Published in final edited form as:

Ann Hum Genet. 2016 March ; 80(2): 113–122. doi:10.1111/ahg.12143.

Exploring the major sources and extent of heterogeneity in a genome-wide association meta-analysis

Yu-Fang Pei^{1,2}, Qing Tian³, Lei Zhang^{2,4,*}, and Hong-Wen Deng^{3,*}

¹ Department of Epidemiology and Medical Statistics, School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu 215123, P. R. China.

² Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Soochow University, Jiangsu 215123, P. R. China.

³ Center for Bioinformatics and Genomics, Department of Biostatistics and Bioinformatics, Tulane University, New Orleans, LA 70112, USA.

⁴ Center for Genetic Epidemiology and Genomics, School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu 215123, P. R. China.

SUMMARY

Genome-wide association (GWA) meta-analysis has become a popular approach for discovering genetic variants responsible for complex diseases. The between-study heterogeneity effect is a severe issue that may complicate the interpretation of results. Aiming to improve the interpretation of meta-analysis results, we empirically explored the extent and source of heterogeneity effect. We analyzed a previously reported GWA meta-analysis of obesity, in which over 21,000 subjects from seven individual samples were meta-analyzed. We first evaluated the extent and distribution of heterogeneity across the entire genome. We then studied the effects of several potentially confounding factors, including age, ethnicity, gender composition, study type and genotype imputation on heterogeneity with a random-effects meta-regression model. Of the total 4,325,550 SNPs being tested, heterogeneity was moderate to very large for 25.4% of the total SNPs.

Heterogeneity was more severe in SNPs with stronger association signals. Ethnicity, average age and genotype imputation accuracy had significant effects on the heterogeneity. Exploring the effects of ethnicity can provide clues to the potential ethnic-specific effects for two loci known to affect obesity, *MC4R* and *MTCH2*. Our analysis can help to clarify understanding of the obesity mechanism and may provide guidance for an effective design of future GWA meta-analysis.

Keywords

Genome-wide association study; obesity; heterogeneity; meta-analysis; meta-regression

*Corresponding authors: Lei Zhang, Ph.D., Center for Genetic Epidemiology and Genomics, School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu 215123, P. R. China. Tel: 86-051265883871 :lzhang6@suda.edu.cn, Hong-Wen Deng, Ph.D., Professor, Center for Bioinformatics and Genomics, Chair, Department of Biostatistics and Bioinformatics, School of Public Health and Tropical Medicine, Tulane University, 1440 Canal St., Suite 2001, New Orleans, LA 70112, USA, Tel: 504-988-1310: hdeng2@tulane.edu.

Conflict of Interest Statement: No competing interests exist.

Introduction

Genome-wide association (GWA) studies are commonly used to identify genetic variants underlying complex diseases/traits (Donnelly, 2008, Hindorff *et al.*, 2009). Meta-analysis of GWA data on the same research question can integrate the information from multiple individual GWA studies (Zeggini & Ioannidis, 2009). Compared to individual GWA studies, meta-analysis increases study sample size and therefore provides an increase in statistical power. It has become a popular approach for discovering genetic variants responsible for complex diseases. A variety of GWA meta-analyses have been conducted and have identified many additional novel genetic loci underlying complex diseases/traits (Zhang *et al.*, 2014a, Pei *et al.*, 2014a, Pharoah *et al.*, 2013).

Although meta-analysis is more powerful than individual GWA studies, it suffers from heterogeneity effect which is not introduced in individual study analyses (Pei *et al.*, 2014b). In the presence of between-study heterogeneity effect, the results of meta-analysis will be misleading due to an elevated rate of false positive and/or negative findings (Pei *et al.*, 2014b). Nonetheless, the natural progression of current GWA meta-analysis tends to include a maximal number of individual studies into analysis for power consideration. As these individuals studies may stem from a variety of international research groups and ethnic populations, the heterogeneity effect has become an increasingly severe problem.

Consequently, most GWA meta-analyses being conducted to date focus only on fixed overall effect sizes and their statistical significance. SNPs whose effects were shown to be heterogeneous were usually discarded from subsequent analysis regardless of their statistical significance. In view of this, it is therefore critical to identify the source, extent and distribution of heterogeneity effects to enable proper interpretation of meta-analysis results. Detecting the source of between-study heterogeneity effects could also offer valuable insights for further clarification of gene-disease association (Ioannidis *et al.*, 2007) and may reveal interesting facts about biology, for example, the mechanism through which the variant is acting on disease risk (Zeggini & Ioannidis, 2009).

In the present study, we explored empirically the source and distribution of heterogeneity effects arising from a real GWA meta-analysis of obesity. The possible cause of heterogeneity is extensive: any difference across individual studies could potentially cause heterogeneity. Examples include different patterns of linkage disequilibrium (LD) as a result of different populations being combined, differences in the distribution, frequency or effect size of the causal alleles at a given locus (due to, for example, drift or selection, or differences in case ascertainment), and the impact of non-additive interactions with other genetic variants or environmental exposures (Begum *et al.*, 2012). Besides heterogeneity due to chance, we still have limited insight into the systematic causes of heterogeneity. Keeping these complications in mind, we restrict the factors to be investigated to the following five moderator variables: ethnicity, average age, gender composition, study type and genotype imputation accuracy. We first investigated the extent and distribution of heterogeneity in the genome-wide scale. We then studied the effects of these factors on heterogeneity by meta-regression analysis.

Methods and materials

Datasets

The datasets to be used include seven GWA samples from different research and/or clinical centers. All samples were approved for use by the respective institutional ethics review boards, and all participants provided written informed consent. Detailed descriptions of these studies can be found elsewhere (Pei *et al.*, 2014a).

Three of the seven samples were from in-house studies and four were accessed from the database of genotype and phenotype (dbGaP) (Mailman *et al.*, 2007). The three in-house samples were namely the Omaha Osteoporosis Study (OOS, n=998) (Liu *et al.*, 2008), the Kansas-City Osteoporosis Study (KCOS, n=2,283)(Pei *et al.*, 2012), and the China Osteoporosis Study (COS, n=1,624)(Pei *et al.*, 2012). The fourth sample was composed of the original and offspring generations of the Framingham Heart Study (FHS, n=4,760) (Dawber *et al.*, 1951, Feinleib *et al.*, 1975). The fifth sample was from the Indiana Fragility Study (IFS, n=1,478) (Koller *et al.*). The last two samples were from the Women's Health Initiative (WHI) observational study (The Women's Health Initiative Study Group, 1998). The sixth sample included individuals of African-American ancestry (WHI-AA, n=7,478) and the seventh sample included individuals of Hispanic ancestry (WHI-HIS, n=3,348). Individual GWA samples were genotyped by high-throughput SNP genotyping arrays (Affymetrix Inc., Santa Clara, CA, USA; or Illumina Inc., San Diego, CA, USA) following the manufacturer protocols. Basic information of the seven studies was listed in Table 1.

Quality control and genotype imputation

Pre- and post-imputation quality control steps were applied in the samples. Before imputation, the same cut-offs for genotype call rates, individual missingness and Hardy–Weinberg equilibrium (HWE) P-value were used in all seven data sets to filter out low quality SNPs and samples. Genotype imputation was performed for each GWA study using 1000G sequence variants as a reference panel (as of August 2010). Imputation was performed by comparing the respective panel with the closest ancestry, which included 283 individuals of European ancestry, 193 individuals of Asian ancestry and 174 individuals of African ancestry. Haplotypes of the individual GWA study were phased by a MArkov Chain Haplotyping algorithm (MACH)(Li *et al.*, 2009, Li *et al.*, 2010) and untyped genotypes were then imputed by a Minimac (Howie *et al.*, 2012) based on phased haplotypes. SNPs with r^2 score less than 0.3 or with minor allele frequency (MAF) less than 0.01 in any one of the samples were excluded from subsequent association analyses. Finally, a total of 4,325,550 SNPs were included in the following association tests. Detailed descriptions of quality control steps can be found elsewhere (Pei *et al.*, 2014a).

Meta-analysis

Associations between body mass index (BMI) and fat body mass (FBM) and SNPs were tested under an additive mode of inheritance in each study separately. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). FBM was measured/calculated with dual-energy X-ray absorptiometry scanners (Lunar Corp., Madison, WI, USA; or Hologic Inc., Bedford, MA, USA) following the manufacturer protocols. Raw BMI

and FBM measurements were adjusted by significant covariates. Then residual phenotypes after adjustment were normalized by inverse quantile of the standard normal distribution to impose a normal distribution on phenotypes that were analyzed subsequently. Prior to meta-analysis, the first five principle components derived from genome-wide genotype data were included as covariates to correct for potential population stratification/admixture (Price *et al.*, 2006) in the admixed WHI-AA and WHI-HIS samples. Furthermore, association statistics in each individual sample were corrected using the genomic control (GC) approach ($\lambda \sim 0.98\text{--}1.08$) (Devlin & Roeder, 1999). Summary statistics were then combined for meta-analysis using an inverse-variance weighted fixed-effects model, as implemented in the software METAL (Willer *et al.*, 2009).

Heterogeneity test

Cochran's Q statistic (Cochran, 1954) and I^2 inconsistency metric (Higgins & Thompson, 2002, Higgins *et al.*, 2003) were taken as measures of between-study heterogeneity. Cochran's Q statistic is defined as

$$Q = \sum_i w_i (\beta_i - \hat{\beta})^2,$$

where β_i is the study-specific effect size; $\hat{\beta}$ is the overall effect size estimated by the fixed-effects model and w_i the weight of each study. The Q statistic follows a χ^2 distribution with $k-1$ degrees of freedom (k is the number of studies) in the absence of heterogeneity effects. A significance level of $p < 0.1$ suggests the existence of significant heterogeneity (Cochran, 1954). The I^2 index is another widely used measure for quantifying degree of heterogeneity (Higgins & Thompson, 2002, Higgins *et al.*, 2003),

$$I^2 = \begin{cases} \frac{Q - (k-1)}{Q} \times 100\% & \text{for } Q > (k-1) \\ 0 & \text{for } Q \leq (k-1) \end{cases}.$$

It is a measure of the percentage of total variation across studies due to heterogeneity beyond chance. I^2 takes values between 0% and 100% with higher values denoting greater degree of heterogeneity ($I^2=0\text{--}25\%$: no heterogeneity; $I^2=25\text{--}50\%$: moderate heterogeneity; $I^2=50\text{--}75\%$: large heterogeneity; $I^2=75\text{--}100\%$: extreme heterogeneity) (Higgins *et al.*, 2003).

Meta-regression analyses

In this study, we focused on exploring the sources of heterogeneity for BMI among SNPs with significant association signals. SNPs of significant association for BMI ($p < 1.0 \times 10^{-5}$) and of significant heterogeneity effect ($I^2 > 25\%$) were selected for study of their heterogeneity effects. The random-effects meta-regression model (also known as the mixed-effects model) was used to explore the role of potential causes of heterogeneity for each studied SNP. For each individual study (i), we have data on effect size estimate (β_i), variance of effect size (σ_i^2), and a number of moderator variables ($x_1, x_2, \dots, x_p$). The meta-regression of the study-level effect size was specified as

$$\beta_i = \gamma_0 + \gamma_1 x_1 + \dots + \gamma_p x_p + \eta_i + \varepsilon_i,$$

where γ_0 is the grand mean; $\gamma_1, \dots, \gamma_p$ are regression coefficients for the p moderator variables; η_i is study-specific random effect with zero expectation and variance τ^2 ; ε_i is sampling error with zero expectation and variance σ_i^2 (van Houwelingen *et al.*, 2002). The DerSimonian-Laird estimator (DerSimonian & Laird, 1986) was used to estimate τ^2 , and the Omnibus test was used to test the significance of regression coefficients. For each SNP, we regressed the effect size per cohort on five moderator variables. The first four moderator variables were ethnicity, average age, percentage of female subjects and study type for each cohort. Within each study, these four moderator variables were identical for all SNPs. The last moderator variable was imputation accuracy, which was measured by r^2 score from the software Minimac (Howie *et al.*, 2012) and which varied among SNPs. The statistical analyses were implemented in the R package *metafor* (Viechtbauer, 2010).

Results

Extent and distribution of heterogeneity across the genome

We first investigated the extent of heterogeneity in the genome-wide scan. A total of 4,325,550 SNPs across the whole genome were included in the meta-analysis. For BMI, significant between-study heterogeneity (p-value for *Cochran's* Q statistic < 0.1) was detected for 475,469 (11.0%) of the total SNPs. We performed χ^2 testing to compare the expected and real number of SNPs with significant heterogeneity. Results showed that the difference was significant (p < 0.001). Inconsistency of the genetic effects across the seven studies was very large ($I^2 > 75\%$) for 2827 (0.06%) SNPs; large (I^2 between 50-75%) for 296,687 (6.86%) SNPs and moderate (I^2 between 25-50%) for 798,064 (18.45%) SNPs.

The distribution of I^2 for BMI under different association p-value intervals is shown in Table 2. Moderate or larger between-study heterogeneity effects were found to be enriched in SNPs with small association p-values. For example, the proportion of SNPs with $I^2 > 50\%$ was 6.92% among SNPs across the whole genome, while the proportion increased to 21.12% within SNPs with association p-value less than 1.0×10^{-5} .

The extent and distribution of heterogeneity for FBM was similar to those for BMI (Table 3). Significant between-study heterogeneity was detected for 10.3% of the total SNPs. Inconsistency of the genetic effects across the seven studies was very large, large and moderate for 0.05%, 6.39% and 17.75% of total SNPs, respectively. Moderate or larger between-study heterogeneity effects were also found to be enriched in SNPs with small association p-values.

Sources of heterogeneity

SNPs of significant association for BMI (p < 1.0×10^{-5}) and of significant heterogeneity effect ($I^2 > 25\%$) were further studied for their heterogeneity effects. A total of 190 SNPs qualified within these criteria. These SNPs were located in 15 distinct genomic region. We performed random-effects meta-regression analyses for the 190 identified SNPs. We first explored the

effect of each moderator variable separately. Results are listed in Table 4. The two most significant moderator variables were ethnicity and average age, which had significant influence on the heterogeneity for 66 (34.7%) and 43 (22.6%) SNPs, respectively. They were followed by imputation accuracy, which had significant influence on the heterogeneity for 29 (15.3%) SNPs. Both gender composition and study type had significant influence on the heterogeneity for only five (2.6%) SNPs. We then explored the combined effects of all five moderator variables. Results showed that they jointly accounted for significant heterogeneity of 79 SNPs (41.6% of the total) (Table 4).

The p-value of *Cochran's Q* test was less than 0.1 for 130 of the 190 SNPs mentioned above. Focusing on these 130 SNPs, we further compared the significance of *Cochran's Q* test before and after adjusting for moderator variables. As illustrated by Table 4, after adjusting for average age, gender composition, imputation accuracy, ethnicity, and study type, significant heterogeneity was removed for 51 (39.2%), 17 (13.1%), 51 (39.2%), 57 (43.8%), and 13 (10%) SNPs, respectively. After adjusting for the combined effects of all five moderator variables, significant heterogeneity was largely removed for 125 (96.2%) of the 130 SNPs.

As mentioned above, the most significant moderator variable was ethnicity, which had significant influence on the heterogeneity for 66 SNPs. The top ten of the 66 SNPs are located within two genomic loci known to affect obesity, 18q22 (*MC4R*) and 11p11 (*MTCH2*). One SNP with the highest I^2 was selected from each region. We further calculated ethnic specific effects for these two SNPs (Table 5). The allele frequencies and association significance of these SNPs varied among different ethnicities. The SNP near the *MTCH2* gene was significantly associated with BMI in Caucasian and Hispanic individuals, but not in Chinese and African-American individuals. The SNP near the *MC4R* gene was significant in all samples except for African-Americans.

Discussion

In this study, we evaluated empirically the extent and distribution of between-study heterogeneity in a meta-analysis of GWA studies. We also explored the potential causes of between-study heterogeneity. Using data from a meta-analysis of seven GWA studies on obesity, we concluded that moderate or larger heterogeneity was common in meta-analysis of GWA studies. Ethnicity, average age and genotype imputation accuracy had significant influence on between-study heterogeneity. Our results may have implications for the study design and interpretation of results in widely implemented GWA meta-analyses.

From the view of meta-analysis across the whole genome, we showed that between-study heterogeneity was common. Across the whole genome, moderate or larger heterogeneity effects were detected for more than one quarter of the tested SNPs. To confirm our results, we permuted samples and found that heterogeneity was still common under the setting of no true effects. We further simulated seven homogeneous studies and set the effect size of SNPs to vary from 0 to 1%. We found that the estimated heterogeneity remained at a low level (I^2 values for all SNPs were less than 25%). Compared to the simulation results, we consider that our observed results reflected the common existence of heterogeneity.

Considering that the heterogeneity tests were usually underpowered (Pei *et al.*, 2014b), the extent of heterogeneity in reality may be more severe than that which we observed. In particular, we noticed that significant heterogeneity effects were enriched in SNPs with small association p-values. We performed simulations to explore the relationship between heterogeneity and SNP effects. We used the real sample sizes and set the SNP effect to vary between 0 and 0.01. Results showed that the observed heterogeneity effect increased with increasing SNP effects. This observation may be partially explained by the theory that between-study heterogeneity could introduce false positive results (Pei *et al.*, 2014b). On the other hand, greater effect sizes may imply greater between-study variation for the causal SNPs, and thus a greater chance of observing heterogeneity (Li *et al.*, 2012).

Among various factors contributing to between-study heterogeneity, difference in ethnicity plays an important role in our sample. This observation may be partially due to the fact that Caucasians are the biggest group in our sample. However, considering that it is a common phenomenon that Caucasians are the biggest group in the majority of GWAS meta-analyses and that ethnic-specific association exists between genetic variants and obesity-related traits (Tan *et al.*, 2014), we believe that the difference in ethnicity plays an important role in GWAS meta-analyses. The effects of ethnicity may be explained by the following reasons: first, the tested SNP may be a marker in LD with the causal variant and the LD levels vary across different ethnicities; second, even if the tested SNP itself is the causal variant, it may have varying properties (e.g. MAF and effect size) across different ethnicities; and third, there may exist different patterns of interaction between the genetic variant and environmental exposures across different ethnicities.

Genotype imputation accuracy is another significant moderator variable contributing to heterogeneity. These results are not unexpected as the accuracy of imputation could be influenced by many factors, e.g. MAF, LD levels, reference sample size and marker density, and these influential factors may vary among different studies (Pei *et al.*, 2008).

An interesting observation from our study is that the average age of the study subjects also plays an important role in between-study heterogeneity. One potential explanation of this observation may be that the association between genetic variants and obesity-related traits is age-dependent (Zhang *et al.*, 2014b, Hakanen *et al.*, 2009).

The moderator variables we discussed here are ubiquitous in the recently published GWA meta-analysis. Genotype imputation can enhance meta-analysis of GWA data from studies using different genotyping platforms and thus it was performed in almost all the recently published GWA meta-analysis papers (Hinds *et al.*, 2013, DIABetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium *et al.* (2014). Although some communities have been aware of the difference in genetic associations between ethnic groups (Cai *et al.*, 2011, Unoki *et al.*, 2008), many recently published GWA meta-analyses involved studies from more than one ethnic group ((Hinds *et al.*, 2013, DIABetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium *et al.* (2014), Sabater-Lleal *et al.*, 2013, Torgerson *et al.*, 2011). In addition, it is often observed that individual studies have different study designs and different sample characteristics. Consequently, researchers should exercise

caution when combining samples from different ethnicities, or should recognize that heterogeneity exists even for samples from the same ethnicity.

Exploring the potential causes of heterogeneity can offer useful insights for further clarification of gene-disease associations. Re-analysis of SNPs whose effect sizes were significantly influenced by ethnicity showed that the associations observed between SNPs in or near the *MTCH2* and *MC4R* genes and obesity were more significant in Caucasian and Hispanic individuals than those observed in Chinese and African-Americans. Previous studies have reported that *MC4R* and *MTCH2* were associated with obesity in Europeans (Willer *et al.*, 2009) and Hispanics (Comuzzie *et al.*, 2012), but the association of *MTCH2* did not extend to Chinese (Zhang *et al.*, 2014b, Wang *et al.*, 2012) and the association of *MC4R* did not extend to African-Americans (Grant *et al.*, 2009). Our observation together with previous reports may provide clues to ethnic-specific effects for these genetic variants.

We acknowledge that unless many data sets are combined, there will be a larger degree of uncertainty about the amount of estimated between-study heterogeneity. We only included one meta-analysis with seven cohorts in this study, thus caution should be exercised when generalizing our conclusions to other studies. Basically, the significant moderator variables are closely related to the characteristics of the cohorts included in the meta-analysis. For example, the most significant moderator variable in this study is ethnicity, which may be partially due to the variation of cohort numbers from each ethnicity. Meta-regressions with seven points could have very influential points if one study is different from all the others. To investigate the stability of our results, we removed one study each time, and performed meta-regression on the remaining six studies. Results showed that the most significant moderator was still ethnicity, which was followed by age and genotype imputation accuracy. Additional research investigations including large numbers of studies and more moderator variables can help to further clarify the issue of between-study heterogeneity. In cases where the sources of heterogeneity are identified, we can correct for their effects through the mixed-effects (van Houwelingen *et al.*, 2002) meta-analysis, or Bayesian models (Morris, 2011), or by sub-group analysis (Bhattacharjee *et al.*, 2012).

In summary, between-study heterogeneity is common among GWA meta-analysis. Many factors, including ethnicity, average age and imputation accuracy can introduce significant between-study heterogeneity. Heterogeneity should not be ignored and should be carefully factored in the interpretation of emerging genetic association studies. We hope our analysis can help to clarify understanding of the disease mechanism and may provide guidance for an effective design of future GWA meta-analysis, for example, by eliminating or adjusting (using random-effects meta-regression analyses) the design factors which can influence the effect size estimation.

Acknowledgements

The authors are grateful to the two anonymous expert reviewers for their constructive comments and suggestions. The authors are also grateful to Dr. Yong Lin and Dr. Shu Ran for their support of the computing service for this study, and Dr. Jian Li for his assistance in obtaining the samples through dbGap.

This work was supported by grants from the National Natural Science Foundation of China (31501026 and 31571291); the Natural Science Foundation of Jiangsu Province (BK20150323); the Scientific Research Foundation

for the Returned Overseas Chinese Scholars, State Education Ministry; startup Fund from Soochow University (Q413900114); and grants from the National Institutes of Health (P50AR055081, R01AG026564, R01AR050496, R01AR057049 and R03TW008221).

The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195). This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University or NHLBI. Funding for SHARe Affymetrix genotyping was provided by NHLBI Contract N02-HL-64278. The datasets used for the analyses described in this manuscript were obtained from dbGaP at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap> through dbGaP accession phs000007.v14.p6. Funding support for the Genetic Determinants of Bone Fragility was provided through the NIA Division of Geriatrics and Clinical Gerontology. Genetic Determinants of Bone Fragility is a genome-wide association study funded as part of the NIA Division of Geriatrics and Clinical Gerontology. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the NIA Division of Geriatrics and Clinical Gerontology and the NIA Division of Aging Biology. Support for the collection of data sets and samples was provided by the parent grant, Genetic Determinants of Bone Fragility (P01-AG018397). Funding support for the genotyping which was performed at the Johns Hopkins University Center for Inherited Diseases Research was provided by the NIH NIA. The datasets used for the analyses described in this manuscript were obtained from dbGaP at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap> through dbGaP accession phs000138.v2.p1. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32 and 44221. This manuscript was not prepared in collaboration with investigators of the WHI, has not been reviewed and/or approved by the Women's Health Initiative (WHI) and does not necessarily reflect the opinions of the WHI investigators or the NHLBI. WHI PAGE is funded through the NHGRI Population Architecture Using Genomics and Epidemiology (PAGE) network (Grant Number U01 HG004790). Assistance with phenotype harmonization, SNP selection, data cleaning, meta-analyses, data management and dissemination, and general study coordination, was provided by the PAGE Coordinating Center (U01HG004801-01). The data sets used for the analyses described in this manuscript were obtained from dbGaP at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap> through dbGaP accession phs000200.v6.p2.

References

- Begum F, Ghosh D, Tseng GC, Feingold E. Comprehensive literature review and statistical considerations for GWAS meta-analysis. *Nucleic Acids Res.* 2012; 40:3777–84. [PubMed: 22241776]
- Bhattacharjee S, Rajaraman P, Jacobs KB, Wheeler WA, Melin BS, Hartge P, Yeager M, Chung CC, Chanock SJ, Chatterjee N. A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. *Am J Hum Genet.* 2012; 90:821–35. [PubMed: 22560090]
- Cai Y, Yi J, Ma Y, Fu D. Meta-analysis of the effect of HHEX gene polymorphism on the risk of type 2 diabetes. *Mutagenesis.* 2011; 26:309–14. [PubMed: 21059810]
- Cochran W. The combination of estimates from different experiments. *Biometrics.* 1954; 10:101–129.
- Comuzzie AG, Cole SA, Laston SL, Voruganti VS, Haack K, Gibbs RA, Butte NF. Novel genetic loci identified for the pathophysiology of childhood obesity in the Hispanic population. *PLoS One.* 2012; 7:e51954. [PubMed: 23251661]
- Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health.* 1951; 41:279–81. [PubMed: 14819398]
- Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7:177–88. [PubMed: 3802833]
- Devlin B, Roeder K. Genomic control for association studies. *Biometrics.* 1999; 55:997–1004. [PubMed: 11315092]
- DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; Mexican American Type 2 Diabetes (MAT2D) Consortium; Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in multi-Ethnic Samples (T2D-GENES) Consortium. Mahajan A, Go MJ, Zhang W, Below JE, Gaulton KJ, Ferreira T, Horikoshi M, Johnson AD, Ng MC, Prokopenko I, Saleheen D, Wang X, Zeggini E, Abecasis GR, Adair LS, Almgren P, Atalay M, Aung T, Baldassarre D, Balkau B, Bao Y, Barnett AH, Barroso I, Basit A, Been LF, Beilby J, Bell GI, Benediktsson R, Bergman RN, Boehm BO, Boerwinkle E, Bonnycastle

- LL, Burtt N, Cai Q, Campbell H, Carey J, Cauchi S, Caulfield M, Chan JC, Chang LC, Chang TJ, Chang YC, Charpentier G, Chen CH, Chen H, Chen YT, Chia KS, Chidambaram M, Chines PS, Cho NH, Cho YM, Chuang LM, Collins FS, Cornelis MC, Couper DJ, Crenshaw AT, van Dam RM, Danesh J, Das D, de Faire U, Dedoussis G, Deloukas P, Dimas AS, Dina C, Doney AS, Donnelly PJ, Dorkhan M, van Duijn C, Dupuis J, Edkins S, Elliott P, Emilsson V, Erbel R, Eriksson JG, Escobedo J, Esko T, Eury E, Florez JC, Fontanillas P, Forouhi NG, Forsen T, Fox C, Fraser RM, Frayling TM, Froguel P, Frossard P, Gao Y, Gertow K, Gieger C, Gigante B, Grallert H, Grant GB, Grrop LC, Groves CJ, Grundberg E, Guiducci C, Hamsten A, Han BG, Hara K, Hassani N, Hattersley AT, Hayward C, Hedman AK, Herder C, Hofman A, Holmen OL, Hovingh K, Hreidarsson AB, Hu C, Hu FB, Hui J, Humphries SE, Hunt SE, Hunter DJ, Hveem K, Hydrie ZI, Ikegami H, Illig T, Ingelsson E, Islam M, Isomaa B, Jackson AU, Jafar T, James A, Jia W, Jöckel KH, Jonsson A, Jowett JB, Kadowaki T, Kang HM, Kanoni S, Kao WH, Kathiresan S, Kato N, Katulanda P, Keinänen-Kiukaanniemi KM, Kelly AM, Khan H, Khaw KT, Khor CC, Kim HL, Kim S, Kim YJ, Kinnunen L, Klopp N, Kong A, Korpi-Hyövälti E, Kowlessur S, Kraft P, Kravic J, Kristensen MM, Krithika S, Kumar A, Kumate J, Kuusisto J, Kwak SH, Laakso M, Lagou V, Lakka TA, Langenberg C, Langford C, Lawrence R, Leander K, Lee JM, Lee NR, Li M, Li X, Li Y, Liang J, Liju S, Lim WY, Lind L, Lindgren CM, Lindholm E, Liu CT, Liu JJ, Lobbens S, Long J, Loos RJ, Lu W, Luan J, Lyssenko V, Ma RC, Maeda S, Mägi R, Männistö S, Matthews DR, Meigs JB, Melander O, Metspalu A, Meyer J, Mirza G, Mihailov E, Moebus S, Mohan V, Mohlke KL, Morris AD, Mühleisen TW, Müller-Nurasyid M, Musk B, Nakamura J, Nakashima E, Navarro P, Ng PK, Nica AC, Nilsson PM, Njølstad I, Nöthen MM, Ohnaka K, Ong TH, Owen ER, Palmer CN, Pankow JS, Park KS, Parkin M, Pechlivanis S, Pedersen NL, Peltonen L, Perry JR, Peters A, Pinidiyapathirage JM, Platou CG, Potter S, Price JF, Qi L, Radha V, Rallidis L, Rasheed A, Rathman W, Rauramaa R, Raychaudhuri S, Rayner NW, Rees SD, Rehnberg E, Ripatti S, Robertson N, Roden M, Rossin EJ, Rudan I, Rybin D, Saaristo TE, Salomaa V, Saltevo J, Samuel M, Sanghera DK, Saramies J, Scott J, Scott LJ, Scott RA, Segrè AV, Sehmi J, Sennblad B, Shah N, Shah S, Shera AS, Shu XO, Shuldiner AR, Sigursson G, Sijbrands E, Silveira A, Sim X, Sivapalaratnam S, Small KS, So WY, Stanáková A, Stefansson K, Steinbach G, Steinthorsdottir V, Stirrups K, Strawbridge RJ, Stringham HM, Sun Q, Suo C, Syvänen AC, Takayanagi R, Takeuchi F, Tay WT, Teslovich TM, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tikkanen E, Trakalo J, Tremoli E, Trip MD, Tsai FJ, Tuomi T, Tuomilehto J, Uitterlinden AG, Valladares-Salgado A, Vedantam S, Veglia F, Voight BF, Wang C, Wareham NJ, Wrennauer R, Wickremasinghe AR, Wilsgaard T, Wilson JF, Wiltshire S, Winckler W, Wong TY, Wood AR, Wu JY, Wu Y, Yamamoto K, Yamauchi T, Yang M, Yengo L, Yokota M, Young R, Zabaneh D, Zhang F, Zhang R, Zheng W, Zimmet PZ, Altshuler D, Bowden DW, Cho YS, Cox NJ, Cruz M, Hanis CL, Kooner J, Lee JY, Seielstad M, Teo YY, Boehnke M, Parra EJ, Chambers JC, Tai ES, McCarthy MI, Morris AP. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet.* 2014; 46:234–44. [PubMed: 24509480]
- Donnelly P. Progress and challenges in genome-wide association studies in humans. *Nature.* 2008; 456:728–31. [PubMed: 19079049]
- Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med.* 1975; 4:518–25. [PubMed: 1208363]
- Grant SF, Bradfield JP, Zhang H, Wang K, Kim CE, Annaiah K, Santa E, Glessner JT, Thomas K, Garriss M, Frackelton EC, Otieno FG, Shaner JL, Smith RM, Imielinski M, Chiavacci RM, Li M, Berkowitz RI, Hakonarson H. Investigation of the locus near MC4R with childhood obesity in Americans of European and African ancestry. *Obesity (Silver Spring).* 2009; 17:1461–5. [PubMed: 19265794]
- Hakanen M, Raitakari OT, Lehtimäki T, Peltonen N, Pakkala K, Sillanmäki L, Lagstrom H, Viikari J, Simell O, Ronnema T. FTO genotype is associated with body mass index after the age of seven years but not with energy intake or leisure-time physical activity. *J Clin Endocrinol Metab.* 2009; 94:1281–7. [PubMed: 19158205]
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002; 21:1539–58. [PubMed: 12111919]
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327:557–60. [PubMed: 12958120]

- Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, Manolio TA. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci U S A*. 2009; 106:9362–7. [PubMed: 19474294]
- Hinds DA, McMahon G, Kiefer AK, Do CB, Eriksson N, Evans DM, St Pourcain B, Ring SM, Mountain JL, Francke U, Davey-Smith G, Timpson NJ, Tung JY. A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci. *Nat Genet*. 2013; 45:907–11. [PubMed: 23817569]
- Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet*. 2012; 44:955–9. [PubMed: 22820512]
- Ioannidis JP, Patsopoulos NA, Evangelou E. Heterogeneity in meta-analyses of genome-wide association investigations. *PLoS One*. 2007; 2:e841. [PubMed: 17786212]
- Koller DL, Ichikawa S, Lai D, Padgett LR, Doheny KF, Pugh E, Paschall J, Hui SL, Edenberg HJ, Xuei X, Peacock M, Econs MJ, Foroud T. Genome-wide association study of bone mineral density in premenopausal European-American women and replication in African-American women. *J Clin Endocrinol Metab*. 2010; 95:1802–9. [PubMed: 20164292]
- Li J, Guo YF, Pei Y, Deng HW. The impact of imputation on meta-analysis of genome-wide association studies. *PLoS One*. 2012; 7:e34486. [PubMed: 22496814]
- Li Y, Willer C, Sanna S, Abecasis G. Genotype imputation. *Annu Rev Genomics Hum Genet*. 2009; 10:387–406. [PubMed: 19715440]
- Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. 2010; 34:816–34. [PubMed: 21058334]
- Liu YJ, Liu XG, Wang L, Dina C, Yan H, Liu JF, Levy S, Papasian CJ, Drees BM, Hamilton JJ, Meyre D, Delplanque J, Pei YF, Zhang L, Recker RR, Froguel P, Deng HW. Genome-wide association scans identified CTNNB1 as a novel gene for obesity. *Hum Mol Genet*. 2008; 17:1803–13. [PubMed: 18325910]
- Mailman MD, Feolo M, Jin Y, Kimura M, Tryka K, Bagoutdinov R, Hao L, Kiang A, Paschall J, Phan L, Popova N, Pretel S, Ziyabari L, Lee M, Shao Y, Wang ZY, Sirotkin K, Ward M, Kholodov M, Zbicz K, Beck J, Kimelman M, Shevelev S, Preuss D, Yaschenko E, Graeff A, Ostell J, Sherry ST. The NCBI dbGaP database of genotypes and phenotypes. *Nat Genet*. 2007; 39:1181–6. [PubMed: 17898773]
- Morris AP. Transethnic meta-analysis of genomewide association studies. *Genet Epidemiol*. 2011; 35:809–22. [PubMed: 22125221]
- Pei YF, Li J, Zhang L, Papasian CJ, Deng HW. Analyses and comparison of accuracy of different genotype imputation methods. *PLoS One*. 2008; 3:e3551. [PubMed: 18958166]
- Pei YF, Zhang L, Liu Y, Li J, Shen H, Liu YZ, Tian Q, He H, Wu S, Ran S, Han Y, Hai R, Lin Y, Zhu J, Zhu XZ, Papasian CJ, Deng HW. Meta-analysis of genome-wide association data identifies novel susceptibility loci for obesity. *Hum Mol Genet*. 2014a; 23:820–30. [PubMed: 24064335]
- Pei YF, Zhang L, Papasian CJ, Wang YP, Deng HW. On individual genome-wide association studies and their meta-analysis. *Hum Genet*. 2014b; 133:265–79. [PubMed: 24114349]
- Pei YF, Zhang L, Yang TL, Han Y, Hai R, Ran S, Tian Q, Shen H, Li J, Zhu XZ, Luo X, Deng HW. Genome-wide association study of copy number variants suggests LTBP1 and FGD4 are important for alcohol drinking. *PLoS One*. 2012; 7:e30860. [PubMed: 22295116]
- Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, Buckley M, Fridley BL, Tyrer JP, Shen H, Weber R, Karevan R, Larson MC, Song H, Tessier DC, Bacot F, Vincent D, Cunningham JM, Dennis J, Dicks E, Aben KK, Anton-Culver H, Antonenkova N, Armasu SM, Baglietto L, Bandera EV, Beckmann MW, Birrer MJ, Bloom G, Bogdanova N, Brenton JD, Brinton LA, Brooks-Wilson A, Brown R, Butzow R, Campbell I, Carney ME, Carvalho RS, Chang-Claude J, Chen YA, Chen Z, Chow WH, Cicek MS, Coetzee G, Cook LS, Cramer DW, Cybulski C, Dansonka-Mieszkowska A, Despiere E, Doherty JA, Dork T, Du Bois A, Durst M, Eccles D, Edwards R, Ekici AB, Fasching PA, Fenstermacher D, Flanagan J, Gao YT, Garcia-Closas M, Gentry-Maharaj A, Giles G, Gjyshi A, Gore M, Gronwald J, Guo Q, Halle MK, Harter P, Hein A, Heitz F, Hillemanns P, Hoatlin M, Hogdall E, Hogdall CK, Hosono S, Jakubowska A, Jensen A, Kalli KR, Karlan BY, Kelemen LE, Kiemeny LA, Kjaer SK, Konecny GE, Krakstad C, Kupryjanczyk J, Lambrechts D, Lambrechts S, Le ND, Lee N, Lee J, Leminen A, Lim BK,

Lissowska J, Lubinski J, Lundvall L, Lurie G, Massuger LF, Matsuo K, McGuire V, McLaughlin JR, Menon U, Modugno F, Moysich KB, Nakanishi T, Narod SA, Ness RB, Nevanlinna H, Nickels S, Noushmehr H, Odunsi K, Olson S, Orlov I, Paul J, Pejovic T, Peltari LM, Permut-Wey J, Pike MC, Poole EM, Qu X, Risch HA, Rodriguez-Rodriguez L, Rossing MA, Rudolph A, Runnebaum I, Rzepecka IK, Salvesen HB, Schwaab I, Severi G, Shen H, Shridhar V, Shu XO, Sieh W, Southey MC, Spellman P, Tajima K, Teo SH, Terry KL, Thompson PJ, Timorek A, Tworoger SS, van Altena AM, van den Berg D, Vergote I, Vierkant RA, Vitonis AF, Wang-Gohrke S, Wentzensen N, Whittemore AS, Wik E, Winterhoff B, Woo YL, Wu AH, Yang HP, Zheng W, Ziogas A, Zulkifli F, Goodman MT, Hall P, Easton DF, Pearce CL, Berchuck A, Chenevix-Trench G, Iversen E, Monteiro AN, Gayther SA, Schildkraut JM, Sellers TA. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. *Nat Genet.* 2013; 45:362–70. 370, e1–2. [PubMed: 23535730]

Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet.* 2006; 38:904–9. [PubMed: 16862161]

Sabater-Lleal M, Huang J, Chasman D, Naitza S, Dehghan A, Johnson AD, Teumer A, Reiner AP, Folkersen L, Basu S, Rudnicka AR, Trompet S, Malarstig A, Baumert J, Bis JC, Guo X, Hottenga JJ, Shin SY, Lopez LM, Lahti J, Tanaka T, Yanek LR, Oudot-Mellakh T, Wilson JF, Navarro P, Huffman JE, Zemunik T, Redline S, Mehra R, Pulanic D, Rudan I, Wright AF, Kolcic I, Polasek O, Wild SH, Campbell H, Curb JD, Wallace R, Liu S, Eaton CB, Becker DM, Becker LC, Bandinelli S, Raikonen K, Widen E, Palotie A, Fornage M, Green D, Gross M, Davies G, Harris SE, Liewald DC, Starr JM, Williams FM, Grant PJ, Spector TD, Strawbridge RJ, Silveira A, Sennblad B, Rivadeneira F, Uitterlinden AG, Franco OH, Hofman A, Van Dongen, Willemsen G, Boomsma DI, Yao J, Swords Jenny N, Haritunians T, Mcknight B, Lumley T, Taylor KD, Rotter JJ, Psaty BM, Peters A, Gieger C, Illig T, Grotevendt A, Homuth G, Volzke H, Kocher T, Goel A, Franzosi MG, Seedorf U, Clarke R, Steri M, Tarasov KV, Sanna S, Schlessinger D, Stott DJ, Sattar N, Buckley BM, Rumley A, Lowe GD, Mcardle WL, Chen MH, Tofler GH, Song J, Boerwinkle E, Folsom AR, Rose LM, Franco-Cereceda A, Teichert M, Ikram MA, Mosley TH, Bevan S, Dichgans M, Rothwell PM, Sudlow CL, Hopewell JC, Chambers JC, Saleheen D, Kooner JS, Danesh J, Nelson CP, Erdmann J, Reilly MP, Kathiresan S, Schunkert H, Morange PE, Ferrucci L, Eriksson JG, Jacobs D, Deary IJ, Soranzo N, Witteman JC, de Geus EJ, Tracy RP, Hayward C, Koenig W, Cucca F, Jukema JW, Eriksson P, Seshadri S, Markus HS, Watkins H, Samani NJ, VTE Consortium; STROKE Consortium; Wellcome Trust Case Control Consortium 2 (WTCCC2); C4D Consortium; CARDIoGRAM Consortium. Wallaschofski H, Smith NL, Tregouet D, Ridker PM, Tang W, Strachan DP, Hamsten A, O'Donnell CJ. Multiethnic meta-analysis of genome-wide association studies in >100 000 subjects identifies 23 fibrinogen-associated loci but no strong evidence of a causal association between circulating fibrinogen and cardiovascular disease. *Circulation.* 2013; 128:1310–24. [PubMed: 23969696]

Tan LJ, Zhu H, He H, Wu KH, Li J, Chen XD, Zhang JG, Shen H, Tian Q, Krousel-Wood M, Papasian CJ, Bouchard C, Perusse L, Deng HW. Replication of 6 obesity genes in a meta-analysis of genome-wide association studies from diverse ancestries. *PLoS One.* 2014; 9:e96149. [PubMed: 24879436]

The Women's Health Initiative Study Group, W. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials.* 1998; 19:61–109. [PubMed: 9492970]

Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, Himes BE, Levin AM, Mathias RA, Hancock DB, Baurley JW, Eng C, Stern DA, Celedon JC, Rafaels N, Capurso D, Conti DV, Roth LA, Soto-Quiros M, Toggias A, Li X, Myers RA, Romieu I, Van Den Berg DJ, Hu D, Hansel NN, Hernandez RD, Israel E, Salam MT, Galanter J, Avila PC, Avila L, Rodriguez-Santana JR, Chapela R, Rodriguez-Cintron W, Diette GB, Adkinson NF, Abel RA, Ross KD, Shi M, Faruque MU, Dunston GM, Watson HR, Mantese VJ, Ezurum SC, Liang L, Ruczinski I, Ford JG, Huntsman S, Chung KF, Vora H, Li X, Calhoun WJ, Castro M, Sienra-Monge JJ, Del Rio-Navarro B, Deichmann KA, Heinzmann A, Wenzel SE, Busse WW, Gern JE, Lemanske RF Jr, Beaty TH, Bleecker ER, Raby BA, Meyers DA, London SJ, Gilliland FD, Burchard EG, Martinez FD, Weiss ST, Williams LK, Barnes KC, Ober C, Nicolae DL. Meta-analysis of genome-wide

- association studies of asthma in ethnically diverse North American populations. *Nat Genet.* 2011; 43:887–92. [PubMed: 21804549]
- Unoki H, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, Ng DP, Holmkvist J, Borch-Johnsen K, Jorgensen T, Sandbaek A, Lauritzen T, Hansen T, Nurbaya S, Tsunoda T, Kubo M, Babazono T, Hirose H, Hayashi M, Iwamoto Y, Kashiwagi A, Kaku K, Kawamori R, Tai ES, Pedersen O, Kamatani N, Kadowaki T, Kikkawa R, Nakamura Y, Maeda S. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet.* 2008; 40:1098–102. [PubMed: 18711366]
- Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med.* 2002; 21:589–624. [PubMed: 11836738]
- Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw.* 2010; 36
- Wang J, Mei H, Chen W, Jiang Y, Sun W, Li F, Fu Q, Jiang F. Study of eight GWAS-identified common variants for association with obesity-related indices in Chinese children at puberty. *Int J Obes (Lond).* 2012; 36:542–7. [PubMed: 22083549]
- Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, Mccarroll SA, Papadakis K, Qi L, Randall JC, Roccascaccia RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P, Kuokkanen M, Kuusisto J, Laitinen J, Lakatta EG, Luan J, Luben RN, Mangino M, Mcardle WL, Meitinger T, Mulas A, Munroe PB, Narisu N, Ness AR, Northstone K, O'rahilly S, Purmann C, Rees MG, Ridderstrale M, Ring SM, Rivadeneira F, Ruukonen A, Sandhu MS, Saramies J, Scott LJ, Scuteri A, Silander K, Sims MA, Song K, Stephens J, Stevens S, Stringham HM, Tung YC, Valle TT, Van Duijn CM, Vimalaswaran KS, Vollenweider P, Waeber G, Wallace C, Watanabe RM, Waterworth DM, Watkins N, Wellcome Trust Case Control Consortium, Witteman JC, Zeggini E, Zhai G, Zillikens MC, Altshuler D, Caulfield MJ, Chanock SJ, Farooqi IS, Ferrucci L, Guralnik JM, Hattersley AT, Hu FB, Jarvelin MR, Laakso M, Mooser V, Ong KK, Ouwehand WH, Salomaa V, Samani NJ, Spector TD, Tuomi T, Tuomilehto J, Uda M, Uitterlinden AG, Wareham NJ, Deloukas P, Frayling TM, Groop LC, Hayes RB, Hunter DJ, Mohlke KL, Peltonen L, Schlessinger D, Strachan DP, Wichmann HE, McCarthy MI, Boehnke M, Barroso I, Abecasis GR, Hirschhorn JN, Genetic Investigation of ANthropometric Traits Consortium. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet.* 2009; 41:25–34. [PubMed: 19079261]
- Zeggini E, Ioannidis JP. Meta-analysis in genome-wide association studies. *Pharmacogenomics.* 2009; 10:191–201. [PubMed: 19207020]
- Zhang L, Choi HJ, Estrada K, Leo PJ, Li J, Pei YF, Zhang Y, Lin Y, Shen H, Liu YZ, Liu Y, Zhao Y, Zhang JG, Tian Q, Wang YP, Han Y, Ran S, Hai R, Zhu XZ, Wu S, Yan H, Liu X, Yang TL, Guo Y, Zhang F, Guo YF, Chen Y, Chen X, Tan L, Zhang L, Deng FY, Deng H, Rivadeneira F, Duncan EL, Lee JY, Han BG, Cho NH, Nicholson GC, McCloskey E, Eastell R, Prince RL, Eisman JA, Jones G, Reid IR, Sambrook PN, Dennison EM, Danoy P, Yerges-Armstrong LM, Streeten EA, Hu T, Xiang S, Papasian CJ, Brown MA, Shin CS, Uitterlinden AG, Deng HW. Multistage genome-wide association meta-analyses identified two new loci for bone mineral density. *Hum Mol Genet.* 2014a; 23:1923–33. [PubMed: 24249740]
- Zhang M, Zhao X, Cheng H, Wang L, Xi B, Shen Y, Hou D, Mi J. Age- and sex-dependent association between FTO rs9939609 and obesity-related traits in Chinese children and adolescents. *PLoS One.* 2014b; 9:e97545. [PubMed: 24827155]

Table 1

Basic information for the seven GWA studies.

Sample	Sample Size	Ethnicity	Female (%)	Age(yrs)	Study design	Genotyping platform
OOS	998	Caucasian	49.9	50.3(18.3)	Population-based	Affymetrix 500K
KCOS	2,283	Caucasian	75.5	51.4(13.8)	Population-based	Affymetrix 6.0
COS	1,624	Han Chinese	50.7	34.8(13.4)	Population-based	Affymetrix 6.0
FHS	4,760	Caucasian	54.7	60.3(10.7)	Family-based	Affymetrix 550K
IFS	1,478	Caucasian	100	32.7(7.2)	Family-based	Illumina Human610
WHI-AA	7,478	African American	100	60.9(6.9)	Population-based	Affymetrix 6.0
WHI-HIS	3,348	Hispanic	100	60.7(7.2)	Population-based	Affymetrix 6.0

Note: Age is presented as means (standard deviation).

Table 2

Distribution of between-study heterogeneity measures for BMI.

Heterogeneity measure	Association p-value intervals(-log(p))						total
	0~1	1~2	2~3	3~4	4~5	>5	
$I^2 > 75\%$	0.07	0.05	0.03	0.02	0.15	0.43	0.06
$50\% < I^2 < 75\%$	6.85	6.91	7.23	6.23	8.96	20.69	6.86
$25\% < I^2 < 50\%$	18.47	18.03	19.86	22.17	31.54	20.26	18.45
$I^2 < 25\%$	74.61	75.00	72.88	71.58	59.49	58.60	74.62
$p(Q) \leq 0.1$	11.00	10.80	11.40	10.70	16.90	28.30	11.00

Note: The results are presented as the percentage of SNPs (percentage) under each association p-value interval.

Table 3

Distribution of between-study heterogeneity measures for FBM.

Heterogeneity measure	Association p-value intervals(-log(p))						Total
	0~1	1~2	2~3	3~4	4~5	>5	
$I^2 > 75\%$	0.05	0.04	0.02	0.04	0.00	0.00	0.05
$50\% < I^2 < 75\%$	6.38	6.52	6.34	6.06	12.32	10.94	6.39
$25\% < I^2 < 50\%$	17.79	17.48	17.64	15.48	14.79	41.41	17.75
$I^2 < 25\%$	75.78	75.95	76	78.42	72.89	47.66	75.8
$p(Q) \leq 0.1$	10.30	10.41	9.50	9.50	15.70	21.90	10.30

Note: The results are presented as the percentage of SNPs (percentage) under each association p-value interval.

Table 4

Results for meta-regression analysis.

Moderator variable	Significant SNPs (%)	Significant heterogeneity removed (%)
Ethnicity	66 (34.7%)	57 (43.8%)
Average Age	43 (22.6%)	51 (39.2%)
Gender composition	5 (2.6%)	17 (13.1%)
Genotype imputation	29 (15.3%)	51 (39.2%)
Study type	5 (2.6%)	13 (10.0%)
All five variables	79 (41.6%)	125 (96.2%)

Note: The results are presented as number of SNPs (percentage). The total number of SNPs used for meta-regression analysis was 190. 130 of the 190 SNPs were used in comparing the significance of heterogeneity before and after adjusting for moderator variables.

Table 5

Ethnic-specific characteristics and association results for the selected SNPs.

SNP	Gene	Frequencies of the effect allele				Ethnic-specific association p-values			
		Caucasian	Chinese	African-American	Hispanic	Caucasian	Chinese	African-American	Hispanic
<i>rs7228430</i>	<i>MC4R</i>	0.74	0.81	0.52	0.8	1.05×10^{-5}	0.03	0.91	1.44×10^{-4}
<i>rs7107356</i>	<i>MTCH2</i>	0.51	0.34	0.43	0.38	6.21×10^{-4}	0.11	0.45	1.63×10^{-4}

Note: These SNPs rank in the top ten of SNPs whose effect sizes were significantly influenced by ethnicity.