Body composition (fat, skeletal muscle and bone mass) is an important determinant of overall health and risk of endocrine disorders such as type 2 diabetes and osteoporosis. Although diet and physical activity are strongly implicated, body composition is also heritable. We conducted a discovery genome-wide association study on 31 phenotypes from the three-compartment body composition model (fat, lean and bone mass) in a set of 4,386 individuals (n = 2,109 males, n = 2,294 females) from the UK Biobank pilot imaging enhancement program that underwent a dual energy X-ray absorptiometry (DXA) scan for assessment of body composition and genetic screening. From 6,137,607 imputed single nucleotide polymorphisms (SNPs) we identified 17 body composition loci (P < 5.0 x 10^{-8}). GWAS from the combined dataset identified four statistically significant SNPs (rs7592270, rs145972737, rs13212044, rs77772562). In sex-stratified GWAS, 10 male specific SNPs across all traits were identified and five female specific SNPs. Of the 17 SNPs, six were in or close to a gene where there was a plausible functional connection. Three SNPs (rs7592270, rs77772562 and rs7752312) were correlated with obesity phenotypes, one SNP (rs2236705) with lean phenotypes and two with bone mass phenotypes (rs112098641 and rs113380185). These results highlight candidate genes and biological pathways related to body composition, including glucose metabolism and estrogen regulation, that are of interest to replicate in future studies.

**Keywords:** dual energy X-ray absorptiometry, genome-wide association study, loci, bone mass, fat mass, lean mass, body composition, genetics
INTRODUCTION

Body composition is implicated in the progression of many chronic diseases, including endocrine disorders such as type 2 diabetes (T2D) (1). The heritability of body composition is high, with total and regional distribution of fat, lean and bone mass governed by genetic susceptibility (2). The increasing availability of genetic data from large population-based cohorts provides an opportunity for Genome-Wide-Association Studies (GWAS) to identify causal Single Nucleotide Polymorphisms (SNPs) with multiple body composition phenotypes.

Most body composition GWAS research has focused on the genetics of body mass index (BMI) (2), waist and hip circumference (3) or singular compartments of body composition, such as lean or fat mass (4, 5). While previous GWAS have investigated the role of bone content of specific regions (6), few have investigated the genetics of total and regional bone mass. These studies have advanced understanding of the role and potential mechanisms of common genetic variations in BMI and body fat distribution, including sexual dimorphisms in the genetic regulation of these traits. Specifically, pathway analyses suggest that adipose tissue deposition and BMI are closely linked with insulin regulation and lipid biology, and thus share pathways with T2D and glycemic traits (2, 3). These phenotypes have also been linked with skeletal growth processes (3), yet the common genetic variations in fat, lean and bone phenotypes remain unclear as they have not been investigated simultaneously. To our knowledge, no GWAS have investigated the genetics of all three body composition compartments simultaneously. Understanding the genetics of the three-compartment model of body composition will provide new insights into the shared heritability of and inter-connection between fat, lean and bone traits. Moreover, the majority of research has derived estimates of fat and lean mass from bio-electrical impedance analysis, which has inflexible hydration assumptions and is unable to assess bone mass (7). While dual energy X-ray absorptiometry (DXA) is the gold standard for assessing the three-compartment model of body composition, the high cost and exposure to radiation has largely precluded application in a large population cohort (8).

The availability of gold standard DXA data on 5170 participants from the UK Biobank (UKB) pilot imaging enhancement program provided an opportunity to perform a discovery GWAS on the genetic determinants of fat, lean and bone body composition. Sex-stratified analyses were performed to identify SNPs that differed between males and females.

RESULTS

A total of 4386 participants (n=2109 male, n=2294 female) were included (Figure S1). Mean age at recruitment was 55.9 (SD 7.5). Mean (SD) of obesity-, lean-, and bone-related body composition phenotypes, as well as body composition ratios, are presented in Table 1. The genomic inflation factors for the combined and sex-stratified GWAS are presented in Table S1. For the combined dataset, genomic inflation factors ranged between 1.010 (SE 2.12 X 10^-6) to 1.046 (SE 4.52 X 10^-6)
six SNPs were in or close to a gene where there was a plausible functional connection (rs7592270, rs77772562, rs7552312, rs2236705, rs112098641 and rs113380185; Figure 1, Table 1, Figures S3 and S4). Three SNPs were associated with obesity phenotypes in the combined dataset. SNP rs7592270 was correlated with female android fat mass, android total mass, trunk total mass, VAT mass and VAT volume, SNP rs7552312 was correlated with trunk total fat ratio and SNP rs77772562 was correlated with the trunk peripheral ratio. One SNP rs2236705 was correlated with lean phenotypes and two SNPs (rs112098641 and rs113380185) were correlated with bone phenotypes. In sex-stratified datasets, SNP rs2236705 was correlated with female lean mass, SNP rs112098641 was associated with female gynoid bone mass and SNP rs113380185 was correlated with male android bone mass (Table 1, Figures S3 and S4).

**DISCUSSION**

The aim of this discovery GWAS was to provide preliminary evidence for the role of genetics in the three-compartment model of body composition. From the 6,137,607 imputed SNPs and 31 body composition phenotypes investigated, our main findings were that 17 SNPs were significantly associated with either fat, lean or bone phenotypes. Of these, six SNPs were linked to genes with known functional outcomes and thus help to explain the physiological mechanisms leading to body composition. These preliminary findings support the need for clinicians to consider the interaction between fat, lean and bone mass and provide new insights into biological pathways, including glucose metabolism and estrogen regulation, that will inform future research aimed at understanding the complex biology of body composition.

We identified three SNPs related to obesity that have been previously reported to be associated with risk of T2D (12, 13). Thus, these SNPs may exert their effects at increasing T2D risk by modifying body composition (specifically fat) and by altering glucose and insulin pathways (3). More specifically, SNP rs7592270 was associated with female android fat mass, android total mass, trunk total mass, VAT mass and volume, all of which are indicators of harmful accumulation of central regional body fat often associated with increased risk of T2D (12). SNP rs7592270 is found in the noncoding gene LINC01122, which is correlated with anthropometric extremes and is near SNPs correlated to obesity class I (rs929641) and being overweight (rs887912) (14). SNPs rs7592270, rs929641 and rs887912 were in or very close to LINC01122. This SNP is found in the antisense noncoding gene ZMIZ1-ASI, sharing a bidirectional promoter with ZMIZ1. ZMIZ1, a transcription factor regulator, is involved in glucose regulation and diabetes (15). SNP rs7552312 was correlated with male trunk fat mass and glucose metabolism, while excess fat mass distribution within the central region may increase fat infiltration within the muscle and risk of insulin resistance (16), further supporting that these obesogenic SNPs are also linked to T2D risk.

**TABLE 1** | Mean (SD) of body composition phenotypes in combined, female and male datasets.

| Body composition phenotype | Combined (n=4386) | Female (n=2294) | Male (n=2092) |
|----------------------------|------------------|----------------|--------------|
| Obesity-related            |                  |                |              |
| Android fat mass (g)       | 2.456 (1229)     | 2.213 (1151)   | 2.715 (1257) |
| Gynoid fat mass (g)        | 4.166 (1544)     | 4.086 (1544)   | 3.986 (1327) |
| Arms fat mass (g)          | 2.664 (976)      | 2.926 (1045)   | 2.377 (802)  |
| Legs fat mass (g)          | 7.744 (3084)     | 9.088 (3081)   | 6.278 (2318) |
| Trunk fat mass (g)         | 14.677 (6182)    | 14.001 (6033)  | 15.386 (6260) |
| VAT mass (g)               | 1.225 (912)      | 781 (580)      | 1.703 (963)  |
| Total mass (kg)            | 76.0 (15.4)      | 68.8 (13.0)    | 83.8 (13.9)  |
| Total lean mass (g)        | 47,356 (9821)    | 39,702 (4760)  | 55,673 (6649) |
| Total bone mineral content (g) | 2,644 (572)     | 2,229 (537)    | 3,094 (413)  |
| Trunk fat: peripheral fat  | 1.88 (0.67)      | 1.64 (0.49)    | 2.13 (0.81)  |
| Android lean mass (g)      | 3.488 (766)      | 2.911 (413)    | 4.115 (535)  |
| Gynoid lean mass (g)       | 7.333 (1604)     | 6.123 (797)    | 8.649 (1170) |
| Arms lean mass (g)         | 5.381 (1594)     | 4.091 (368)    | 6.783 (1044) |
| Legs lean mass (g)         | 15.975 (3704)    | 13.279 (2043)  | 18.905 (2773) |
| Trunk lean mass (g)        | 22.866 (4445)    | 19.468 (2273)  | 26.556 (3080) |
| Bone-related               |                  |                |              |
| Android bone mass (g)      | 49.3 (13.1)      | 42.5 (9.5)     | 56.6 (12.5)  |
| Gynoid bone mass (g)       | 275.6 (67.5)     | 227.3 (37.5)   | 328.5 (52.0) |
| Arms bone mineral content (g) | 365 (100)       | 283 (44.3)     | 453 (62.4)  |
| Legs bone mineral content (g) | 985 (237)       | 805 (124)      | 1,180 (165) |
| Trunk bone mineral content (g) | 780 (203)       | 651 (131)      | 919 (172)   |
| Arm fat: total fat (g)      | 0.10 (0.02)      | 0.11 (0.02)    | 0.10 (0.01)  |
| Leg fat: total fat (g)      | 0.30 (0.07)      | 0.35 (0.06)    | 0.26 (0.04)  |
| Trunk fat: total fat (g)    | 0.56 (0.08)      | 0.51 (0.07)    | 0.60 (0.06)  |
| Android fat: gynoid fat    | 0.59 (0.22)      | 0.46 (0.15)    | 0.74 (0.18)  |
| Trunk fat: peripheral fat   | 1.45 (0.47)      | 1.16 (0.31)    | 1.77 (0.39)  |
| Total body fat mass (g)     | 5.99 (1.72)      | 5.17 (1.40)    | 6.89 (1.58)  |
| Android gynoid mass (g)     | 11.8 (2.29)      | 11.0 (2.12)    | 12.6 (2.20)  |
| Gynoid trunk fat mass (g)   | 8.41 (1.95)      | 7.30 (1.54)    | 9.61 (1.61)  |
| Arms trunk fat mass (g)     | 24.7 (4.91)      | 23.2 (4.71)    | 26.4 (4.56)  |
| Legs trunk fat mass (g)     | 38.3 (8.81)      | 34.1 (7.26)    | 42.9 (8.06)  |
| Total body fat mass (g)     | 2.644 (572)      | 2.229 (537)    | 3.094 (413)  |
| Total fat mass (g)          | 25.967 (9805)    | 28.826 (9670)  | 25.003 (9072) |
| Total lean mass (g)         | 47.356 (9821)    | 39.702 (4760)  | 55.673 (6649) |
| Total mass (kg)             | 76.0 (15.4)      | 68.8 (13.0)    | 83.8 (13.9)  |

1VAT mass and volume were available in n = 4,338 (combined), 2,266 (female) and 2,082 (male). Visceral Adipose Tissue, VAT. Arm, leg and trunk fat ratio were calculated by dividing arm, leg and trunk fat mass (g) by total fat mass (g), respectively. We estimated android gynoid fat ratio by dividing android fat mass (g) by gynoid fat mass (g). Trunk peripheral ratio was estimated by dividing trunk fat mass (g) by the sum of arms and legs fat mass (g).
TABLE 2 | List of SNPs in combined, female and male datasets significant at p< 5.0 x 10^-8.

| Chr | Position | SNP ID     | Ref allele | Alt allele | Eff allele | Annotation | Combined (n=4 386) Beta | Combined (n=4 386) P-value | Female (n=2 294) Beta | Female (n=2 294) P-value | Male (n=2 109) Beta | Male (n=2 109) P-value |
|-----|----------|------------|------------|------------|------------|------------|------------------------|--------------------------|------------------------|--------------------------|------------------------|------------------------|
|     |          |            |            |            |            |            | Beta                   | P-value                  | Beta                   | P-value                  | Beta                   | P-value                  |
| Obesity-related phenotypes |          |            |            |            |            |            |                       |                          |                       |                          |                       |                          |
| Android fat mass | 2 | 58799070 | rs7592270 | C | T | T | LINC01122(0) | 0.49 | 1.63 x 10^-8 | – | – | – | – |
| Gynoid fat mass | 6 | 17429040 | rs113380185 | C | T | T | CAP2(0) | – | – | – | – | 0.65 | 2.15 x 10^-8 | – | – |
| Arms fat mass | 12 | 11727655 | rs117686994 | T | G | G | – | – | – | – | – | 0.98 | 1.05 x 10^-8 | – | – |
| Legs fat mass | 7 | 15845439 | rs143707182 | C | G | G | – | – | – | – | – | – | 3.06 | 7.04 x 10^-9 | – | – |
| Trunk fat mass | 13 | 72584929 | rs7592270 | C | T | T | LINC01122(0) | 2485.64 | 10.74 x 10^-10 | – | – | – | – |
| VAT mass | 2 | 58799070 | rs7592270 | C | T | T | LINC01122(0) | 250.04 | 4.49 x 10^-8 | – | – | – | – |
| VAT volume | 2 | 58799070 | rs7592270 | C | T | T | LINC01122(0) | 266.09 | 4.49 x 10^-8 | – | – | – | – |
| Lean-related phenotypes |          |            |            |            |            |            |                       |                          |                       |                          |                       |                          |
| Gynoid lean mass | 3 | 32262434 | rs145972737 | G | A | A | – | – | – | – | – | 11.23 | 8.69 x 10^-9 | – | – |
| Legs lean mass | 21 | 43732828 | rs2236705 | C | A | A | TFF3(0) | – | – | – | – | 26.29 | 3.20 x 10^-9 | – | – |
| Trunk lean mass | 6 | 127025661 | rs13212044 | G | T | T | – | – | – | – | – | 107.64 | 4.12 x 10^-8 | – | – |
| Bone-related phenotypes |          |            |            |            |            |            |                       |                          |                       |                          |                       |                          |
| Android bone mass | 6 | 33901724 | rs13986597 | G | A | A | – | – | – | – | – | 30.62 | 4.54 x 10^-9 | – | – |
| Gynoid bone mass | 9 | 114333327 | rs72748040 | T | A | A | PTGR1(0) ZNF483(0) | – | – | – | – | – | 26.29 | 3.20 x 10^-9 | – | – |
| Arms bone mineral content | 17 | 39911373 | rs55634776 | C | T | T | JUP(0) | – | – | – | – | 39.77 | 1.17 x 10^-8 | – | – |
| Trunk bone mineral content | 14 | 27073424 | rs112098641 | T | G | G | NOVA1(+6.464kb) | – | – | – | – | – | – | – | – |
| Total |          |            |            |            |            |            |                       |                          |                       |                          |                       |                          |
| Android total mass | 2 | 58799070 | rs7592270 | C | T | T | LINC01122(0) | 0.49 | 1.63 x 10^-8 | – | – | – | – |
| Arms total mass | 3 | 11244120 | rs3592350 | C | T | T | HRH1(0) | – | – | – | – | 0.65 | 2.15 x 10^-8 | – | – |
| Legs total mass | 12 | 11727655 | rs117686994 | T | G | G | – | – | – | – | – | 0.98 | 1.05 x 10^-8 | – | – |
| Trunk total mass | 2 | 58799070 | rs7592270 | C | T | T | LINC01122(0) | 2485.64 | 10.74 x 10^-10 | – | – | – | – |
| Ratios |          |            |            |            |            |            |                       |                          |                       |                          |                       |                          |
| Trunk:total fat | 1 | 46657220 | rs7552312 | C | T | T | POMGNT1(0) TSPAN1(+5.58kb) | – | – | – | – | 0.01 | 4.19 x 10^-9 | – | – |
| Android: gynoid | 17 | 6289883 | rs1567843 | G | C | C | – | – | – | – | – | – | 0.05 | 3.86 x 10^-9 | – | – |
| Trunk: peripheral | 10 | 50755929 | rs7777562 | C | A | A | ZMIZ1-AS1(0) | 0.18 | 4.97 x 10^-6 | – | – | – | – |

VAT (visceral adipose tissue) mass and volume were available in n=4 336 (combined), 2 266 (female) and 2 088 (male). A positive beta indicates that as the number of copies of the minor allele increases the outcome increases by beta*number of copies of the minor frequency allele, while a negative beta indicates that the outcome variable decreases by beta*number of copies of the minor frequency allele. Trunk fat ratio was calculated by dividing trunk fat mass (g) by total fat mass (g).

We estimated android gynoid ratio by dividing android fat mass (g) by gynoid fat mass (g). Trunk peripheral ratio was estimated by dividing trunk fat mass (g) by the sum of arms and legs fat mass (g). VAT, visceral adipose tissue; Ref, reference; Alt, alternative.
We observed that three SNPs were related to lean and bone mass phenotypes and are likely to impact body composition via estrogen pathways. SNP rs2236705 was correlated with female lean leg mass. This SNP is found in the intron of the *TFF3* gene, which is involved in skeletal metabolism, is estrogen regulated and regulates glucose metabolism (17). SNP rs112098641 is associated with female gynoid bone mass. The SNP is 6kb upstream from the *NOVA1* gene in the intron of a lncRNA gene, which is estrogenically regulated (18). Moreover, estrogen plays a role in the development of lean tissue mass and bone mass regulation in adulthood (19). Estrogen acts through two receptors – the alpha and beta receptors – which are important in lean and bone metabolism, respectively. Through these receptors, estrogen protects bone metabolism by regulating the survival of osteoclasts, if circulating levels of estrogen are low, bone mass will be lost, such as that observed in post-menopausal women (19). Similarly, the estrogen-receptor alpha located on skeletal muscle may activate signalling pathways, such as Insulin-like Growth Factor-1, that mediates skeletal metabolism (20). SNP rs113380185, found in the *CAP2* gene, was correlated with male android bone mass and has been associated with human height (21) (Table S1, Figures S3 and S4).

We acknowledge some limitations. Our findings are not generalizable to non-white populations. Our sample size is relatively small and we are likely underpowered to detect variants with small effect sizes. Nonetheless, these findings are from a pilot study and are designed to be replicated and to inform future research in the full 100,000 participants from the UKB imaging enhancement programme. Strengths of this study include the investigation of 31 phenotypes from the three-
compartment model of body composition. These have been largely under-researched due to the high cost and participant burden of collecting DXA measures.

The present study identified six loci that help explain the physiological mechanisms leading to body composition. These preliminary findings support the connection between fat, lean and bone mass and the need for these compartments of body composition to be considered concurrently by clinicians. The biological pathways highlighted by this study, including glucose metabolism and estrogen regulation, will inform future research aimed at understanding the complex biology of body composition. Potential candidate genes, such as LINC01122 and POMGNT1, are of interest to investigate in future studies, including the full UKB imaging enhancement programme dataset when it becomes available.

The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

KL, JW, RD, MM, and SB designed the analysis. MT, GA, SB, JW, and LC conducted the statistical analysis. KL, MT, MK, and SB drafted the manuscript. All authors contributed to the article and approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: [https://www.frontiersin.org/articles/10.3389/fendo.2021.692677/full#supplementary-material](https://www.frontiersin.org/articles/10.3389/fendo.2021.692677/full#supplementary-material)

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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