels and Coronary Artery Disease, *Circ Genom Precis Med* **11**, e002239 (2018).

35. L. M. Huckins, A. Dobbyn, D. M. Ruderfer, G. Hoffman, W. Wang, A. F. Pardiñas, V. M. Rajagopal, T. D. Als, H. T. Nguyen, K. Girdhar, J. Boocock, P. Roussos, M. Fromer, R. Kramer, E. Domenici, E. R. Gamazon, S. Purcell, J. S. Johnson, H. R. Shah, L. L. Klein, K. K. Dang, B. A. Logsdon, M. C. Mahajan, L. M. Mangravite, H. Toyoshima, R. E. Gur, C.-G. Hahn, E. Schadt, D. A. Lewis, V. Haroutunian, M. A. Peters, B. K. Lipska, J. Buxbaum, K. Hirai, T. M. Perumal, L. Essioux, S. Ripke, B. M. Neale, A. Corvin, I. T. R. Walters, K.-H. Farh, P. A. Holmans, P. Lee, B. Bulik-Sullivan, D. A. Collier, H. Huang, T. H. Pers, I. Agartz, E. Agerbo, M. Albus, M. Alexander, F. Amin, S. A. Bacanu, M. Begemann, R. A. Belliveau, J. Bene, S. E. Bergen, E. Bevilacqua, T. B. Bigdeli, D. W. Black, R. Bruggeman, N. G. Buccola, R. L. Buckner, W. Byerley, W. Cahn, G. Cai, D. Campion, R. M. Cantor, V. J. Carr, N. Carrera, S. V. Catts, K. D. Chambert, R. C. K. Chan, R. Y. L. Chen, E. Y. H. Chen, W. Cheng, E. F. C. Cheung, S. A. Chong, C. R. Cloninger, D. Cohen, N. Cohen, P. Cormican, N. Craddock, J. J. Crowley, D. Curtis, M. Davidson, K. L. Davis, F. Degenhardt, J. Del Favero, D. Demontis, D. Dikeos, T. Dinan, S. Djurovic, G. Donohoe, E. Drapeau, J. Duan, F. Dudbridge, N. Durmishi, P. Eichhammer, J. Eriksson, V. Escott-Price, L. Essioux, A. H. Fanous, M. S. Farrell, J. Frank, L. Franke, R. Freedman, N. B. Freimer, M. Friedl, J. I. Friedman, M. Fromer, G. Genovese, L. Georgieva, I. Giegling, P. Giusti-Rodríguez, S. Godard, J. I. Goldstein, V. Golimbet, S. Gopal, J. Gratten, L. de Haan, C. Hammer, M. L. Hamshere, M. Hansen, T. Hansen, V. Haroutunian, A. M. Hartmann, F. A. Henskens, S. Herms, J. N. Hirschhorn, P. Hoffmann, A. Hofman, M. V. Hollegaard, D. M. Hougaard, M. Ikeda, I. Joa, A. Julia, R. S. Kahn, L. Kalaydjieva, S. Karachanak-Yankova, J. Karjalainen, D. Kavanagh, M. C. Keller, J. L. Kennedy, A. Khrunin, Y. Kim, J. Klovins, J. A. Knowles, B. Konte, V. Kucinskis, Z. A. Kucinskiene, H. Kuzelova-Ptackova, A. K. Kahler, C. Laurent, J. L. C. Keong, S. H. Lee, S. E. Legge, B. Lerer, M. Li, T. Li, K.-Y. Liang, J. Lieberman, S. Limborska, C. M. Loughland, J. Lubinski, J. Lonnqvist, M. Macek, P. K. E. Magnusson, B. S. Maher, W. Maier, J. Mallet, S. Marsal, M. Mattheisen, M. Mattingsdal, R. W. McCarley, C. McDonald, A. M. McIntosh, S. Meier, C. J. Meijer, B. Melegh, I. Melle, R. I. Meshulam-Gately, A. Metspalu, P. T. Michie, L. Milani, V. Milanova, Y. Mokrab, D. W. Morris, O. Mors, K. C. Murphy, R. M. Murray, I. Myin-Germeys, B. Muller-Myhsok, M. Nelis, I. Nenadic, D. A. Nertney, G. Nestadt, K. K. Nicodemus, L. Nikitina-Zake, L. Nisenbaum, A. Nordin, E. O'Callaghan, C. O'Dushlaine, F. A. O'Neill, S.-Y. Oh, A. Olincy, L. Olsen, J. Van Os, C. Pantelis, G. N. Papadimitriou, S. Papiol, E. Parkhomenko, M. T. Pato, T. Paunio, M. Pejovic-Milovancevic, D. O. Perkins, O. Pietiläinen, J. Pimm, A. J. Pocklington, J. Powell, A. Price, A. E. Pulver, S. M. Purcell, D. Quested, H. B. Rasmussen, A. Reichenberg, M. A. Reimers, A. L. Richards, J. L. Roffman, P. Roussos, D. M. Ruderfer, V. Salomaa, A. R. Sanders, U. Schall, C. R. Schubert, T. G. Schulze, S. G. Schwab, E. M. Scolnick, R. J. Scott, L. J. Seidman, J. Shi, E. Sigurdsson, T. Silagadze, J. M. Silverman, K. Sim, P. Slominsky, J. W. Smoller, H.-C. So, C. C. A. Spencer, E. A. Stahl, H. Stefansson, S. Steinberg, E. Stogmann, R. E. Straub, E. Strengman, J. Strohmaier, T. S. Stroup, M. Subramaniam, J. Suvisaari, D. M. Svrakic, J. P. Szatkiewicz, E. Soderman, S. Thirumalai, D. Toncheva, S. Tosato, J. Veijola, J. Waddington, D. Walsh, D. Wang, Q. Wang, B. T. Webb, M. Weiser, D. B. Wildenauer, N. M. Williams, S. Williams, S. H. Witt, A. R. Wolen, E. H. M. Wong, B. K. Wormley, H. S. Xi, C. C. Zai, X. Zheng, F. Zimprich, N. R. Wray, K. Stefansson, P. M. Visscher, R. Adolfsson, O. A. Andreassen, D. H. R. Blackwood, E. Bramon, J. Buxbaum, A. D. Børglum, S. Cichon, A. Darvasi, E. Domenici, H. Ehrenreich, T. Esko, P. V. Gejman, CommonMind Consortium, The Schizophrenia Working Group of the Psychiatric Genomics Consortium, Gene expression imputation across multiple brain regions provides insights into schizophrenia risk, *Nat. Genet.* **51**, 659–674 (2019).

36. O. L. Sabik, G. M. Calabrese, E. Taleghani, C. L. Ackert-Bicknell, C. R. Farber, Identification of a core module for bone mineral density through the integration of a co-expression network and GWAS *dataRx*, 803197 (2019).

37. A. Andaleon, L. S. Mogil, H. E. Wheeler, Genetically regulated gene expression underlies lipid traits in Hispanic cohorts, *PLoS One* **14**, e0220827 (2019).
38. H.-F. Zheng, V. Forgetta, Y.-H. Hsu, K. Estrada, A. Rosello-Diez, P. J. Leo, C. L. Dahia, K. H. Park-Min, J. H. Tobias, C. Kooperberg, A. Kleinman, U. Stykarsdottir, C.-T. Liu, C. Uggla, D. S. Evans, C. M. Nielson, K. Walter, U. Pettersson-Kymmer, S. McCarthy, J. Eriksson, T. Kwan, M. Jhamai, K. Trajanoska, Y. Memari, J. Min, J. Huang, P. Danecek, B. Wilmoth, R. Li, W.-C. Chou, L. E. Mokry, A. Moayyeri, M. Claussnitzer, C.-H. Cheng, W. Cheung, C. Medina-Gómez, B. Ge, S.-H. Chen, K. Choi, L. Oei, J. Fraser, R. Kraaij, M. A. Hibbs, C. L. Gregson, D. Paquette, A. Hofman, C. Wibom, G. J. Tranah, M. Marshall, B. B. Gardiner, K. Cremin, P. Auer, L. Hsu, S. Ring, J. Y. Tung, G. Thorleifsson, A. W. Ennenman, N. M. van Schoor, L. C. P. G. M. de Groot, N. van der Velde, B. Melin, J. P. Kemp, C. Christiansen, A. Sayers, Y. Zhou, S. Calderari, J. van Rooij, C. Carlson, U. Peters, S. Berlivet, J. Dostie, A. G. Uitterlinden, S. R. Williams, C. Farber, D. Grinberg, A. Z. LaCroix, J. Haessler, D. I. Chasman, F. Giulianini, L. M. Rose, P. M. Ridker, J. A. Eisman, T. V. Nguyen, J. R. Center, X. Nogues, N. Garcia-Giralt, L. L. Launer, V. Gudnason, D. Mellström, L. Vandenput, N. Amin, C. M. van Duijn, M. K. Karlsson, Ö. Ljunggren, O. Svensson, G. Hallmans, F. Rousseau, S. Giroux, J. Bussière, P. P. Arp, F. Koromani, R. L. Prince, J. R. Lewis, B. L. Langdahl, A. P. Hermann, J.-E. B. Jensen, S. Kaptoge, K.-T. Khaw, J. Reeve, M. M. Formosa, A. Xuereb-Anastasi, K. Åkesson, F. E. McGuigan, G. Garg, J. M. Olmos, M. T. Zarrabeitia, J. A. Riancho, S. H. Ralston, N. Alonso, X. Jiang, D. Goltzman, T. Pastinen, E. Grundberg, D. Gauguier, E. S. Orwoll, D. Karasik, G. Davey-Smith, AOGC Consortium, A. V. Smith, K. Siggeirsdottir, T. B. Harris, M. C. Zillikens, J. B. J. van Meurs, U. Thorsteinsdottir, M. T. Maurano, N. J. Timpson, N. Soranzo, R. Durbin, S. G. Wilson, E. E. Ntzani, M. A. Brown, K. Stefansson, D. A. Hinds, T. Spector, L. A. Cupples, C. Ohlsson, C. M. T. Greenwood, UK10K Consortium, R. D. Jackson, D. W. Rowe, C. A. Loomis, D. M. Evans, C. L. Ackert-Bicknell, A. L. Joyner, E. L. Duncan, D. P. Kiel, F. Rivadeneira, J. B. Richards, Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture, *Nature* **526**, 112–117 (2015).
39. H. Ishibashi, D. B. Crittenden, A. Miyauchi, C. Libanati, J. Maddox, M. Fan, L. Chen, A. Grauer, Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study, *Bone* **103**, 209–215 (2017).
40. J. A. Morris, J. P. Kemp, S. E. Youtten, L. Laurent, J. G. Logan, R. C. Chai, N. A. Vulpescu, V. Forgetta, A. Kleinman, S. T. Mohanty, C. M. Sergio, J. Quinn, L. Nguyen-Yamamoto, A.-L. Luco, J. Vijay, M.-M. Simon, A. Pramatarova, C. Medina-Gomez, K. Trajanoska, E. J. Ghirardello, N. C. Butterfield, K. F. Curry, V. D. Leitch, P. C. Sparkes, A.-T. Adoum, N. S. Mannan, D. S. K. Komla-Ebri, A. S. Pollard, H. F. Dewhurst, T. A. D. Hassall, M.-J. G. Beltejar, 23andMe Research Team, D. J. Adams, S. M. Vaillancourt, S. Kaptoge, P. Baldock, C. Cooper, J. Reeve, E. E. Ntzani, E. Evangelou, C. Ohlsson, D. Karasik, F. Rivadeneira, D. P. Kiel, J. H. Tobias, C. L. Gregson, N. C. Harvey, E. Grundberg, D. Goltzman, D. J. Adams, C. J. Lelliott, D. A. Hinds, C. L. Ackert-Bicknell, Y.-H. Hsu, M. T. Maurano, P. I. Croucher, G. R. Williams, J. H. D. Bassett, D. M. Evans, J. B. Richards, An atlas of genetic influences on osteoporosis in humans and mice, *Nat. Genet.* **51**, 258–266 (2019).
41. D. A. Lawlor, K. Tilling, G. Davey Smith, Triangulation in aetiological epidemiology, *Int. J. Epidemiol.* **45**, 1866–1886 (2016).
42. N. M. Davies, M. V. Holmes, G. Davey Smith, Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians, *BMJ* **362**, k601 (2018).
43. W. Gan, R. J. Clarke, A. Mahajan, B. Kulohoma, H. Kitajima, N. R. Robertson, N. W. Rayner, R. G. Walters, M. V. Holmes, Z. Chen, M. I. McCarthy, Bone mineral density and risk of type 2 diabetes and coronary heart disease: A Mendelian randomization study, *Wellcome Open Res* **2**, 68 (2017).
44. K. W. Lyles, C. S. Colón-Emeric, J. S. Magaziner, J. D. Adachi, C. F. Pieper, C. Mautalen, L. Hyldstrup, C. Recknor, L. Nordsletten, K. A. Moore, C. Lavecchia, J. Zhang, P. Mesenbrink, P. K. Hodgson, K. Abrams, J. J. Orloff, Z. Horowitz, E. F. Eriksen, S. Boonen, HORIZON Recurrent Fracture Trial, Zoledronic acid and clinical fractures and mortality after hip fracture, *N. Engl. J. Med.* **357**, 1799–1809 (2007).

45. B. A. Ference, How to use Mendelian randomization to anticipate the results of randomized trials, *Eur. Heart J.* **39**, 360–362 (2018).
46. D. Zhu, N. C. W. Mackenzie, J. L. Millán, C. Farquharson, V. E. MacRae, The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells, *PLoS One* **6**, e19595 (2011).
47. V. M. Brandenburg, R. Kramann, R. Koos, T. Krüger, L. Schurgers, G. Mühlenbruch, S. Hübner, U. Gladziwa, C. Drechsler, M. Ketteler, Relationship between sclerostin and cardiovascular calcification in hemodialysis patients: a cross-sectional study, *BMC Nephrol.* **14**, 219 (2013).
48. K. J. Claes, L. Viaene, S. Heye, B. Meijers, P. d'Haese, P. Evenepoel, Sclerostin: Another vascular calcification inhibitor?, *J. Clin. Endocrinol. Metab.* **98**, 3221–3228 (2013).
49. C. Novo-Rodríguez, B. García-Fontana, J. D. D. Luna-Del Castillo, F. Andújar-Vera, V. Ávila-Rubio, C. García-Fontana, S. Morales-Santana, P. Rozas-Moreno, M. Muñoz-Torres, Circulating levels of sclerostin are associated with cardiovascular mortality, *PLoS One* **13**, e0199504 (2018).
50. Y.-C. Chang, B.-G. Hsu, H.-H. Liou, C.-J. Lee, J.-H. Wang, Serum levels of sclerostin as a potential biomarker in central arterial stiffness among hypertensive patients, *BMC Cardiovasc. Disord.* **18**, 214 (2018).
51. K. Mathold, P. Wanby, L. Brudin, S. P. Von, M. Carlsson, Alterations in bone turnover markers in patients with noncardio-embolic ischemic stroke, *PLoS One* **13**, e0207348 (2018).
52. M. K. Saadeldin, S. S. Elshaer, I. A. Emara, M. Maged, A. K. Abdel-Aziz, Serum sclerostin and irisin as predictive markers for atherosclerosis in Egyptian type II diabetic female patients: A case control study, *PLoS One* **13**, e0206761 (2018).
53. R. S. Albassam, S. Sabico, A. M. Alnaami, M. N. K. Khattak, K. Y. Lei, N. M. Al-Daghri, J.-Y. Reginster, M. S. Alokail, Bone metabolism markers are associated with neck circumference in adult Arab women, *Osteoporos. Int.* (2019), doi:10.1007/s00198-018-04830-6.
54. S. Reppe, A. Noer, R. M. Grimholt, B. V. Halldórsson, C. Medina-Gomez, V. T. Gautvik, O. K. Olstad, J. P. Berg, H. Datta, K. Estrada, A. Hofman, A. G. Uitterlinden, F. Rivadeneira, R. Lyle, P. Collas, K. M. Gautvik, Methylation of bone SOST, its mRNA, and serum sclerostin levels correlate strongly with fracture risk in postmenopausal women, *J. Bone Miner. Res.* **30**, 249–256 (2015).
55. S. A. Polyzos, A. D. Anastasilakis, C. Bratengeier, W. Woloszczuk, A. Papatheodorou, E. Terpos, Serum sclerostin levels positively correlate with lumbar spinal bone mineral density in postmenopausal women--the six-month effect of risedronate and teriparatide, *Osteoporos. Int.* **23**, 1171–1176 (2012).
56. S. P. Kim, J. L. Frey, Z. Li, P. Kushwaha, M. L. Zoch, R. E. Tomlinson, H. Da, S. Aja, H. L. Noh, J. K. Kim, M. A. Hussain, D. L. J. Thorek, M. J. Wolfgang, R. C. Riddle, Sclerostin influences body composition by regulating catabolic and anabolic metabolism in adipocytes, *Proc. Natl. Acad. Sci. U. S. A.* **114**, E11238–E11247 (2017).
57. S. M. Krishna, S.-W. Seto, R. J. Jose, J. Li, S. K. Morton, E. Biros, Y. Wang, V. Nsengiyumva, J. H. N. Lindeman, G. G. Loots, C. M. Rush, J. M. Craig, J. Golledge, Wnt Signaling Pathway Inhibitor Sclerostin Inhibits Angiotensin II-Induced Aortic Aneurysm and Atherosclerosis, *Arterioscler. Thromb. Vasc. Biol.* **37**, 553–566 (2017).
58. B. Javaheri, E. Herbert, M. Hopkinson, A. Al-Jazzar, A. A. Pitsillides, Sost haploinsufficiency provokes peracute lethal cardiac tamponade without rescuing the osteopenia in a mouse model of excess glucocorticoids, *Am. J. Pathol.* (2019), doi:10.1016/j.ajpath.2018.12.007.
59. H. B. van der Worp, D. W. Howells, E. S. Sena, M. J. Porritt, S. Rewell, V. O'Collins, M. R. Macleod, Can animal models of disease reliably inform human studies?, *PLoS Med.* **7**, e1000245 (2010).

60. P. Pound, M. B. Bracken, Is animal research sufficiently evidence based to be a cornerstone of biomedical research?, *BMJ* **348**, g3387 (2014).
61. M. K. Wojczynski, M. Li, L. F. Bielak, K. F. Kerr, A. P. Reiner, N. D. Wong, L. R. Yanek, L. Qu, C. C. White, L. A. Lange, J. F. Ferguson, J. He, T. Young, T. H. Mosley, J. A. Smith, B. G. Kral, X. Guo, Q. Wong, S. K. Ganesh, S. R. Heckbert, M. E. Griswold, D. H. O'Leary, M. Budoff, J. J. Carr, H. A. Taylor Jr, D. A. Bluemke, S. Demissie, S.-J. Hwang, D. N. Paltoo, J. F. Polak, B. M. Psaty, D. M. Becker, M. A. Province, W. S. Post, C. J. O'Donnell, J. G. Wilson, T. B. Harris, M. Kavousi, L. A. Cupples, J. I. Rotter, M. Fornage, L. C. Becker, P. A. Peyser, I. B. Borecki, M. P. Reilly, Genetics of coronary artery calcification among African Americans, a meta-analysis, *BMC Med. Genet.* **14**, 75 (2013).
62. K. I. Boström, N. M. Rajamannan, D. A. Towler, The regulation of valvular and vascular sclerosis by osteogenic morphogens, *Circ. Res.* **109**, 564–577 (2011).
63. W. A. Touw, T. Ueland, J. Bollerslev, J. T. Schousboe, W. H. Lim, G. Wong, P. L. Thompson, D. P. Kiel, R. L. Prince, F. Rivadeneira, J. R. Lewis, Association of Circulating Wnt Antagonists With Severe Abdominal Aortic Calcification in Elderly Women, *J Endocr Soc* **1**, 26–38 (2017).
64. X. Li, Y. Zhang, H. Kang, W. Liu, P. Liu, J. Zhang, S. E. Harris, D. Wu, Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling, *J. Biol. Chem.* **280**, 19883–19887 (2005).
65. A. Mani, J. Radhakrishnan, H. Wang, A. Mani, M.-A. Mani, C. Nelson-Williams, K. S. Carew, S. Mane, H. Najmabadi, D. Wu, R. P. Lifton, LRP6 mutation in a family with early coronary disease and metabolic risk factors, *Science* **315**, 1278–1282 (2007).
66. A. Saarinen, T. Saukkonen, T. Kivelä, U. Lahtinen, C. Laine, M. Somer, S. Toiviainen-Salo, W. G. Cole, A.-E. Lehesjoki, O. Mäkitie, Low density lipoprotein receptor-related protein 5 (LRP5) mutations and osteoporosis, impaired glucose metabolism and hypercholesterolaemia, *Clin. Endocrinol.* **72**, 481–488 (2010).
67. M. T. Drake, B. L. Clarke, M. J. Oursler, S. Khosla, Cathepsin K Inhibitors for Osteoporosis: Biology, Potential Clinical Utility, and Lessons Learned, *Endocr. Rev.* **38**, 325–350 (2017).
68. R. Clarke, L. Li, D. Bennett, I. Y. Millwood, R. G. Walters, Y. Guo, Z. Bian, R. Peto, R. Collins, S. Parish, Z. M. Chen, Abstract 16532: Impact of Systolic Blood Pressure on Cardiovascular Disease in a Chinese Population: A Mendelian Randomization Study, *Circulation* (2014) (available at https://www.ahajournals.org/doi/abs/10.1161/circ.130.suppl_2.16532).
69. C. E. Dale, G. Fatemifar, T. M. Palmer, J. White, D. Prieto-Merino, D. Zabaneh, J. E. L. Engmann, T. Shah, A. Wong, H. R. Warren, S. McLachlan, S. Trompet, M. Moldovan, R. W. Morris, R. Sofat, M. Kumari, E. Hyppönen, B. J. Jefferis, T. R. Gaunt, Y. Ben-Shlomo, A. Zhou, A. Gentry-Maharaj, A. Ryan, UCLEB Consortium; METASTROKE Consortium, R. de Mutsert, R. Noordam, M. J. Caulfield, J. W. Jukema, B. B. Worrall, P. B. Munroe, U. Menon, C. Power, D. Kuh, D. A. Lawlor, S. E. Humphries, D. O. Mook-Kanamori, N. Sattar, M. Kivimäki, J. F. Price, G. Davey Smith, F. Dudbridge, A. D. Hingorani, M. V. Holmes, J. P. Casas, Causal Associations of Adiposity and Body Fat Distribution With Coronary Heart Disease, Stroke Subtypes, and Type 2 Diabetes Mellitus: A Mendelian Randomization Analysis, *Circulation* **135**, 2373–2388 (2017).
70. E. J. Samelson, P. D. Miller, C. Christiansen, N. S. Daizadeh, L. Grazette, M. S. Anthony, O. Egbuna, A. Wang, S. R. Siddhanti, A. M. Cheung, N. Franchimont, D. P. Kiel, RANKL inhibition with denosumab does not influence 3-year progression of aortic calcification or incidence of adverse cardiovascular events in postmenopausal women with osteoporosis and high cardiovascular risk, *J. Bone Miner. Res.* **29**, 450–457 (2014).
71. D. H. Kim, J. R. Rogers, L. A. Fulchino, C. A. Kim, D. H. Solomon, S. C. Kim, Bisphosphonates and risk of cardiovascular events: a meta-analysis, *PLoS One* **10**, e0122646 (2015).

72. G. Kranenburg, J. W. Bartstra, M. Weijmans, P. A. de Jong, W. P. Mali, H. J. Verhaar, F. L. J. Visseren, W. Spiering, Bisphosphonates for cardiovascular risk reduction: A systematic review and meta-analysis, *Atherosclerosis* **252**, 106–115 (2016).
73. J. Zheng, W. Maerz, I. Gergei, M. Kleber, C. Drechsler, C. Wanner, V. Brandenburg, S. Reppe, K. M. Gautvik, C. Medina-Gomez, E. Shevroja, A. Gilly, Y.-C. Park, G. Dedoussis, E. Zeggini, M. Lorentzon, P. Henning, U. H. Lerner, K. Nilsson, S. Movérare-Skrtic, D. Baird, B. Elsworth, L. Falk, A. Groom, T. D. Capellini, E. Grundberg, M. Nethander, C. Ohlsson, G. Davey Smith, J. H. Tobias, Mendelian Randomization analysis reveals a causal influence of circulating sclerostin levels on bone mineral density and fractures, *J. Bone Miner. Res.* (2019), doi:10.1002/jbmr.3803.
74. R. M. Plenge, E. M. Scolnick, D. Altshuler, Validating therapeutic targets through human genetics, *Nat. Rev. Drug Discov.* **12**, 581–594 (2013).
75. M. Lek, K. J. Karczewski, E. V. Minikel, K. E. Samocha, E. Banks, T. Fennell, A. H. O'Donnell-Luria, J. S. Ware, A. J. Hill, B. B. Cummings, T. Tukiainen, D. P. Birnbaum, J. A. Kosmicki, L. E. Duncan, K. Estrada, F. Zhao, J. Zou, E. Pierce-Hoffman, J. Berghout, D. N. Cooper, N. Deflaux, M. DePristo, R. Do, J. Flannick, M. Fromer, L. Gauthier, J. Goldstein, N. Gupta, D. Howrigan, A. Kiezun, M. I. Kurki, A. L. Moonshine, P. Natarajan, L. Orozco, G. M. Peloso, R. Poplin, M. A. Rivas, V. Ruano-Rubio, S. A. Rose, D. M. Ruderfer, K. Shakir, P. D. Stenson, C. Stevens, B. P. Thomas, G. Tiao, M. T. Tusie-Luna, B. Weisburd, H.-H. Won, D. Yu, D. M. Altshuler, D. Ardissino, M. Boehnke, J. Danesh, S. Donnelly, R. Elosua, J. C. Florez, S. B. Gabriel, G. Getz, S. J. Glatt, C. M. Hultman, S. Kathiresan, M. Laakso, S. McCarroll, M. I. McCarthy, D. McGovern, R. McPherson, B. M. Neale, A. Palotie, S. M. Purcell, D. Saleheen, J. M. Scharf, P. Sklar, P. F. Sullivan, J. Tuomilehto, M. T. Tsuang, H. C. Watkins, J. G. Wilson, M. J. Daly, D. G. MacArthur, Exome Aggregation Consortium, Analysis of protein-coding genetic variation in 60,706 humans, *Nature* **536**, 285–291 (2016).
76. A. Sebastian, G. G. Loots, Genetics of Sost/SOST in sclerosteosis and van Buchem disease animal models, *Metabolism* **80**, 38–47 (2018).
77. L. J. Corbin, V. Y. Tan, D. A. Hughes, K. H. Wade, D. S. Paul, K. E. Tansey, F. Butcher, F. Dudbridge, J. M. Howson, M. W. Jallow, C. John, N. Kingston, C. M. Lindgren, M. O'Donovan, S. O'Rahilly, M. J. Owen, C. N. A. Palmer, E. R. Pearson, R. A. Scott, D. A. van Heel, J. Whittaker, T. Frayling, M. D. Tobin, L. V. Wain, G. Davey Smith, D. M. Evans, F. Karpe, M. I. McCarthy, J. Danesh, P. W. Franks, N. J. Timpson, Formalising recall by genotype as an efficient approach to detailed phenotyping and causal inference, *Nat. Commun.* **9**, 711 (2018).
78. T. L. McGregor, K. A. Hunt, P. Nioi, D. Mason, S. Ticau, M. Pelosi, L. Perry, S. Finer, C. Griffiths, D. MacArthur, R. C. Trembath, D. Oglesbee, J. Lieske, J. Wright, D. Erbe, D. van Heel, Deep phenotyping of a healthy human HAO1 knockout informs therapeutic development for primary hyperoxaluria type 1 *bioRxiv*, 524256 (2019).
79. L. B. Tankó, C. Christiansen, D. A. Cox, M. J. Geiger, M. A. McNabb, S. R. Cummings, Relationship between osteoporosis and cardiovascular disease in postmenopausal women, *J. Bone Miner. Res.* **20**, 1912–1920 (2005).
80. Y. Yesil, Z. Ulger, M. Halil, B. Halaçlı, B. B. Yavuz, N. K. Yeşil, M. E. Kuyumcu, M. Cankurtaran, S. Ariogul, Coexistence of osteoporosis (OP) and coronary artery disease (CAD) in the elderly: it is not just a by chance event, *Arch. Gerontol. Geriatr.* **54**, 473–476 (2012).
81. A. F. Schmidt, D. I. Swerdlow, M. V. Holmes, R. S. Patel, Z. Fairhurst-Hunter, D. M. Lyall, F. P. Hartwig, B. L. Horta, E. Hyppönen, C. Power, M. Moldovan, E. van Iperen, G. K. Hovingh, I. Demuth, K. Norman, E. Steinhagen-Thiessen, J. Demuth, L. Bertram, T. Liu, S. Coassin, J. Willeit, S. Kiechl, K. Willeit, D. Mason, J. Wright, R. Morris, G. Wanamethee, P. Whincup, Y. Ben-Shlomo, S. McLachlan, J. F. Price, M. Kivimaki, C. Welch, A. Sanchez-Galvez, P. Marques-Vidal, A. Nicolaidis, A. G. Panayiotou, N. C. Onland-Moret, Y. T. van der Schouw, G. Matullo, G. Fiorito, S. Guarrera, C. Sacerdote, N. J. Wareham, C. Langenberg, R. Scott, J. 'an Luan, M. Bobak, S. Malyutina, A. Pajak, R. Kubinova, A.

Tamosiunas, H. Pikhart, L. L. N. Husemoen, N. Grarup, O. Pedersen, T. Hansen, A. Linneberg, K. S. Simonsen, J. Cooper, S. E. Humphries, M. Brilliant, T. Kitchner, H. Hakonarson, D. S. Carrell, C. A. McCarty, H. L. Kirchner, E. B. Larson, D. R. Crosslin, M. de Andrade, D. M. Roden, J. C. Denny, C. Carty, S. Hancock, J. Attia, E. Holliday, M. O'Donnell, S. Yusuf, M. Chong, G. Pare, P. van der Harst, M. A. Said, R. N. Eppinga, N. Verweij, H. Snieder, LifeLines Cohort study group, T. Christen, D. O. Mook-Kanamori, S. Gustafsson, L. Lind, E. Ingelsson, R. Pazoki, O. Franco, A. Hofman, A. Uitterlinden, A. Dehghan, A. Teumer, S. Baumeister, M. Dörr, M. M. Lerch, U. Völker, H. Völzke, J. Ward, J. P. Pell, D. J. Smith, T. Meade, A. H. Maitland-van der Zee, E. V. Baranova, R. Young, I. Ford, A. Campbell, S. Padmanabhan, M. L. Bots, D. E. Grobbee, P. Froguel, D. Thuillier, B. Balkau, A. Bonnefond, B. Cariou, M. Smart, Y. Bao, M. Kumari, A. Mahajan, P. M. Ridker, D. I. Chasman, A. P. Reiner, L. A. Lange, M. D. Ritchie, F. W. Asselbergs, J.-P. Casas, B. J. Keating, D. Preiss, A. D. Hingorani, UCLEB consortium, N. Sattar, PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study, *Lancet Diabetes Endocrinol* **5**, 97–105 (2017).

82. D. B. Resnik, Postmarketing Research and Surveillance: Issues and Challenges, *Monitor* **22**, 45–48 (2008).

83. A. Spelsberg, C. Prugger, P. Doshi, K. Ostrowski, T. Witte, D. Hüsken, U. Keil, Working Group on Health and Working Group on Freedom of Information, Transparency International Deutschland eV, Contribution of industry funded post-marketing studies to drug safety: survey of notifications submitted to regulatory agencies, *BMJ* **356**, j337 (2017).

84. D. Diogo, C. Tian, C. S. Franklin, M. Alanne-Kinnunen, M. March, C. C. A. Spencer, C. Vangjeli, M. E. Weale, H. Mattsson, E. Kilpeläinen, P. M. A. Sleiman, D. F. Reilly, J. McElwee, J. C. Maranville, A. K. Chatterjee, A. Bhandari, K.-D. H. Nguyen, K. Estrada, M.-P. Reeve, J. Hutz, N. Bing, S. John, D. G. MacArthur, V. Salomaa, S. Ripatti, H. Hakonarson, M. J. Daly, A. Palotie, D. A. Hinds, P. Donnelly, C. S. Fox, A. G. Day-Williams, R. M. Plenge, H. Runz, Phenome-wide association studies across large population cohorts support drug target validation, *Nat. Commun.* **9**, 4285 (2018).

85. C. Bycroft, C. Freeman, D. Petkova, G. Band, L. T. Elliott, K. Sharp, A. Motyer, D. Vukcevic, O. Delaneau, J. O'Connell, A. Cortes, S. Welsh, A. Young, M. Effingham, G. McVean, S. Leslie, N. Allen, P. Donnelly, J. Marchini, The UK Biobank resource with deep phenotyping and genomic data, *Nature* **562**, 203–209 (2018).

86. A. Manichaikul, J. C. Mychaleckyj, S. S. Rich, K. Daly, M. Sale, W.-M. Chen, Robust relationship inference in genome-wide association studies, *Bioinformatics* **26**, 2867–2873 (2010).

87. L. V. Wain, N. Shrine, S. Miller, V. E. Jackson, I. Ntalla, M. Soler Artigas, C. K. Billington, A. K. Kheirallah, R. Allen, J. P. Cook, K. Probert, M. 'en Obeidat, Y. Bossé, K. Hao, D. S. Postma, P. D. Paré, A. Ramasamy, UK Brain Expression Consortium (UKBEC), R. Mägi, E. Mihailov, E. Reinmaa, E. Melén, J. O'Connell, E. Frangou, O. Delaneau, OxGSK Consortium, C. Freeman, D. Petkova, M. McCarthy, I. Sayers, P. Deloukas, R. Hubbard, I. Pavord, A. L. Hansell, N. C. Thomson, E. Zeggini, A. P. Morris, J. Marchini, D. P. Strachan, M. D. Tobin, I. P. Hall, Novel insights into the genetics of smoking behaviour, lung function, and chronic obstructive pulmonary disease (UK BiLEVE): a genetic association study in UK Biobank, *Lancet Respir Med* **3**, 769–781 (2015).

88. S. McCarthy, S. Das, W. Kretzschmar, O. Delaneau, A. R. Wood, A. Teumer, H. M. Kang, C. Fuchsberger, P. Danecek, K. Sharp, Y. Luo, C. Sidore, A. Kwong, N. Timpson, S. Koskinen, S. Vrieze, L. J. Scott, H. Zhang, A. Mahajan, J. Veldink, U. Peters, C. Pato, C. M. van Duijn, C. E. Gillies, I. Gandin, M. Mezzavilla, A. Gilly, M. Cocca, M. Traglia, A. Angius, J. C. Barrett, D. Boomsma, K. Branham, G. Breen, C. M. Brummett, F. Busonero, H. Campbell, A. Chan, S. Chen, E. Chew, F. S. Collins, L. J. Corbin, G. Davey Smith, G. Dedoussis, M. Dorr, A.-E. Farmaki, L. Ferrucci, L. Forer, R. M. Fraser, S. Gabriel, S. Levy, L. Groop, T. Harrison, A. Hattersley, O. L. Holmen, K. Hveem, M. Kretzler, J. C. Lee, M. McGue, T. Meitinger, D. Melzer, J. L. Min, K. L. Mohlke, J. B. Vincent, M. Nauck, D. Nickerson, A. Palotie, M. Pato, N. Pirastu, M. McInnis, J. B. Richards, C. Sala, V. Salomaa, D. Schlessinger, S. Schoenherr, P. E. Slagboom, K. Small, T. Spector, D. Stambolian, M. Tuke, J. Tuomilehto, L. H. Van den Berg, W. Van Rheenen, U. Volker, C. Wijmenga, D. Toniolo, E. Zeggini, P. Gasparini, M. G. Sampson, J. F. Wilson, T.

Frayling, P. I. W. de Bakker, M. A. Swertz, S. McCarroll, C. Kooperberg, A. Dekker, D. Altshuler, C. Willer, W. Iacono, S. Ripatti, N. Soranzo, K. Walter, A. Swaroop, F. Cucca, C. A. Anderson, R. M. Myers, M. Boehnke, M. I. McCarthy, R. Durbin, Haplotype Reference Consortium, A reference panel of 64,976 haplotypes for genotype imputation, *Nat. Genet.* **48**, 1279–1283 (2016).

89. K. Trajanoska, J. A. Morris, L. Oei, H.-F. Zheng, D. M. Evans, D. P. Kiel, C. Ohlsson, J. B. Richards, F. Rivadeneira, GEFOS/GENOMOS consortium and the 23andMe research team, Assessment of the genetic and clinical determinants of fracture risk: genome wide association and mendelian randomisation study, *BMJ* **362**, k3225 (2018).

90. A. A. Ismail, T. W. O'Neill, W. Cockerill, J. D. Finn, J. B. Cannata, K. Hoszowski, O. Johnell, C. Matthis, H. Raspe, A. Raspe, J. Reeve, A. J. Silman, Validity of self-report of fractures: results from a prospective study in men and women across Europe. EPOS Study Group. European Prospective Osteoporosis Study Group, *Osteoporos. Int.* **11**, 248–254 (2000).

91. E. Evangelou, H. R. Warren, D. Mosen-Ansorena, B. Mifsud, R. Pazoki, H. Gao, G. Ntritsos, N. Dimou, C. P. Cabrera, I. Karaman, F. L. Ng, M. Evangelou, K. Witkowska, E. Tzanis, J. N. Hellwege, A. Giri, D. R. Velez Edwards, Y. V. Sun, K. Cho, J. M. Gaziano, P. W. F. Wilson, P. S. Tsao, C. P. Kovesdy, T. Esko, R. Mägi, L. Milani, P. Almgren, T. Boutin, S. Debette, J. Ding, F. Giulianini, E. G. Holliday, A. U. Jackson, R. Li-Gao, W.-Y. Lin, J. 'an Luan, M. Mangino, C. Oldmeadow, B. P. Prins, Y. Qian, M. Sargurupremraj, N. Shah, P. Surendran, S. Thériault, N. Verweij, S. M. Willems, J.-H. Zhao, P. Amouyel, J. Connell, R. de Mutsert, A. S. F. Doney, M. Farrall, C. Menni, A. D. Morris, R. Noordam, G. Paré, N. R. Poulter, D. C. Shields, A. Stanton, S. Thom, G. Abecasis, N. Amin, D. E. Arking, K. L. Ayers, C. M. Barbieri, C. Batini, J. C. Bis, T. Blake, M. Bochud, M. Boehnke, E. Boerwinkle, D. I. Boomsma, E. P. Bottinger, P. S. Braund, M. Brumat, A. Campbell, H. Campbell, A. Chakravarti, J. C. Chambers, G. Chauhan, M. Ciullo, M. Cocca, F. Collins, H. J. Cordell, G. Davies, M. H. de Borst, E. J. de Geus, I. J. Deary, J. Deelen, F. Del Greco M, C. Y. Demirkale, M. Dörr, G. B. Ehret, R. Elosua, S. Enroth, A. M. Erzurumluoglu, T. Ferreira, M. Fränberg, O. H. Franco, I. Gandin, P. Gasparini, V. Giedraitis, C. Gieger, G. Grotto, A. Goel, A. J. Gow, V. Gudnason, X. Guo, U. Gyllensten, A. Hamsten, T. B. Harris, S. E. Harris, C. A. Hartman, A. S. Havulinna, A. A. Hicks, E. Hofer, A. Hofman, J.-J. Hottenga, J. E. Huffman, S.-J. Hwang, E. Ingelsson, A. James, R. Jansen, M.-R. Jarvelin, R. Joehanes, Å. Johansson, A. D. Johnson, P. K. Joshi, P. Jousilahti, J. W. Jukema, A. Jula, M. Kähönen, S. Kathiresan, B. D. Keavney, K.-T. Khaw, P. Knekt, J. Knight, I. Kolcic, J. S. Kooner, S. Koskinen, K. Kristiansson, Z. Kutalik, M. Laan, R. J. Larson, L. J. Launer, B. Lehne, T. Lehtimäki, D. C. M. Liewald, L. Lin, L. Lind, C. M. Lindgren, Y. Liu, R. J. F. Loos, L. M. Lopez, Y. Lu, L.-P. Lyytikäinen, A. Mahajan, C. Mamasoula, J. Marrugat, J. Marten, Y. Milaneschi, A. Morgan, A. P. Morris, A. C. Morrison, P. J. Munson, M. A. Nalls, P. Nandakumar, C. P. Nelson, T. Niiranen, I. M. Nolte, T. Nütle, A. J. Oldehinkel, B. A. Oostra, P. F. O'Reilly, E. Org, S. Padmanabhan, W. Palmas, A. Palotie, A. Pattie, B. W. J. H. Penninx, M. Perola, A. Peters, O. Polasek, P. Pramstaller, Q. T. Nguyen, O. T. Raitakari, M. Ren, R. Rettig, K. Rice, P. M. Ridker, J. S. Ried, H. Riese, S. Ripatti, A. Robino, L. M. Rose, J. I. Rotter, I. Rudan, D. Ruggiero, Y. Saba, C. F. Sala, V. Salomaa, N. J. Samani, A.-P. Sarin, R. Schmidt, H. Schmidt, N. Shrine, D. Siscovick, A. V. Smith, H. Snieder, S. Söber, R. Sorice, J. M. Starr, D. J. Stott, D. P. Strachan, R. J. Strawbridge, J. Sundström, M. A. Swertz, K. D. Taylor, A. Teumer, M. D. Tobin, M. Tomaszewski, D. Toniolo, M. Traglia, S. Trompet, J. Tuomilehto, C. Tzourio, A. G. Uitterlinden, A. Vaez, P. J. van der Most, C. M. van Duijn, A.-C. Vergnaud, G. C. Verwoert, V. Vitart, U. Völker, P. Vollenweider, D. Vuckovic, H. Watkins, S. H. Wild, G. Willemssen, J. F. Wilson, A. F. Wright, J. Yao, T. Zemunik, W. Zhang, J. R. Attia, A. S. Butterworth, D. I. Chasman, D. Conen, F. Cucca, J. Danesh, C. Hayward, J. M. M. Howson, M. Laakso, E. G. Lakatta, C. Langenberg, O. Melander, D. O. Mook-Kanamori, C. N. A. Palmer, L. Risch, R. A. Scott, R. J. Scott, P. Sever, T. D. Spector, P. van der Harst, N. J. Wareham, E. Zeggini, D. Levy, P. B. Munroe, C. Newton-Cheh, M. J. Brown, A. Metspalu, A. M. Hung, C. J. O'Donnell, T. L. Edwards, Million Veteran Program, B. M. Psaty, I. Tzoulaki, M. R. Barnes, L. V. Wain, P. Elliott, M. J. Caulfield, Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits, *Nat. Genet.* **50**, 1412–1425 (2018).

92. M. D. Tobin, N. A. Sheehan, K. J. Scurrah, P. R. Burton, Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure, *Stat. Med.* **24**, 2911–2935 (2005).

93. S. L. Pulit, C. Stoneman, A. P. Morris, A. R. Wood, C. A. Glastonbury, J. Tyrrell, L. Yengo, T. Ferreira, E. Marouli, Y. Ji, J. Yang, S. Jones, R. Beaumont, D. C. Croteau-Chonka, T. W. Winkler, C. Giant, A. T. Hattersley, R. J. F. Loos, J. N. Hirschhorn, P. M. Visscher, T. M. Frayling, H. Yaghootkar, C. M. Lindgren, Meta-analysis of genome-wide association studies for body fat distribution in 694,649 individuals of European ancestry, *Hum. Mol. Genet.* **ddy327** (2018), doi:10.1093/hmg/ddy327.

94. A. E. Locke, B. Kahali, S. I. Berndt, A. E. Justice, T. H. Pers, F. R. Day, C. Powell, S. Vedantam, M. L. Buchkovich, J. Yang, D. C. Croteau-Chonka, T. Esko, T. Fall, T. Ferreira, S. Gustafsson, Z. Kutalik, J. 'an Luan, R. Mägi, J. C. Randall, T. W. Winkler, A. R. Wood, T. Workalemahu, J. D. Faul, J. A. Smith, J. H. Zhao, W. Zhao, J. Chen, R. Fehrmann, Å. K. Hedman, J. Karjalainen, E. M. Schmidt, D. Absher, N. Amin, D. Anderson, M. Beekman, J. L. Bolton, J. L. Bragg-Gresham, S. Buyske, A. Demirkan, G. Deng, G. B. Ehret, B. Feenstra, M. F. Feitosa, K. Fischer, A. Goel, J. Gong, A. U. Jackson, S. Kanoni, M. E. Kleber, K. Kristiansson, U. Lim, V. Lotay, M. Mangino, I. M. Leach, C. Medina-Gomez, S. E. Medland, M. A. Nalls, C. D. Palmer, D. Pasko, S. Pechlivanis, M. J. Peters, I. Prokopenko, D. Shungin, A. Stančáková, R. J. Strawbridge, Y. J. Sung, T. Tanaka, A. Teumer, S. Trompet, S. W. van der Laan, J. van Setten, J. V. Van Vliet-Ostaptchouk, Z. Wang, L. Yengo, W. Zhang, A. Isaacs, E. Albrecht, J. Ärnlöv, G. M. Arscott, A. P. Attwood, S. Bandinelli, A. Barrett, I. N. Bas, C. Bellis, A. J. Bennett, C. Berne, R. Blagieva, M. Blüher, S. Böhringer, L. L. Bonnycastle, Y. Böttcher, H. A. Boyd, M. Bruinenberg, I. H. Caspersen, Y.-D. I. Chen, R. Clarke, E. W. Daw, A. J. M. de Craen, G. Delgado, M. Dimitriou, A. S. F. Doney, N. Eklund, K. Estrada, E. Eury, L. Folkersen, R. M. Fraser, M. E. Garcia, F. Geller, V. Giedraitis, B. Gigante, A. S. Go, A. Golay, A. H. Goodall, S. D. Gordon, M. Gorski, H.-J. Grabe, H. Grallert, T. B. Grammer, J. Gräßler, H. Grönberg, C. J. Groves, G. Gusto, J. Haessler, P. Hall, T. Haller, G. Hallmans, C. A. Hartman, M. Hassinen, C. Hayward, N. L. Heard-Costa, Q. Helmer, C. Hengstenberg, O. Holmen, J.-J. Hottenga, A. L. James, J. M. Jeff, Å. Johansson, J. Jolley, T. Juliusdottir, L. Kinnunen, W. Koenig, M. Koskenvuo, W. Kratzer, J. Laitinen, C. Lamina, K. Leander, N. R. Lee, P. Lichtner, L. Lind, J. Lindström, K. S. Lo, S. Lobbens, R. Lorbeer, Y. Lu, F. Mach, P. K. E. Magnusson, A. Mahajan, W. L. McArdle, S. McLachlan, C. Menni, S. Merger, E. Mihailov, L. Milani, A. Moayyeri, K. L. Monda, M. A. Morken, A. Mulas, G. Müller, M. Müller-Nurasyid, A. W. Musk, R. Nagaraja, M. M. Nöthen, I. M. Nolte, S. Pilz, N. W. Rayner, F. Renstrom, R. Rettig, J. S. Ried, S. Ripke, N. R. Robertson, L. M. Rose, S. Sanna, H. Scharnagl, S. Scholtens, F. R. Schumacher, W. R. Scott, T. Seufferlein, J. Shi, A. V. Smith, J. Smolonska, A. V. Stanton, V. Steinthorsdottir, K. Stirrups, H. M. Stringham, J. Sundström, M. A. Swertz, A. J. Swift, A.-C. Syvänen, S.-T. Tan, B. O. Tayo, B. Thorand, G. Thorleifsson, J. P. Tyrer, H.-W. Uh, L. Vandenput, F. C. Verhulst, S. H. Vermeulen, N. Verweij, J. M. Vonk, L. L. Waite, H. R. Warren, D. Waterworth, M. N. Weedon, L. R. Wilkens, C. Willenborg, T. Wilsgaard, M. K. Wojczynski, A. Wong, A. F. Wright, Q. Zhang, LifeLines Cohort Study, E. P. Brennan, M. Choi, Z. Dastani, A. W. Drong, P. Eriksson, A. Franco-Cereceda, J. R. Gådin, A. G. Gharavi, M. E. Goddard, R. E. Handsaker, J. Huang, F. Karpe, S. Kathiresan, S. Keildson, K. Kiryluk, M. Kubo, J.-Y. Lee, L. Liang, R. P. Lifton, B. Ma, S. A. McCarroll, A. J. McKnight, J. L. Min, M. F. Moffatt, G. W. Montgomery, J. M. Murabito, G. Nicholson, D. R. Nyholt, Y. Okada, J. R. B. Perry, R. Dorajoo, E. Reinmaa, R. M. Salem, N. Sandholm, R. A. Scott, L. Stolk, A. Takahashi, T. Tanaka, F. M. van 't Hooft, A. A. E. Vinkhuyzen, H.-J. Westra, W. Zheng, K. T. Zondervan, ADIPOGen Consortium, AGEN-BMI Working Group, CARDIOGRAMplusC4D Consortium, CKDGen Consortium, GLGC, ICBP, MAGIC Investigators, MuTHER Consortium, MIGen Consortium, PAGE Consortium, ReproGen Consortium, GENIE Consortium, International Endogene Consortium, A. C. Heath, D. Arveiler, S. J. L. Bakker, J. Beilby, R. N. Bergman, J. Blangero, P. Bovet, H. Campbell, M. J. Caulfield, G. Cesana, A. Chakravarti, D. I. Chasman, P. S. Chines, F. S. Collins, D. C. Crawford, L. A. Cupples, D. Cusi, J. Danesh, U. de Faire, H. M. den Ruijter, A. F. Dominiczak, R. Erbel, J. Erdmann, J. G. Eriksson, M. Farrall, S. B. Felix, E. Ferrannini, J. Ferrières, I. Ford, N. G. Forouhi, T. Forrester, O. H. Franco, R. T. Gansevoort, P. V. Gejman, C. Gieger, O. Gottesman, V. Gudnason, U. Gyllenstein, A. S. Hall, T. B. Harris, A. T. Hattersley, A. A. Hicks, L. A. Hindorf, A. D. Hingorani, A. Hofman, G. Homuth, G. K. Hovingh, S. E. Humphries, S. C. Hunt, E. Hyppönen, T. Illig, K. B. Jacobs, M.-R. Jarvelin, K.-H. Jöckel, B. Johansen, P. Jousilahti, J. W. Jukema, A. M. Jula, J. Kaprio, J. J. P. Kastelein, S. M. Keinänen-Kiukaanniemi, L. A. Kiemeny, P. Knekt, J. S. Kooner, C. Kooperberg, P. Kovacs, A. T. Kraja, M. Kumari, J. Kuusisto, T. A. Lakka, C. Langenberg, L. L. Marchand, T. Lehtimäki, V. Lyssenko, S. Männistö, A. Marette, T. C. Matise, C. A. McKenzie, B. McKnight, F. L. Moll, A. D. Morris, A. P. Morris, J. C. Murray, M. Nelis, C. Ohlsson, A. J. Oldehinkel, K. K. Ong, P. A. F. Madden, G. Pasterkamp, J. F. Peden, A. Peters, D. S. Postma, P. P. Pramstaller, J. F. Price, L. Qi, O. T. Raitakari, T. Rankinen, D. C. Rao, T. K. Rice, P.

M. Ridker, J. D. Rioux, M. D. Ritchie, I. Rudan, V. Salomaa, N. J. Samani, J. Saramies, M. A. Sarzynski, H. Schunkert, P. E. H. Schwarz, P. Sever, A. R. Shuldiner, J. Sinisalo, R. P. Stolk, K. Strauch, A. Tönjes, D.-A. Trégouët, A. Tremblay, E. Tremoli, J. Virtamo, M.-C. Vohl, U. Völker, G. Waeber, G. Willemsen, J. C. Witteman, M. C. Zillikens, L. S. Adair, P. Amouyel, F. W. Asselbergs, T. L. Assimes, M. Bochud, B. O. Boehm, E. Boerwinkle, S. R. Bornstein, E. P. Bottinger, C. Bouchard, S. Cauchi, J. C. Chambers, S. J. Chanock, R. S. Cooper, P. I. W. de Bakker, G. Dedoussis, L. Ferrucci, P. W. Franks, P. Froguel, L. C. Groop, C. A. Haiman, A. Hamsten, J. Hui, D. J. Hunter, K. Hveem, R. C. Kaplan, M. Kivimaki, D. Kuh, M. Laakso, Y. Liu, N. G. Martin, W. März, M. Melbye, A. Metspalu, S. Moebus, P. B. Munroe, I. Njølstad, B. A. Oostra, C. N. A. Palmer, N. L. Pedersen, M. Perola, L. Pérusse, U. Peters, C. Power, T. Quertermous, R. Rauramaa, F. Rivadeneira, T. E. Saaristo, D. Saleheen, N. Sattar, E. E. Schadt, D. Schlessinger, P. E. Slagboom, H. Snieder, T. D. Spector, U. Thorsteinsdottir, M. Stumvoll, J. Tuomilehto, A. G. Uitterlinden, M. Uusitupa, P. van der Harst, M. Walker, H. Wallaschofski, N. J. Wareham, H. Watkins, D. R. Weir, H.-E. Wichmann, J. F. Wilson, P. Zanen, I. B. Borecki, P. Deloukas, C. S. Fox, I. M. Heid, J. R. O'Connell, D. P. Strachan, K. Stefansson, C. M. van Duijn, G. R. Abecasis, L. Franke, T. M. Frayling, M. I. McCarthy, P. M. Visscher, A. Scherag, C. J. Willer, M. Boehnke, K. L. Mohlke, C. M. Lindgren, J. S. Beckmann, I. Barroso, K. E. North, E. Ingelsson, J. N. Hirschhorn, R. J. F. Loos, E. K. Speliotes, Genetic studies of body mass index yield new insights for obesity biology, *Nature* **518**, 197–206 (2015).

95. D. Shungin, T. W. Winkler, D. C. Croteau-Chonka, T. Ferreira, A. E. Locke, R. Mägi, R. J. Strawbridge, T. H. Pers, K. Fischer, A. E. Justice, T. Workalemahu, J. M. W. Wu, M. L. Buchkovich, N. L. Heard-Costa, T. S. Roman, A. W. Drong, C. Song, S. Gustafsson, F. R. Day, T. Esko, T. Fall, Z. Kutalik, J. 'an Luan, J. C. Randall, A. Scherag, S. Vedantam, A. R. Wood, J. Chen, R. Fehrmann, J. Karjalainen, B. Kahali, C.-T. Liu, E. M. Schmidt, D. Absher, N. Amin, D. Anderson, M. Beekman, J. L. Bragg-Gresham, S. Buyske, A. Demirkan, G. B. Ehret, M. F. Feitosa, A. Goel, A. U. Jackson, T. Johnson, M. E. Kleber, K. Kristiansson, M. Mangino, I. M. Leach, C. Medina-Gomez, C. D. Palmer, D. Pasko, S. Pechlivanis, M. J. Peters, I. Prokopenko, A. Stančáková, Y. J. Sung, T. Tanaka, A. Teumer, J. V. Van Vliet-Ostaptchouk, L. Yengo, W. Zhang, E. Albrecht, J. Ärnlöv, G. M. Arscott, S. Bandinelli, A. Barrett, C. Bellis, A. J. Bennett, C. Berne, M. Blüher, S. Böhringer, F. Bonnet, Y. Böttcher, M. Bruinenberg, D. B. Carba, I. H. Caspersen, R. Clarke, E. W. Daw, J. Deelen, E. Deelman, G. Delgado, A. S. Doney, N. Eklund, M. R. Erdos, K. Estrada, E. Eury, N. Friedrich, M. E. Garcia, V. Giedraitis, B. Gigante, A. S. Go, A. Golay, H. Grallert, T. B. Grammer, J. Gräßler, J. Grewal, C. J. Groves, T. Haller, G. Hallmans, C. A. Hartman, M. Hassinen, C. Hayward, K. Heikkilä, K.-H. Herzig, Q. Helmer, H. L. Hillege, O. Holmen, S. C. Hunt, A. Isaacs, T. Ittermann, A. L. James, I. Johansson, T. Juliusdottir, I.-P. Kalafati, L. Kinnunen, W. Koenig, I. K. Kooner, W. Kratzer, C. Lamina, K. Leander, N. R. Lee, P. Lichtner, L. Lind, J. Lindström, S. Lobbens, M. Lorentzon, F. Mach, P. K. Magnusson, A. Mahajan, W. L. McArdle, C. Menni, S. Merger, E. Mihailov, L. Milani, R. Mills, A. Moayyeri, K. L. Monda, S. P. Mooijart, T. W. Mühleisen, A. Mulas, G. Müller, M. Müller-Nurasyid, R. Nagaraja, M. A. Nalls, N. Narisu, N. Glorioso, I. M. Nolte, M. Olden, N. W. Rayner, F. Renstrom, J. S. Ried, N. R. Robertson, L. M. Rose, S. Sanna, H. Scharnagl, S. Scholtens, B. Sennblad, T. Seufferlein, C. M. Sitlani, A. V. Smith, K. Stirrups, H. M. Stringham, J. Sundström, M. A. Swertz, A. J. Swift, A.-C. Syvänen, B. O. Tayo, B. Thorand, G. Thorleifsson, A. Tomaschitz, C. Troffa, F. V. van Oort, N. Verweij, J. M. Vonk, L. L. Waite, R. Wennauer, T. Wilsgaard, M. K. Wojczynski, A. Wong, Q. Zhang, J. H. Zhao, E. P. Brennan, M. Choi, P. Eriksson, L. Folkersen, A. Franco-Cereceda, A. G. Gharavi, Å. K. Hedman, M.-F. Hivert, J. Huang, S. Kanoni, F. Karpe, S. Keildson, K. Kiryluk, L. Liang, R. P. Lifton, B. Ma, A. J. McKnight, R. McPherson, A. Metspalu, J. L. Min, M. F. Moffatt, G. W. Montgomery, J. M. Murabito, G. Nicholson, D. R. Nyholt, C. Olsson, J. R. Perry, E. Reinmaa, R. M. Salem, N. Sandholm, E. E. Schadt, R. A. Scott, L. Stolk, E. E. Vallejo, H.-J. Westra, K. T. Zondervan, ADIPOGen Consortium, CARDIOGRAMplusC4D Consortium, CKDGen Consortium, GEFOS Consortium, GENIE Consortium, GLGC, ICBP, International Endogene Consortium, LifeLines Cohort Study, MAGIC Investigators, MuTHER Consortium, PAGE Consortium, ReproGen Consortium, P. Amouyel, D. Arveiler, S. J. Bakker, J. Beilby, R. N. Bergman, J. Blangero, M. J. Brown, M. Burnier, H. Campbell, A. Chakravarti, P. S. Chines, S. Claudi-Boehm, F. S. Collins, D. C. Crawford, J. Danesh, U. de Faire, E. J. de Geus, M. Dörr, R. Erbel, J. G. Eriksson, M. Farrall, E. Ferrannini, J. Ferrières, N. G. Forouhi, T. Forrester, O. H. Franco, R. T. Gansevoort, C. Gieger, V. Gudnason, C. A. Haiman, T. B. Harris, A. T. Hattersley, M. Heliövaara, A. Hicks, A. D. Hingorani, W. Hoffmann, A. Hofman, G. Homuth, S. E. Humphries, E. Hyppönen, T. Illig, M.-R. Jarvelin, B. Johansen, P. Jousilahti, A. M. Jula, J. Kaprio, F. Kee, S. M. Keinänen-Kiukaanniemi, J. S. Kooner, C. Kooperberg, P. Kovacs, A. T. Kraja, M. Kumari, K. Kuulasmaa, J. Kuusisto, T. A. Lakka, C.

Langenberg, L. Le Marchand, T. Lehtimäki, V. Lyssenko, S. Männistö, A. Marette, T. C. Matise, C. A. McKenzie, B. McKnight, A. W. Musk, S. Möhlenkamp, A. D. Morris, M. Nelis, C. Ohlsson, A. J. Oldehinkel, K. K. Ong, L. J. Palmer, B. W. Penninx, A. Peters, P. P. Pramstaller, O. T. Raitakari, T. Rankinen, D. C. Rao, T. K. Rice, P. M. Ridker, M. D. Ritchie, I. Rudan, V. Salomaa, N. J. Samani, J. Saramies, M. A. Sarzynski, P. E. Schwarz, A. R. Shuldiner, J. A. Staessen, V. Steinthorsdottir, R. P. Stolk, K. Strauch, A. Tönjes, A. Tremblay, E. Tremoli, M.-C. Vohl, U. Völker, P. Vollenweider, J. F. Wilson, J. C. Witteman, L. S. Adair, M. Bochud, B. O. Boehm, S. R. Bornstein, C. Bouchard, S. Cauchi, M. J. Caulfield, J. C. Chambers, D. I. Chasman, R. S. Cooper, G. Dedoussis, L. Ferrucci, P. Froguel, H.-J. Grabe, A. Hamsten, J. Hui, K. Hveem, K.-H. Jöckel, M. Kivimäki, D. Kuh, M. Laakso, Y. Liu, W. März, P. B. Munroe, I. Njølstad, B. A. Oostra, C. N. Palmer, N. L. Pedersen, M. Perola, L. Pérusse, U. Peters, C. Power, T. Quertermous, R. Rauramaa, F. Rivadeneira, T. E. Saaristo, D. Saleheen, J. Sinisalo, P. E. Slagboom, H. Snieder, T. D. Spector, K. Stefansson, M. Stumvoll, J. Tuomilehto, A. G. Uitterlinden, M. Uusitupa, P. van der Harst, G. Veronesi, M. Walker, N. J. Wareham, H. Watkins, H.-E. Wichmann, G. R. Abecasis, T. L. Assimes, S. I. Berndt, M. Boehnke, I. B. Borecki, P. Deloukas, L. Franke, T. M. Frayling, L. C. Groop, D. J. Hunter, R. C. Kaplan, J. R. O'Connell, L. Qi, D. Schlessinger, D. P. Strachan, U. Thorsteinsdottir, C. M. van Duijn, C. J. Willer, P. M. Visscher, J. Yang, J. N. Hirschhorn, M. C. Zillikens, M. I. McCarthy, E. K. Speliotes, K. E. North, C. S. Fox, I. Barroso, P. W. Franks, E. Ingelsson, I. M. Heid, R. J. Loos, L. A. Cupples, A. P. Morris, C. M. Lindgren, K. L. Mohlke, New genetic loci link adipose and insulin biology to body fat distribution, *Nature* **518**, 187–196 (2015).

96. C. P. Nelson, A. Goel, A. S. Butterworth, S. Kanoni, T. R. Webb, E. Marouli, L. Zeng, I. Ntalla, F. Y. Lai, J. C. Hopewell, O. Giannakopoulou, T. Jiang, S. E. Hamby, E. Di Angelantonio, T. L. Assimes, E. P. Bottinger, J. C. Chambers, R. Clarke, C. N. A. Palmer, R. M. Cubbon, P. Ellinor, R. Ermel, E. Evangelou, P. W. Franks, C. Grace, D. Gu, A. D. Hingorani, J. M. M. Howson, E. Ingelsson, A. Kastrati, T. Kessler, T. Kyriakou, T. Lehtimäki, X. Lu, Y. Lu, W. März, R. McPherson, A. Metspalu, M. Pujades-Rodriguez, A. Ruusalepp, E. E. Schadt, A. F. Schmidt, M. J. Sweeting, P. A. Zalloua, K. AlGhalayini, B. D. Keavney, J. S. Kooner, R. J. F. Loos, R. S. Patel, M. K. Rutter, M. Tomaszewski, I. Tzoulaki, E. Zeggini, J. Erdmann, G. Dedoussis, J. L. M. Björkegren, EPIC-CVD Consortium, CARDIoGRAMplusC4D, UK Biobank CardioMetabolic Consortium CHD working group, H. Schunkert, M. Farrall, J. Danesh, N. J. Samani, H. Watkins, P. Deloukas, Association analyses based on false discovery rate implicate new loci for coronary artery disease, *Nat. Genet.* **49**, 1385–1391 (2017).

97. J. W. Smoller, E. W. Karlson, R. C. Green, S. Kathiresan, D. G. MacArthur, M. E. Talkowski, S. N. Murphy, S. T. Weiss, An eMERGE Clinical Center at Partners Personalized Medicine, *J Pers Med* **6** (2016), doi:10.3390/jpm6010005.

98. V. S. Gainer, A. Cagan, V. M. Castro, S. Duey, B. Ghosh, A. P. Goodson, S. Goryachev, R. Metta, T. D. Wang, N. Wattanasin, S. N. Murphy, The Biobank Portal for Partners Personalized Medicine: A Query Tool for Working with Consented Biobank Samples, Genotypes, and Phenotypes Using i2b2, *J Pers Med* **6** (2016), doi:10.3390/jpm6010011.

99. M. Mitt, M. Kals, K. Pärn, S. B. Gabriel, E. S. Lander, A. Palotie, S. Ripatti, A. P. Morris, A. Metspalu, T. Esko, R. Mägi, P. Palta, Improved imputation accuracy of rare and low-frequency variants using population-specific high-coverage WGS-based imputation reference panel, *Eur. J. Hum. Genet.* **25**, 869–876 (2017).

100. Z. Chen, J. Chen, R. Collins, Y. Guo, R. Peto, F. Wu, L. Li, China Kadoorie Biobank (CKB) collaborative group, China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up, *Int. J. Epidemiol.* **40**, 1652–1666 (2011).

101. the CARDIoGRAMplusC4D Consortium, A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease, *Nat. Genet.* **47**, 1121 (2015).

102. R. Malik, G. Chauhan, M. Traylor, M. Sargurupremraj, Y. Okada, A. Mishra, L. Rutten-Jacobs, A.-K. Giese, S. W. van der Laan, S. Gretarsdottir, C. D. Anderson, M. Chong, H. H. H. Adams, T. Ago, P. Almgren, P. Amouyel, H. Ay, T. M. Bartz, O. R. Benavente, S. Bevan, G. B. Boncoraglio, R. D. Brown, A. S. Butterworth, C. Carrera, C. L. Carty, D. I. Chasman, W.-M. Chen, J. W. Cole, A. Correa, I. Cotlarciuc,

C. Cruchaga, J. Danesh, P. I. W. de Bakker, A. L. DeStefano, M. den Hoed, Q. Duan, S. T. Engelter, G. J. Falcone, R. F. Gottesman, R. P. Grewal, V. Gudnason, S. Gustafsson, J. Haessler, T. B. Harris, A. Hassan, A. S. Havulinna, S. R. Heckbert, E. G. Holliday, G. Howard, F.-C. Hsu, H. I. Hyacinth, M. A. Ikram, E. Ingelsson, M. R. Irvin, X. Jian, J. Jiménez-Conde, J. A. Johnson, J. W. Jukema, M. Kanai, K. L. Keene, B. M. Kissela, D. O. Kleindorfer, C. Kooperberg, M. Kubo, L. A. Lange, C. D. Langefeld, C. Langenberg, L. J. Launer, J.-M. Lee, R. Lemmens, D. Leys, C. M. Lewis, W.-Y. Lin, A. G. Lindgren, E. Lorentzen, P. K. Magnusson, J. Maguire, A. Manichaikul, P. F. McArdle, J. F. Meschia, B. D. Mitchell, T. H. Mosley, M. A. Nalls, T. Ninomiya, M. J. O'Donnell, B. M. Psaty, S. L. Pulit, K. Rannikmäe, A. P. Reiner, K. M. Rexrode, K. Rice, S. S. Rich, P. M. Ridker, N. S. Rost, P. M. Rothwell, J. I. Rotter, T. Rundek, R. L. Sacco, S. Sakaue, M. M. Sale, V. Salomaa, B. R. Sapkota, R. Schmidt, C. O. Schmidt, U. Schminke, P. Sharma, A. Slowik, C. L. M. Sudlow, C. Tanislav, T. Tatlisumak, K. D. Taylor, V. N. S. Thijs, G. Thorleifsson, U. Thorsteinsdottir, S. Tiedt, S. Trompet, C. Tzourio, C. M. van Duijn, M. Walters, N. J. Wareham, S. Wassertheil-Smoller, J. G. Wilson, K. L. Wiggins, Q. Yang, S. Yusuf, J. C. Bis, T. Pastinen, A. Ruusalepp, E. E. Schadt, S. Koplev, J. L. M. Björkegren, V. Codoni, M. Civelek, N. L. Smith, D. A. Trégouët, I. E. Christophersen, C. Roselli, S. A. Lubitz, P. T. Ellinor, E. S. Tai, J. S. Kooner, N. Kato, J. He, P. van der Harst, P. Elliott, J. C. Chambers, F. Takeuchi, A. D. Johnson, D. K. Sanghera, O. Melander, C. Jern, D. Strbian, I. Fernandez-Cadenas, W. T. Longstreth, A. Rolfs, J. Hata, D. Woo, J. Rosand, G. Pare, J. C. Hopewell, D. Saleheen, K. Stefansson, B. B. Worrall, S. J. Kittner, S. Seshadri, M. Fornage, H. S. Markus, J. M. M. Howson, Y. Kamatani, S. Dobbie, M. Dichgans, R. Malik, G. Chauhan, M. Traylor, M. Sargurupremraj, Y. Okada, A. Mishra, L. Rutten-Jacobs, A.-K. Giese, S. W. van der Laan, S. Gretarsdottir, C. D. Anderson, M. Chong, H. H. H. Adams, T. Ago, P. Almgren, P. Amouyel, H. Ay, T. M. Bartz, O. R. Benavente, S. Bevan, G. B. Boncoraglio, R. D. Brown, A. S. Butterworth, C. Carrera, C. L. Carty, D. I. Chasman, W.-M. Chen, J. W. Cole, A. Correa, I. Cotlarciuc, C. Cruchaga, J. Danesh, P. I. W. de Bakker, A. L. DeStefano, M. D. Hoed, Q. Duan, S. T. Engelter, G. J. Falcone, R. F. Gottesman, R. P. Grewal, V. Gudnason, S. Gustafsson, J. Haessler, T. B. Harris, A. Hassan, A. S. Havulinna, S. R. Heckbert, E. G. Holliday, G. Howard, F.-C. Hsu, H. I. Hyacinth, M. A. Ikram, E. Ingelsson, M. R. Irvin, X. Jian, J. Jiménez-Conde, J. A. Johnson, J. W. Jukema, M. Kanai, K. L. Keene, B. M. Kissela, D. O. Kleindorfer, C. Kooperberg, M. Kubo, L. A. Lange, C. D. Langefeld, C. Langenberg, L. J. Launer, J.-M. Lee, R. Lemmens, D. Leys, C. M. Lewis, W.-Y. Lin, A. G. Lindgren, E. Lorentzen, P. K. Magnusson, J. Maguire, A. Manichaikul, P. F. McArdle, J. F. Meschia, B. D. Mitchell, T. H. Mosley, M. A. Nalls, T. Ninomiya, M. J. O'Donnell, B. M. Psaty, S. L. Pulit, K. Rannikmäe, A. P. Reiner, K. M. Rexrode, K. Rice, S. S. Rich, P. M. Ridker, N. S. Rost, P. M. Rothwell, J. I. Rotter, T. Rundek, R. L. Sacco, S. Sakaue, M. M. Sale, V. Salomaa, B. R. Sapkota, R. Schmidt, C. O. Schmidt, U. Schminke, P. Sharma, A. Slowik, C. L. M. Sudlow, C. Tanislav, T. Tatlisumak, K. D. Taylor, V. N. S. Thijs, G. Thorleifsson, U. Thorsteinsdottir, S. Tiedt, S. Trompet, C. Tzourio, C. M. van Duijn, M. Walters, N. J. Wareham, S. Wassertheil-Smoller, J. G. Wilson, K. L. Wiggins, Q. Yang, S. Yusuf, N. Amin, H. S. Aparicio, D. K. Arnett, J. Attia, et al, Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes, *Nat. Genet.* **50**, 524–537 (2018).

103. J. B. Nielsen, R. B. Thoroldsdottir, L. G. Fritsche, W. Zhou, M. W. Skov, S. E. Graham, T. J. Herron, S. McCarthy, E. M. Schmidt, G. Sveinbjornsson, I. Surakka, M. R. Mathis, M. Yamazaki, R. D. Crawford, M. E. Gabrielsen, A. H. Skogholt, O. L. Holmen, M. Lin, B. N. Wolford, R. Dey, H. Dalen, P. Sulem, J. H. Chung, J. D. Backman, D. O. Arnar, U. Thorsteinsdottir, A. Baras, C. O'Dushlaine, A. G. Holst, X. Wen, W. Hornsby, F. E. Dewey, M. Boehnke, S. Kheterpal, B. Mukherjee, S. Lee, H. M. Kang, H. Holm, J. Kitzman, J. A. Shavit, J. Jalife, C. M. Brummett, T. M. Teslovich, D. J. Carey, D. F. Gudbjartsson, K. Stefansson, G. R. Abecasis, K. Hveem, C. J. Willer, Biobank-driven genomic discovery yields new insight into atrial fibrillation biology, *Nat. Genet.* **50**, 1234–1239 (2018).

104. A. Mahajan, D. Taliun, M. Thurner, N. R. Robertson, J. M. Torres, N. W. Rayner, A. J. Payne, V. Steinthorsdottir, R. A. Scott, N. Grarup, J. P. Cook, E. M. Schmidt, M. Wuttke, C. Sarnowski, R. Mägi, J. Nano, C. Gieger, S. Trompet, C. Lecoeur, M. H. Preuss, B. P. Prins, X. Guo, L. F. Bielak, J. E. Below, D. W. Bowden, J. C. Chambers, Y. J. Kim, M. C. Y. Ng, L. E. Petty, X. Sim, W. Zhang, A. J. Bennett, J. Bork-Jensen, C. M. Brummett, M. Canouil, K.-U. Eckardt, K. Fischer, S. L. R. Kardia, F. Kronenberg, K. Läll, C.-T. Liu, A. E. Locke, J. 'an Luan, I. Ntalla, V. Nylander, S. Schönherr, C. Schurmann, L. Yengo, E. P. Bottinger, I. Brandslund, C. Christensen, G. Dedoussis, J. C. Florez, I. Ford, O. H. Franco, T. M. Frayling, V. Giedraitis, S. Hackinger, A. T. Hattersley, C. Herder, M. A. Ikram, M. Ingelsson, M. E. Jørgensen, T.

Jørgensen, J. Kriebel, J. Kuusisto, S. Ligthart, C. M. Lindgren, A. Linneberg, V. Lyssenko, V. Mamakou, T. Meitinger, K. L. Mohlke, A. D. Morris, G. Nadkarni, J. S. Pankow, A. Peters, N. Sattar, A. Stančáková, K. Strauch, K. D. Taylor, B. Thorand, G. Thorleifsson, U. Thorsteinsdottir, J. Tuomilehto, D. R. Witte, J. Dupuis, P. A. Peyser, E. Zeggini, R. J. F. Loos, P. Froguel, E. Ingelsson, L. Lind, L. Groop, M. Laakso, F. S. Collins, J. W. Jukema, C. N. A. Palmer, H. Grallert, A. Metspalu, A. Dehghan, A. Köttgen, G. R. Abecasis, J. B. Meigs, J. I. Rotter, J. Marchini, O. Pedersen, T. Hansen, C. Langenberg, N. J. Wareham, K. Stefansson, A. L. Gloyn, A. P. Morris, M. Boehnke, M. I. McCarthy, Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps, *Nat. Genet.* **50**, 1505–1513 (2018).

105. A. K. Manning, M.-F. Hivert, R. A. Scott, J. L. Grimsby, N. Bouatia-Naji, H. Chen, D. Rybin, C.-T. Liu, L. F. Bielak, I. Prokopenko, N. Amin, D. Barnes, G. Cadby, J.-J. Hottenga, E. Ingelsson, A. U. Jackson, T. Johnson, S. Kanoni, C. Ladenvall, V. Lagou, J. Lahti, C. Lecoeur, Y. Liu, M. T. Martinez-Larrad, M. E. Montasser, P. Navarro, J. R. B. Perry, L. J. Rasmussen-Torvik, P. Salo, N. Sattar, D. Shungin, R. J. Strawbridge, T. Tanaka, C. M. van Duijn, P. An, M. de Andrade, J. S. Andrews, T. Aspelund, M. Atalay, Y. Aulchenko, B. Balkau, S. Bandinelli, J. S. Beckmann, J. P. Beilby, C. Bellis, R. N. Bergman, J. Blangero, M. Boban, M. Boehnke, E. Boerwinkle, L. L. Bonnycastle, D. I. Boomsma, I. B. Borecki, Y. Böttcher, C. Bouchard, E. Brunner, D. Budimir, H. Campbell, O. Carlson, P. S. Chines, R. Clarke, F. S. Collins, A. Corbatón-Anchuelo, D. Couper, U. de Faire, G. V. Dedoussis, P. Deloukas, M. Dimitriou, J. M. Egan, G. Eiriksdottir, M. R. Erdos, J. G. Eriksson, E. Eury, L. Ferrucci, I. Ford, N. G. Forouhi, C. S. Fox, M. G. Franzosi, P. W. Franks, T. M. Frayling, P. Froguel, P. Galan, E. de Geus, B. Gigante, N. L. Glazer, A. Goel, L. Groop, V. Gudnason, G. Hallmans, A. Hamsten, O. Hansson, T. B. Harris, C. Hayward, S. Heath, S. Herberg, A. A. Hicks, A. Hingorani, A. Hofman, J. Hui, J. Hung, M.-R. Jarvelin, M. A. Jhun, P. C. D. Johnson, J. W. Jukema, A. Jula, W. H. Kao, J. Kaprio, S. L. R. Kardia, S. Keinänen-Kiukaanniemi, M. Kivimäki, I. Kolcic, P. Kovacs, M. Kumari, J. Kuusisto, K. O. Kyvik, M. Laakso, T. Lakka, L. Lannfelt, G. M. Lathrop, L. J. Launer, K. Leander, G. Li, L. Lind, J. Lindstrom, S. Lobbens, R. J. F. Loos, J. 'an Luan, V. Lyssenko, R. Mägi, P. K. E. Magnusson, M. Marmot, P. Meneton, K. L. Mohlke, V. Mooser, M. A. Morken, I. Miljkovic, N. Narisu, J. O'Connell, K. K. Ong, B. A. Oostra, L. J. Palmer, A. Palotie, J. S. Pankow, J. F. Peden, N. L. Pedersen, M. Pehlic, L. Peltonen, B. Penninx, M. Pericic, M. Perola, L. Perusse, P. A. Peyser, O. Polasek, P. P. Pramstaller, M. A. Province, K. Rääkkönen, R. Rauramaa, E. Rehnberg, K. Rice, J. I. Rotter, I. Rudan, A. Ruokonen, T. Saaristo, M. Sabater-Lleal, V. Salomaa, D. B. Savage, R. Saxena, P. Schwarz, U. Seedorf, B. Sennblad, M. Serrano-Rios, A. R. Shuldiner, E. J. G. Sijbrands, D. S. Siscovick, J. H. Smit, K. S. Small, N. L. Smith, A. V. Smith, A. Stančáková, K. Stirrups, M. Stumvoll, Y. V. Sun, A. J. Swift, A. Tönjes, J. Tuomilehto, S. Trompet, A. G. Uitterlinden, M. Uusitupa, M. Vikström, V. Vitart, M.-C. Vohl, B. F. Voight, P. Vollenweider, G. Waeber, D. M. Waterworth, H. Watkins, E. Wheeler, E. Widen, S. H. Wild, S. M. Willems, G. Willemsen, J. F. Wilson, J. C. M. Witterman, A. F. Wright, H. Yaghootkar, D. Zelenika, T. Zemunik, L. Zgaga, DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Multiple Tissue Human Expression Resource (MUTHER) Consortium, N. J. Wareham, M. I. McCarthy, I. Barroso, R. M. Watanabe, J. C. Florez, J. Dupuis, J. B. Meigs, C. Langenberg, A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance, *Nat. Genet.* **44**, 659–669 (2012).

106. E. Wheeler, A. Leong, C.-T. Liu, M.-F. Hivert, R. J. Strawbridge, C. Podmore, M. Li, J. Yao, X. Sim, J. Hong, A. Y. Chu, W. Zhang, X. Wang, P. Chen, N. M. Maruthur, B. C. Porneala, S. J. Sharp, Y. Jia, E. K. Kabagambe, L.-C. Chang, W.-M. Chen, C. E. Elks, D. S. Evans, Q. Fan, F. Giulianini, M. J. Go, J.-J. Hottenga, Y. Hu, A. U. Jackson, S. Kanoni, Y. J. Kim, M. E. Kleber, C. Ladenvall, C. Lecoeur, S.-H. Lim, Y. Lu, A. Mahajan, C. Marzi, M. A. Nalls, P. Navarro, I. M. Nolte, L. M. Rose, D. V. Rybin, S. Sanna, Y. Shi, D. O. Stram, F. Takeuchi, S. P. Tan, P. J. van der Most, J. V. Van Vliet-Ostaptchouk, A. Wong, L. Yengo, W. Zhao, A. Goel, M. T. Martinez Larrad, D. Radke, P. Salo, T. Tanaka, E. P. A. van Iperen, G. Abecasis, S. Afaq, B. Z. Alizadeh, A. G. Bertoni, A. Bonnefond, Y. Böttcher, E. P. Bottinger, H. Campbell, O. D. Carlson, C.-H. Chen, Y. S. Cho, W. T. Garvey, C. Gieger, M. O. Goodarzi, H. Grallert, A. Hamsten, C. A. Hartman, C. Herder, C. A. Hsiung, J. Huang, M. Igase, M. Isono, T. Katsuya, C.-C. Khor, W. Kiess, K. Kohara, P. Kovacs, J. Lee, W.-J. Lee, B. Lehne, H. Li, J. Liu, S. Lobbens, J. 'an Luan, V. Lyssenko, T. Meitinger, T. Miki, I. Miljkovic, S. Moon, A. Mulas, G. Müller, M. Müller-Nurasyid, R. Nagaraja, M. Nauck, J. S. Pankow, O. Polasek, I. Prokopenko, P. S. Ramos, L. Rasmussen-Torvik, W. Rathmann, S. S. Rich, N. R. Robertson, M. Roden, R. Roussel, I. Rudan, R. A. Scott, W. R. Scott, B. Sennblad, D. S. Siscovick,

K. Strauch, L. Sun, M. Swertz, S. M. Tajuddin, K. D. Taylor, Y.-Y. Teo, Y. C. Tham, A. Tönjes, N. J. Wareham, G. Willemssen, T. Wilsaard, A. D. Hingorani, EPIC-CVD Consortium, EPIC-InterAct Consortium, Lifelines Cohort Study, J. Egan, L. Ferrucci, G. K. Hovingh, A. Jula, M. Kivimäki, M. Kumari, I. Njølstad, C. N. A. Palmer, M. Serrano Ríos, M. Stumvoll, H. Watkins, T. Aung, M. Blüher, M. Boehnke, D. I. Boomsma, S. R. Bornstein, J. C. Chambers, D. I. Chasman, Y.-D. I. Chen, Y.-T. Chen, C.-Y. Cheng, F. Cucca, E. J. C. de Geus, P. Deloukas, M. K. Evans, M. Fornage, Y. Friedlander, P. Froguel, L. Groop, M. D. Gross, T. B. Harris, C. Hayward, C.-K. Heng, E. Ingelsson, N. Kato, B.-J. Kim, W.-P. Koh, J. S. Kooner, A. Körner, D. Kuh, J. Kuusisto, M. Laakso, X. Lin, Y. Liu, R. J. F. Loos, P. K. E. Magnusson, W. März, M. I. McCarthy, A. J. Oldehinkel, K. K. Ong, N. L. Pedersen, M. A. Pereira, A. Peters, P. M. Ridker, C. Sabanayagam, M. Sale, D. Saleheen, J. Saltevo, P. E. Schwarz, W. H. H. Sheu, H. Snieder, T. D. Spector, Y. Tabara, J. Tuomilehto, R. M. van Dam, J. G. Wilson, J. F. Wilson, B. H. R. Wolffenbuttel, T. Y. Wong, J.-Y. Wu, J.-M. Yuan, A. B. Zonderman, N. Soranzo, X. Guo, D. J. Roberts, J. C. Florez, R. Sladek, J. Dupuis, A. P. Morris, E.-S. Tai, E. Selvin, J. I. Rotter, C. Langenberg, I. Barroso, J. B. Meigs, Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis, *PLoS Med.* **14**, e1002383 (2017).

107. C. J. Willer, E. M. Schmidt, S. Sengupta, G. M. Peloso, S. Gustafsson, S. Kanoni, A. Ganna, J. Chen, M. L. Buchkovich, S. Mora, J. S. Beckmann, J. L. Bragg-Gresham, H.-Y. Chang, A. Demirkan, H. M. Den Hertog, R. Do, L. A. Donnelly, G. B. Ehret, T. Esko, M. F. Feitosa, T. Ferreira, K. Fischer, P. Fontanillas, R. M. Fraser, D. F. Freitag, D. Gurdasani, K. Heikkilä, E. Hyppönen, A. Isaacs, A. U. Jackson, Å. Johansson, T. Johnson, M. Kaakinen, J. Kettunen, M. E. Kleber, X. Li, J. 'an Luan, L.-P. Lyytikäinen, P. K. E. Magnusson, M. Mangino, E. Mihailov, M. E. Montasser, M. Müller-Nurasyid, I. M. Nolte, J. R. O'Connell, C. D. Palmer, M. Perola, A.-K. Petersen, S. Sanna, R. Saxena, S. K. Service, S. Shah, D. Shungin, C. Sidore, C. Song, R. J. Strawbridge, I. Surakka, T. Tanaka, T. M. Teslovich, G. Thorleifsson, E. G. Van den Herik, B. F. Voight, K. A. Volcik, L. L. Waite, A. Wong, Y. Wu, W. Zhang, D. Absher, G. Asiki, I. Barroso, L. F. Been, J. L. Bolton, L. L. Bonnycastle, P. Brambilla, M. S. Burnett, G. Cesana, M. Dimitriou, A. S. F. Doney, A. Döring, P. Elliott, S. E. Epstein, G. Ingi Eyjolfsson, B. Gigante, M. O. Goodarzi, H. Grallert, M. L. Gravito, C. J. Groves, G. Hallmans, A.-L. Hartikainen, C. Hayward, D. Hernandez, A. A. Hicks, H. Holm, Y.-J. Hung, T. Illig, M. R. Jones, P. Kaleebu, J. J. P. Kastelein, K.-T. Khaw, E. Kim, N. Klopp, P. Komulainen, M. Kumari, C. Langenberg, T. Lehtimäki, S.-Y. Lin, J. Lindström, R. J. F. Loos, F. Mach, W. L. McArdle, C. Meisinger, B. D. Mitchell, G. Müller, R. Nagaraja, N. Narisu, T. V. M. Nieminen, R. N. Nsubuga, I. Olafsson, K. K. Ong, A. Palotie, T. Papamarkou, C. Pomilla, A. Pouta, D. J. Rader, M. P. Reilly, P. M. Ridker, F. Rivadeneira, I. Rudan, A. Ruokonen, N. Samani, H. Scharnagl, J. Seeley, K. Silander, A. Stančáková, K. Stirrups, A. J. Swift, L. Tiret, A. G. Uitterlinden, L. J. van Pelt, S. Vedantam, N. Wainwright, C. Wijmenga, S. H. Wild, G. Willemssen, T. Wilsaard, J. F. Wilson, E. H. Young, J. H. Zhao, L. S. Adair, D. Arveiler, T. L. Assimes, S. Bandinelli, F. Bennett, M. Bochud, B. O. Boehm, D. I. Boomsma, I. B. Borecki, S. R. Bornstein, P. Bovet, M. Burnier, H. Campbell, A. Chakravarti, J. C. Chambers, Y.-D. I. Chen, F. S. Collins, R. S. Cooper, J. Danesh, G. Dedoussis, U. de Faire, A. B. Feranil, J. Ferrières, L. Ferrucci, N. B. Freimer, C. Gieger, L. C. Groop, V. Gudnason, U. Gyllenstein, A. Hamsten, T. B. Harris, A. Hingorani, J. N. Hirschhorn, A. Hofman, G. K. Hovingh, C. A. Hsiung, S. E. Humphries, S. C. Hunt, K. Hveem, C. Iribarren, M.-R. Järvelin, A. Jula, M. Kähönen, J. Kaprio, A. Kesäniemi, M. Kivimäki, J. S. Kooner, P. J. Koudstaal, R. M. Krauss, D. Kuh, J. Kuusisto, K. O. Kyvik, M. Laakso, T. A. Lakka, L. Lind, C. M. Lindgren, N. G. Martin, W. März, M. I. McCarthy, C. A. McKenzie, P. Meneton, A. Metspalu, L. Moilanen, A. D. Morris, P. B. Munroe, I. Njølstad, N. L. Pedersen, C. Power, P. P. Pramstaller, J. F. Price, B. M. Psaty, T. Quertermous, R. Rauramaa, D. Saleheen, V. Salomaa, D. K. Sanghera, J. Saramies, P. E. H. Schwarz, W. H.-H. Sheu, A. R. Shuldiner, A. Siegbahn, T. D. Spector, K. Stefansson, D. P. Strachan, B. O. Tayo, E. Tremoli, J. Tuomilehto, M. Uusitupa, C. M. van Duijn, P. Vollenweider, L. Wallentin, N. J. Wareham, J. B. Whitfield, B. H. R. Wolffenbuttel, J. M. Ordovas, E. Boerwinkle, C. N. A. Palmer, U. Thorsteinsdottir, D. I. Chasman, J. I. Rotter, P. W. Franks, S. Ripatti, L. A. Cupples, M. S. Sandhu, S. S. Rich, M. Boehnke, P. Deloukas, S. Kathiresan, K. L. Mohlke, E. Ingelsson, G. R. Abecasis, Global Lipids Genetics Consortium, Discovery and refinement of loci associated with lipid levels, *Nat. Genet.* **45**, 1274–1283 (2013).

108. C. Pattaro, A. Teumer, M. Gorski, A. Y. Chu, M. Li, V. Mijatovic, M. Garnaas, A. Tin, R. Sorice, Y. Li, D. Taliun, M. Olden, M. Foster, Q. Yang, M.-H. Chen, T. H. Pers, A. D. Johnson, Y.-A. Ko, C.

Fuchsberger, B. Tayo, M. Nalls, M. F. Feitosa, A. Isaacs, A. Dehghan, P. d'Adamo, A. Adeyemo, A. K. Dieffenbach, A. B. Zonderman, I. M. Nolte, P. J. van der Most, A. F. Wright, A. R. Shuldiner, A. C. Morrison, A. Hofman, A. V. Smith, A. W. Dreisbach, A. Franke, A. G. Uitterlinden, A. Metspalu, A. Tonjes, A. Lupo, A. Robino, Å. Johansson, A. Demirkan, B. Kollerits, B. I. Freedman, B. Ponte, B. A. Oostra, B. Paulweber, B. K. Krämer, B. D. Mitchell, B. M. Buckley, C. A. Peralta, C. Hayward, C. Helmer, C. N. Rotimi, C. M. Shaffer, C. Müller, C. Sala, C. M. van Duijn, A. Saint-Pierre, D. Ackermann, D. Shriner, D. Ruggiero, D. Toniolo, Y. Lu, D. Cusi, D. Czamara, D. Ellinghaus, D. S. Siscovick, D. Ruderfer, C. Gieger, H. Grallert, E. Rohtchina, E. J. Atkinson, E. G. Holliday, E. Boerwinkle, E. Salvi, E. P. Bottinger, F. Murgia, F. Rivadeneira, F. Ernst, F. Kronenberg, F. B. Hu, G. J. Navis, G. C. Curhan, G. B. Ehret, G. Homuth, S. Coassin, G.-A. Thun, G. Pistis, G. Gambaro, G. Malerba, G. W. Montgomery, G. Eiriksdottir, G. Jacobs, G. Li, H.-E. Wichmann, H. Campbell, H. Schmidt, H. Wallaschofski, H. Völzke, H. Brenner, H. K. Kroemer, H. Kramer, H. Lin, I. M. Leach, I. Ford, I. Guessous, I. Rudan, I. Prokopenko, I. Borecki, I. M. Heid, I. Kolcic, I. Persico, J. W. Jukema, J. F. Wilson, J. F. Felix, J. Divers, J.-C. Lambert, J. M. Stafford, J.-M. Gaspoz, J. A. Smith, J. D. Faul, J. J. Wang, J. Ding, J. N. Hirschhorn, J. Attia, J. B. Whitfield, J. Chalmers, J. Viikari, J. Coresh, J. C. Denny, J. Karjalainen, J. K. Fernandes, K. Endlich, K. Butterbach, K. L. Keene, K. Lohman, L. Portas, L. J. Launer, L.-P. Lyytikäinen, L. Yengo, L. Franke, L. Ferrucci, L. M. Rose, L. Kedenko, M. Rao, M. Struchalin, M. E. Kleber, M. Cavalieri, M. Haun, M. C. Cornelis, M. Ciullo, M. Pirastu, M. de Andrade, M. A. McEvoy, M. Woodward, M. Adam, M. Cocca, M. Nauck, M. Imboden, M. Waldenberger, M. Pruijm, M. Metzger, M. Stumvoll, M. K. Evans, M. M. Sale, M. Kähönen, M. Boban, M. Bochud, M. Rheinberger, N. Verweij, N. Bouatia-Naji, N. G. Martin, N. Hastie, N. Probst-Hensch, N. Soranzo, O. Devuyst, O. Raitakari, O. Gottesman, O. H. Franco, O. Polasek, P. Gasparini, P. B. Munroe, P. M. Ridker, P. Mitchell, P. Muntner, C. Meisinger, J. H. Smit, ICBP Consortium, AGEN Consortium, CARDIOGRAM, CHARGE-Heart Failure Group, ECHOGen Consortium, P. Kovacs, P. S. Wild, P. Froguel, R. Rettig, R. Mägi, R. Biffar, R. Schmidt, R. P. S. Middelberg, R. J. Carroll, B. W. Penninx, R. J. Scott, R. Katz, S. Sedaghat, S. H. Wild, S. L. R. Kardia, S. Ulivi, S.-J. Hwang, S. Enroth, S. Kloiber, S. Trompet, B. Stengel, S. J. Hancock, S. T. Turner, S. E. Rosas, S. Stracke, T. B. Harris, T. Zeller, T. Zemunik, T. Lehtimäki, T. Illig, T. Aspelund, T. Nikopensius, T. Esko, T. Tanaka, U. Gyllensten, U. Völker, V. Emilsson, V. Vitart, V. Aalto, V. Gudnason, V. Chouraki, W.-M. Chen, W. Igl, W. März, W. Koenig, W. Lieb, R. J. F. Loos, Y. Liu, H. Snieder, P. P. Pramstaller, A. Parsa, J. R. O'Connell, K. Susztak, P. Hamet, J. Tremblay, I. H. de Boer, C. A. Böger, W. Goessling, D. I. Chasman, A. Köttgen, W. H. L. Kao, C. S. Fox, Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function, *Nat. Commun.* **7**, 10023 (2016).

109. M. Gorski, P. J. van der Most, A. Teumer, A. Y. Chu, M. Li, V. Mijatovic, I. M. Nolte, M. Cocca, D. Taliun, F. Gomez, Y. Li, B. Tayo, A. Tin, M. F. Feitosa, T. Aspelund, J. Attia, R. Biffar, M. Bochud, E. Boerwinkle, I. Borecki, E. P. Bottinger, M.-H. Chen, V. Chouraki, M. Ciullo, J. Coresh, M. C. Cornelis, G. C. Curhan, A. P. d'Adamo, A. Dehghan, L. Dengler, J. Ding, G. Eiriksdottir, K. Endlich, S. Enroth, T. Esko, O. H. Franco, P. Gasparini, C. Gieger, G. Grotto, O. Gottesman, V. Gudnason, U. Gyllensten, S. J. Hancock, T. B. Harris, C. Helmer, S. Höllerer, E. Hofer, A. Hofman, E. G. Holliday, G. Homuth, F. B. Hu, C. Huth, N. Hutri-Kähönen, S.-J. Hwang, M. Imboden, Å. Johansson, M. Kähönen, W. König, H. Kramer, B. K. Krämer, A. Kumar, Z. Kutalik, J.-C. Lambert, L. J. Launer, T. Lehtimäki, M. de Borst, G. Navis, M. Swertz, Y. Liu, K. Lohman, R. J. F. Loos, Y. Lu, L.-P. Lyytikäinen, M. A. McEvoy, C. Meisinger, T. Meitinger, A. Metspalu, M. Metzger, E. Mihailov, P. Mitchell, M. Nauck, A. J. Oldehinkel, M. Olden, B. W. Jh Penninx, G. Pistis, P. P. Pramstaller, N. Probst-Hensch, O. T. Raitakari, R. Rettig, P. M. Ridker, F. Rivadeneira, A. Robino, S. E. Rosas, D. Ruderfer, D. Ruggiero, Y. Saba, C. Sala, H. Schmidt, R. Schmidt, R. J. Scott, S. Sedaghat, A. V. Smith, R. Sorice, B. Stengel, S. Stracke, K. Strauch, D. Toniolo, A. G. Uitterlinden, S. Ulivi, J. S. Viikari, U. Völker, P. Vollenweider, H. Völzke, D. Vuckovic, M. Waldenberger, J. Jin Wang, Q. Yang, D. I. Chasman, G. Tromp, H. Snieder, I. M. Heid, C. S. Fox, A. Köttgen, C. Pattaro, C. A. Böger, C. Fuchsberger, 1000 Genomes-based meta-analysis identifies 10 novel loci for kidney function, *Sci. Rep.* **7**, 45040 (2017).

110. W. Ye, Y. Wang, B. Mei, S. Hou, X. Liu, G. Wu, L. Qin, K. Zhao, Q. Huang, Computational and functional characterization of four SNPs in the SOST locus associated with osteoporosis, *Bone* **108**, 132–144 (2018).

111. S. Burgess, B. A. Ference, J. R. Staley, D. F. Freitag, A. M. Mason, S. F. Nielsen, P. Willeit, R.

Young, P. Surendran, S. Karthikeyan, T. R. Bolton, J. E. Peters, P. R. Kamstrup, A. Tybjaerg-Hansen, M. Benn, A. Langsted, P. Schnohr, S. Vedel-Krogh, C. J. Kobylecki, I. Ford, C. Packard, S. Trompet, J. W. Jukema, N. Sattar, E. Di Angelantonio, D. Saleheen, J. M. M. Howson, B. G. Nordestgaard, A. S. Butterworth, J. Danesh, European Prospective Investigation Into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD) Consortium, Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis, *JAMA Cardiol* **3**, 619–627 (2018).

112. D. I. Swerdlow, D. Preiss, K. B. Kuchenbaecker, M. V. Holmes, J. E. L. Engmann, T. Shah, R. Sofat, S. Stender, P. C. D. Johnson, R. A. Scott, M. Leusink, N. Verweij, S. J. Sharp, Y. Guo, C. Giambartolomei, C. Chung, A. Peasey, A. Amuzu, K. Li, J. Palmen, P. Howard, J. A. Cooper, F. Drenos, Y. R. Li, G. Lowe, J. Gallacher, M. C. W. Stewart, I. Tzoulaki, S. G. Buxbaum, D. L. van der A, N. G. Forouhi, N. C. Onland-Moret, Y. T. van der Schouw, R. B. Schnabel, J. A. Hubacek, R. Kubinova, M. Baceviciene, A. Tamosiunas, A. Pajak, R. Topor-Madry, U. Stepaniak, S. Malyutina, D. Baldassarre, B. Sennblad, E. Tremoli, U. de Faire, F. Veglia, I. Ford, J. W. Jukema, R. G. J. Westendorp, G. J. de Borst, P. A. de Jong, A. Algra, W. Spiering, A. H. Maitland-van der Zee, O. H. Klungel, A. de Boer, P. A. Doevendans, C. B. Eaton, J. G. Robinson, D. Duggan, DIAGRAM Consortium, MAGIC Consortium, InterAct Consortium, J. Kjekshus, J. R. Downs, A. M. Gotto, A. C. Keech, R. Marchioli, G. Tognoni, P. S. Sever, N. R. Poulter, D. D. Waters, T. R. Pedersen, P. Amarengo, H. Nakamura, J. J. V. McMurray, J. D. Lewsey, D. I. Chasman, P. M. Ridker, A. P. Maggioni, L. Tavazzi, K. K. Ray, S. R. K. Seshasai, J. E. Manson, J. F. Price, P. H. Whincup, R. W. Morris, D. A. Lawlor, G. Davey Smith, Y. Ben-Shlomo, P. J. Schreiner, M. Fornage, D. S. Siscovick, M. Cushman, M. Kumari, N. J. Wareham, W. M. M. Verschuren, S. Redline, S. R. Patel, J. C. Whittaker, A. Hamsten, J. A. Delaney, C. Dale, T. R. Gaunt, A. Wong, D. Kuh, R. Hardy, S. Kathiresan, B. A. Castillo, P. van der Harst, E. J. Brunner, A. Tybjaerg-Hansen, M. G. Marmot, R. M. Krauss, M. Tsai, J. Coresh, R. C. Hoogeveen, B. M. Psaty, L. A. Lange, H. Hakonarson, F. Dudbridge, S. E. Humphries, P. J. Talmud, M. Kivimäki, N. J. Timpson, C. Langenberg, F. W. Asselbergs, M. Voevoda, M. Bobak, H. Pikhart, J. G. Wilson, A. P. Reiner, B. J. Keating, A. D. Hingorani, N. Sattar, HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials, *Lancet* **385**, 351–361 (2015).

113. L. D. Ward, M. Kellis, HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants, *Nucleic Acids Res.* **40**, D930–4 (2012).

114. GTEx Consortium, Laboratory, Data Analysis & Coordinating Center (LDACC)—Analysis Working Group, Statistical Methods groups—Analysis Working Group, Enhancing GTEx (eGTEx) groups, NIH Common Fund, NIH/NCI, NIH/NHGRI, NIH/NIMH, NIH/NIDA, Biospecimen Collection Source Site—NDRI, Biospecimen Collection Source Site—RPCI, Biospecimen Core Resource—VARI, Brain Bank Repository—University of Miami Brain Endowment Bank, Leidos Biomedical—Project Management, ELSI Study, Genome Browser Data Integration & Visualization—EBI, Genome Browser Data Integration & Visualization—UCSC Genomics Institute, University of California Santa Cruz, Lead analysts:, Laboratory, Data Analysis & Coordinating Center (LDACC):, NIH program management:, Biospecimen collection:, Pathology:, eQTL manuscript working group:, A. Battle, C. D. Brown, B. E. Engelhardt, S. B. Montgomery, Genetic effects on gene expression across human tissues, *Nature* **550**, 204–213 (2017).

115. W. Viechtbauer, Conducting meta-analyses in R with the metafor package, *J. Stat. Softw.* **36**, 1–48 (2010).

116. C. Giambartolomei, D. Vukcevic, E. E. Schadt, L. Franke, A. D. Hingorani, C. Wallace, V. Plagnol, Bayesian test for colocalisation between pairs of genetic association studies using summary statistics, *PLoS Genet.* **10**, e1004383 (2014).

117. J. Yang, T. Ferreira, A. P. Morris, S. E. Medland, Genetic Investigation of ANthropometric Traits (GIANT) Consortium, DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, P. A. F. Madden, A. C. Heath, N. G. Martin, G. W. Montgomery, M. N. Weedon, R. J. Loos, T. M. Frayling, M. I. McCarthy, J. N. Hirschhorn, M. E. Goddard, P. M. Visscher, Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits, *Nat. Genet.* **44**, 369–

75, S1–3 (2012).

118. K. Alasoo, J. Rodrigues, S. Mukhopadhyay, A. J. Knights, A. L. Mann, K. Kundu, HIPSCI Consortium, C. Hale, G. Dougan, D. J. Gaffney, Shared genetic effects on chromatin and gene expression indicate a role for enhancer priming in immune response, *Nat. Genet.* **50**, 424–431 (2018).

119. M. Çalışkan, E. Manduchi, H. Shanker Rao, J. A. Segert, M. H. Beltrame, M. Trizzino, Y. Park, S. W. Baker, A. Chesi, M. E. Johnson, K. M. Hodge, M. E. Leonard, B. Loza, D. Xin, A. M. Berrido, N. J. Hand, R. C. Bauer, A. D. Wells, K. M. Olthoff, A. Shaked, D. J. Rader, S. F. A. Grant, C. D. Brown, Genetic and Epigenetic Fine Mapping of Complex Trait Associated Loci in the Human Liver *bioRxiv*, 432823 (2018).

120. B. Liu, M. J. Gloudemans, A. S. Rao, E. Ingelsson, S. B. Montgomery, Abundant associations with gene expression complicate GWAS follow-up, *Nat. Genet.* **51**, 768–769 (2019).

121. J. A. C. Sterne, J. Savović, M. J. Page, R. G. Elbers, N. S. Blencowe, I. Boutron, C. J. Cates, H.-Y. Cheng, M. S. Corbett, S. M. Eldridge, J. R. Emberson, M. A. Hernán, S. Hopewell, A. Hróbjartsson, D. R. Junqueira, P. Jüni, J. J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B. C. Reeves, S. Shepperd, I. Shrier, L. A. Stewart, K. Tilling, I. R. White, P. F. Whiting, J. P. T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials *BMJ* **366**, l4898 (2019).

122. Center for Drug Evaluation, Research, Bone, Reproductive and Urologic Drugs Advisory Committee - 2019 Meeting Materials, Bone, Reproductive and Urologic Drugs Advisory Committee (formerly Advisory Committee for Reproductive Health Drugs (ACRHD)), (available at <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm627362.htm>).

123. M. J. Bradburn, J. J. Deeks, J. A. Berlin, A. Russell Localio, Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events, *Stat. Med.* **26**, 53–77 (2007).

124. M. J. Sweeting, A. J. Sutton, P. C. Lambert, What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data, *Stat. Med.* **23**, 1351–1375 (2004).

125. O. Efthimiou, Practical guide to the meta-analysis of rare events, *Evid. Based. Ment. Health* **21**, 72–76 (2018).

126. D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *BMJ* **339**, b2535 (2009).

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consortium of prospective cohorts. J.B., K.K., C.Y.C., R.B., J.C.C., T.F., S.L.P., C.A.G., S.L.L., I.Y.M., K.L., L.L., Z.C., L.M., G.D.S., R.G.W., R.M., B.M.N., C.M.L., M.V.H. contributed to the data collection and analyses and interpretation of findings. J.B., M.V.H. and C.M.L. contributed to the first draft of the manuscript. All authors contributed to and approved the final version of the manuscript. **Competing Interests:** J.B. has served as a consultant to the Bill and Melinda Gates Foundation Strategic Investment Fund. B.M.N. is a member of the Scientific Advisory Board for Deep Genomics, a consultant for Camp4 Therapeutics Corporation, a consultant for Merck & Co., a consultant for Takeda Pharmaceutical, and a consultant for Avanir Pharmaceuticals, Inc. C.M.L. has collaborated with Novo Nordisk and Bayer in research, and in accordance with a university agreement, did not accept any personal payment. M.V.H. has collaborated with Boehringer Ingelheim in research, and in accordance with the policy of the Clinical Trial Service Unit and Epidemiological Studies Unit (University of Oxford), did not accept any personal payment. Since October 2018, C.A.G. has been a full-time employee of BenevolentAI, United Kingdom. Since January 2019, C.Y.C. has been a full-time employee of Biogen, United States. Since January 2019, S.L.P. has been a full-time employee of Vertex Pharmaceuticals, United Kingdom. Contributions to this manuscript by C.A.G., C.Y.C. and S.L.P. were made prior to commencement of the stated employment. All other authors declare no competing interests. **Data and materials availability:** All allelic estimates generated during analyses are presented in this manuscript. GWAS summary statistics used in our analyses are publicly available.

Figure Legends

Fig. 1. Cumulative meta-analysis of cardiac ischemic events and meta-analysis of romosozumab and risk of cardiovascular events from phase III randomized controlled trials. (A) Meta-cumulative plot of cardiac ischemic events, with RCTs ordered by data availability. Each line represents the addition of a further trial to the meta-analysis. The dashed horizontal line separates RCTs with data that were peer-reviewed and available prior to the US FDA Drugs Advisory Committee meeting in January 2019 (ARCH and BRIDGE trials, with the meta-analysed estimate highlighted in blue), from the FRAME trial. (B) Conventional meta-analysis of data from phase III RCTs of romosozumab, including unpublished data released for the FDA Drugs Advisory Committee meeting in January 2019 (the latter is indicated with a red asterisk). *Events* represents number of events adjudicated per arm, during initial 12-month double-blind period in each trial. The *romosozumab*-group received 210mg romosozumab monthly in all trials; *comparator*-group received placebo (FRAME and BRIDGE trials) or alendronate (ARCH). Estimates were derived using the Mantel-Haenszel method. Boxes represent point estimates of effects. Lines represent 95% confidence intervals. OR, odds ratio; CI, confidence interval.

Fig. 2. Scaled estimates and meta-analysis of BMD-increasing *SOST* variants with risk of osteoporosis (15,239 cases) and fracture (53,074 cases). Estimates are scaled to match the effect of 210mg romosozumab monthly for 12 months on lumbar spine bone mineral density (0.09 g/cm²; see Methods) and aligned to the BMD-increasing alleles. See Methods sections for outcome definitions. Boxes represent point estimates of effects. Lines represent 95% confidence intervals. OR, odds ratio; CI, confidence interval; LS-BMD, lumbar spine bone mineral density.

Fig. 3. Scaled estimates and meta-analysis of BMD-increasing *SOST* variants with risk of myocardial infarction and/or coronary revascularization (up to 69,649 cases), coronary heart disease (up to 106,329 cases) and major adverse cardiovascular events (up to 119,032 cases). Estimates are scaled to match the effect of 210mg romosozumab monthly for 12 months on lumbar spine bone mineral density (0.09 g/cm²; see Methods) and aligned to the BMD-increasing alleles. *Myocardial*

infarction and/or coronary revascularization includes codes pertaining to myocardial infarction, coronary artery bypass graft surgery and/or percutaneous transluminal coronary angioplasty; *Coronary heart disease* includes all codes pertaining to myocardial infarction and/or coronary revascularization, plus codes for angina and chronic stable ischemic heart disease; *Major Adverse Cardiovascular Events* includes codes pertaining to a composite of myocardial infarction and/or coronary revascularization, stroke, or death from either. Boxes represent point estimates of effects. Lines represent 95% confidence intervals. OR, odds ratio; CI, confidence interval.

Fig. 4. Meta-analysis of BMD-increasing *SOST* variants and cardiometabolic risk factors. (A) shows association with hypertension and type 2 diabetes mellitus; (B) shows association with quantitative traits plotted in SD units, with clinical units for each trait indicated in the column on the right. All estimates are scaled to match the effect of 210mg romosozumab monthly for 12 months on lumbar spine bone mineral density (0.09 g/cm²; see Methods) and aligned to the BMD-increasing alleles. The significance threshold was set at 0.0045 (see Methods for details). Boxes represent point estimates of effects in odds ratio (panel A) or standard deviation (panel B) units. Lines represent 95% confidence intervals. OR, odds ratio; CI, confidence interval; mmHg, millimetres of mercury; SD, standard deviations, WHR, waist to hip ratio; adj, adjusted; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Fig. 5. Inhibition of sclerostin and risk of fracture and cardiovascular events derived from meta-analysis of phase III randomized controlled trials of romosozumab and human genetics. *Fracture risk RCT estimate* represents inverse variance weighted fixed-effect meta-analysis of estimates for hazard ratio of ‘clinical fracture’ at 12 months (a composite of non-vertebral or symptomatic vertebral fracture) in the ARCH and FRAME trials. *Coronary event risk RCT estimates* represent fixed-effect meta-analysis (using the Mantel-Haenszel method) of estimates for odds ratio of ‘cardiac ischemic events’ in the ARCH and BRIDGE trials only (*RCT Estimate (pre-FDA)*) and if including unpublished FRAME trial data released for FDA Drugs Advisory Committee meeting in January 2019 (*RCT Estimate (post-FDA)*). Data pertaining to the *MACE* (major adverse cardiovascular events) *risk RCT estimates* were solely sourced from the FDA Drugs Advisory Committee meeting data. *Scaled genetic estimates for fracture*

risk, coronary event risk and MACE risk represent inverse variance weighted fixed-effect meta-analyses of the scaled allelic estimates for the odds ratio of fracture risk, myocardial infarction and/or coronary revascularization, and major adverse cardiovascular events, respectively. All RCT estimates refer to the effect of romosozumab 210mg monthly for 12 months relative to comparator, and all genetic estimates are scaled to match the effect of 210mg romosozumab monthly for 12 months on lumbar spine bone mineral density (0.09 g/cm² increase). Boxes represent point estimates of effects. Lines represent 95% confidence intervals. RR, relative risk; CI, confidence interval.