# Investigating the Genetic Basis of the Influence of Adiposity on Psoriasis: A Cross-Sectional Study in a Large United Kingdom Population–Based Biobank

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## TO THE EDITOR

Psoriasis is a chronic inflammatory skin disease that has a substantial associated global public health burden (Griffiths et al, 2021). Adiposity is prevalent among individuals with psoriasis, particularly those with more severe disease, and evidence suggests a risk-increasing causal relationship between adiposity and psoriasis. First, increasing body mass index, waist circumference, and waist-to-hip ratio have been shown to be associated with increased psoriasis risk in large population-based studies (Snekvik et al, 2017). Second, Mendelian randomization studies have demonstrated a causal relationship between increasing levels of adiposity and psoriasis risk (Budu-Aggrey et al, 2019). In addition, weight loss interventions, including lifestyle, therapeutic, and surgical approaches, have demonstrated reduction in both risk and severity of psoriasis (Mahil et al, 2019). Despite these advances, the specific patterns of adiposity that confer the greatest risk and their relationship with genetic determinants of psoriasis remain incompletely understood. Understanding these relationships is crucial to better elucidate the mechanisms through which adiposity influences psoriasis to enable effective risk stratification and targeted weight management interventions.

Previous studies have largely relied on anthropometric measures (ie, direct physical measurements of the body) such as body mass index, waist circumference, and waist-to-hip ratio. These measures provide a general overview of total and central adiposity but lack the precision required to differentiate between the type of fat (eg, visceral vs subcutaneous fat) and its specific location within the body. This distinction is important because different fat depots, such as visceral and subcutaneous fat, have distinct metabolic and inflammatory profiles that may differentially influence disease risk, including psoriasis (Wajchenberg, 2000). Advanced methods, including bioelectric impedance, dual-energy X-ray absorptiometry, and magnetic resonance imaging, offer greater precision in assessing both the type and location of fat. By examining a comprehensive range of adiposity measures in a large population-based cohort, we aimed to refine our understanding of how both the type and distribution of adipose tissue contribute to psoriasis susceptibility.

There is increasing evidence that the relationship between adiposity and psoriasis may vary by genetic factors, particularly the primary susceptibility allele, *HLA-C*06:02*. Higher adiposity levels have been linked to the absence of *HLA-C*06:02* in severe psoriasis cases (Douroudis et al, 2022). However, it remains unclear whether adiposity exerts a stronger influence on psoriasis risk in *HLA-C*06:02*–negative individuals. A recent GWAS identified 109 independent psoriasis susceptibility loci (Dand et al, 2025), providing the opportunity to extend investigations of adiposity's influence on psoriasis across different levels of genetic risk for psoriasis susceptibility, beyond *HLA-C*06:02*.

To accurately describe and quantify the pattern of adiposity associated with psoriasis, we analyzed data from 336,806 participants in the UK Biobank of White British ancestry, including 9305 individuals with psoriasis (full description is provided in Supplementary Materials and Methods and Supplementary Results). Twenty-five adiposity measures were evaluated, encompassing anthropometric, bioelectric impedance, and imaging-based measures (dual-energy X-ray absorptiometry and magnetic resonance imaging). Four of the 5 measures with the largest effect size for association with psoriasis were central adiposity measures, including waist-to-hip ratio (OR = 1.26, $P = 8.74e\text{-}65$), abdominal fat ratio, total abdominal adipose tissue index, and waist circumference (Table 1). Among total adiposity measures, percentage body fat, assessed through bioelectric impedance, was associated with psoriasis with the largest effect size (OR = 1.29, $P = 3.77e\text{-}69$). These findings underscore the significance of central adiposity as a driver of psoriasis risk.

The relationship between central adiposity and psoriasis was particularly pronounced in females, with larger effect sizes observed across several measures compared with those in males (Table 1). For example, visceral adipose tissue mass exhibited a stronger association in females (interaction with sex $P = 6.70e\text{-}03$).

To explore how measures conferring the greatest risk of psoriasis (percentage body fat and waist-to-hip ratio) relate to genetic determinants of the disease, we conducted interaction testing between adiposity measures and psoriasis polygenic risk scores (PRSs) (both including and excluding *HLA-C*06:02*). The full psoriasis PRS was constructed using 109 psoriasis susceptibility loci (Dand et al, 2025). A significant interaction was observed between the full psoriasis PRS and waist-to-hip ratio (beta = −0.019, $P = .047$) on psoriasis risk (Table 2). However, the interaction effect was no longer significant when *HLA-C*06:02* was excluded from the PRS (beta = 0.015, $P = .141$), suggesting that the presence of *HLA-C*06:02* has a major

*Abbreviation: PRS, polygenic risk score*

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## Table 1. Association between Standardized Measures of Adiposity and Psoriasis

| Measure of Adiposity | | | Association with Psoriasis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Both Sexes (n = 336,806) | | Males (n = 155,775) | | Females (n = 180,714) | |
| | | | Standardized OR | *P*-Value | Standardized OR | *P*-Value | Standardized OR | *P*-Value |
| Total body fat measures | Anthropometric measures | Body mass index (n = 335,626) | 1.18 | **3.60e-65** | 1.19 | **3.00e-30** | 1.17 | **5.37e-37** |
| | | Body weight (n = 335,745) | 1.17 | **4.36e-47** | 1.16 | **2.22e-22** | 1.18 | **9.33e-27** |
| | Impedance measures | Percentage body fat (n = 330,638) | 1.29 | **3.77e-69** | 1.34 | **1.452e-37** | 1.26 | **3.89e-34** |
| | | Whole body fat mass (n = 330,284) | 1.19 | **7.31e-66** | 1.22 | **5.41e-35** | 1.17 | **2.36e-33** |
| | | Whole body fat-free mass (n = 330,810) | 1.13 | **7.08e-11** | 1.10 | **1.34e-05** | 1.20 | **6.39e-08** |
| | Abdominal MRI measures | Subcutaneous fat volume (n = 27,173) | 1.18 | **2.88e-06** | 1.07 | .052 | 1.21 | **8.75e-15** |
| | | Abdominal subcutaneous adipose tissue volume (n = 27,963) | 1.19 | **9.80e-07** | 1.10 | **.027** | 1.25 | **.0001** |
| | DEXA measures | Total fat mass (n = 27,686) | 1.12 | **6.65e-05** | 1.00 | .15 | 1.19 | **.0002** |
| | | Total tissue fat percentage (n = 33,021) | 1.18 | **8.82e-07** | 1.05 | **.012** | 1.13 | **1.65e-05** |
| Body fat distribution measures | Anthropometric measures | Waist circumference[1] (n = 336,158) | 1.23 | **1.43e-75** | 1.23 | **3.82e-35** | 1.23 | **2.34e-42** |
| | | Waist-to-hip ratio[1] (n = 336,087) | 1.26 | **8.74e-65** | 1.25 | **9.55e-30** | 1.27 | **8.09e-37** |
| | Impedance measures | Arm fat ratio (n = 330,130) | 1.08 | **4.52e-16** | 0.99 | .583 | 1.15 | **2.17e-28** |
| | | Leg fat ratio (n = 330,241) | 0.93 | **3.22e-04** | 1.04 | .172 | 0.85 | **8.46e-09** |
| | | Trunk fat ratio (n = 330,060) | 1.01 | .70 | 0.97 | .267 | 1.04 | .161 |
| | Abdominal MRI measures | Abdominal fat ratio[1] (n = 27,421) | 1.24 | **4.70e-08** | 1.19 | **.002** | 1.30 | **4.29e-06** |
| | | Total thigh fat-free muscle volume (n = 27,448) | 1.02 | .814 | 0.98 | .825 | 1.10 | .381 |
| | | Total trunk fat volume (n = 27,904) | 1.19 | **1.16e-07** | 1.13 | **.007** | 1.23 | **1.78e-06** |
| | | Total abdominal adipose tissue index[1] (n = 27,904) | 1.22 | **3.68e-08** | 1.15 | **.006** | 1.22 | **1.12e-06** |
| | | Visceral fat volume[1] (n = 27,173) | 1.20 | **2.71e-06** | 1.13 | **.006** | 1.35 | **1.03e-05** |
| | | Visceral adipose tissue volume[1] (n = 27,971) | 1.20 | **8.31e-07** | 1.14 | **.003** | 1.36 | **3.89e-06** |
| | DEXA measures | Android fat mass[1] (n = 27,686) | 1.15 | **2.11e-05** | 1.09 | .054 | 1.23 | **2.11e-05** |
| | | Android tissue fat percentage[1] (n = 33,021) | 1.18 | **9.44e-07** | 1.12 | **.016** | 1.23 | **8.79e-06** |
| | | Arms fat mass (n = 27,686) | 1.13 | **4.49e-04** | 1.07 | .214 | 1.16 | **.0004** |
| | | Arms tissue fat percentage (n = 33,021) | 1.21 | **1.62e-05** | 1.15 | .076 | 1.32 | **3.39e-05** |
| | | Gynoid fat mass (n = 27,686) | 1.12 | **.001** | 1.06 | .266 | 1.17 | **.001** |
| | | Gynoid tissue fat percentage (n = 33,021) | 1.19 | **2.02e-04** | 1.12 | .096 | 1.26 | **3.58e-04** |
| | | Legs fat mass (n = 27,686) | 1.10 | **.009** | 1.04 | .569 | 1.14 | **.005** |
| | | Legs tissue fat percentage (n = 33,021) | 1.17 | **.003** | 1.10 | .243 | 1.23 | **.003** |
| | | Trunk fat mass[1] (n = 27,686) | 1.15 | **1.46e-05** | 1.09 | .053 | 1.23 | **1.73e-05** |
| | | Trunk tissue fat percentage[1] (n = 33,021) | 1.19 | **3.56e-07** | 1.13 | .0125 | 1.24 | **3.47e-06** |
| | | Visceral adipose tissue mass[1] (n = 27,530) | 1.16 | **4.02e-05** | 1.10 | .034 | 1.39 | **4.45e-06** |
| | | Visceral adipose tissue volume[1] (n = 27,530) | 1.16 | **4.02e-05** | 1.10 | .034 | 1.39 | **4.44e-06** |

(*continued*)

**Table 1. Continued**

| Measure of Adiposity | | | Association with Psoriasis: Both Sexes (n = 336,806) Standardized OR | P-Value | Males (n = 155,775) Standardized OR | P-Value | Females (n = 180,714) Standardized OR | P-Value |
|---|---|---|---|---|---|---|---|---|
| Other | Abdominal MRI measures | Weight to muscle ratio (n = 27,448) | 1.21 | **2.61e-06** | 1.18 | .030 | 1.22 | **2.71e-05** |
| | | Muscle fat infiltration (n = 27,399) | 1.17 | **5.52e-06** | 1.00 | .030 | 1.21 | **2.85e-05** |

Abbreviations: DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.

The table presents an association between measures of adiposity and psoriasis (9305 cases, defined using self-reported questionnaire, hospital episode summary, primary care coding data) in unrelated White British subset of UK Biobank participants in (i) both sexes (standardized OR adjusted for age and sex as covariates), (ii) males (standardized OR adjusted for age as a covariate), and (iii) females (standardized OR adjusted for age as a covariate). Standardized OR is reported as per 1 SD change in the exposure (adiposity measure). Statistically significant results ($P < .05$) are shown in bold.

[1]Central adiposity measures.

contribution to the significant interaction effect observed with the full psoriasis PRSs. In line with these findings, waist-to-hip ratio was associated with psoriasis with a significantly larger effect size in *HLA-C*06:02*−negative versus *HLA-C*06:02*−positive participants (interaction beta = −0.088, $P = 4.35e\text{-}05$), consistent with previous observations (Douroudis et al, 2022) (Supplementary Materials and Methods and Supplementary Results). No significant interaction was found for the full psoriasis PRS with percentage body fat on psoriasis risk ($P = .314$).

To establish whether the causal effect of adiposity measures on psoriasis differed in subgroups of psoriasis genetic risk, Mendelian randomization was used to examine the association between genetic predictors of waist-to-hip ratio and psoriasis (i) between *HLA-C*06:02*−stratified subgroups and (ii) across increasing quartiles of psoriasis PRS scores excluding *HLA-C*06:02*. The causal effect of waist-to-hip ratio on psoriasis risk did not differ significantly between *HLA-C*06:02*−positive and −negative subgroups or across quartiles of psoriasis polygenic risk (Supplementary Materials and Methods and Supplementary Results).

This study highlights the strong association between central adiposity measures and psoriasis risk, aligning with the effects observed in cardiometabolic disease (Dutheil et al, 2018). Importantly, the association was stronger in females than in males, suggesting potential sex-specific differences in how adiposity influences psoriasis risk, consistent with evidence of hormonal and immune variations by sex (Rubtsova et al, 2015). A limitation of our study is the reliance on self-reported, hospital episode statistics, and primary care records for psoriasis diagnoses, because the dataset does not specify whether diagnoses were made by a dermatologist. Although this introduces the potential for misclassification bias, it is important to note that hospital episode statistics primarily captures secondary care diagnoses, where psoriasis is typically managed by dermatologists, making it more likely that cases were confirmed by specialists. To mitigate this limitation, we conducted a sensitivity analysis excluding cases defined using primary care data, where diagnostic uncertainty may be higher. The consistency of our findings in this analysis supports the robustness of our results (Supplementary Materials and Methods and Supplementary Results). In addition, because this study only included individuals of White British ancestry from the UK Biobank, the generalizability of our findings to more diverse populations may be limited. Future studies incorporating datasets with dermatologist-confirmed diagnoses and broader ethnic representation will be important to further validate these associations and refine risk stratification approaches. Although imaging-based measures such as dual-energy X-ray absorptiometry and magnetic resonance imaging provide precise assessments of adiposity, their availability in only a small subset (~8%) of participants may limit statistical power and generalizability. Future studies incorporating larger imaging datasets could help address this limitation.

The relationship between central adiposity and genetic determinants of psoriasis revealed that central adiposity as measured by waist-to-hip ratio had a stronger association with psoriasis in *HLA-C*06:02*−negative individuals than in *HLA-C*06:02*−positive individuals.

**Table 2. Interaction between Psoriasis Polygenic Risk and Standardized Adiposity Measures on Psoriasis Risk**

| Interaction Term | | Measures of Total Body Fat: Percentage Body Fat Beta | P-Value | Measures of Body Fat Distribution: Waist-to-Hip Ratio Beta | P-Value |
|---|---|---|---|---|---|
| Psoriasis polygenic risk score (GWS) | Including *HLA-C*06:02* | −0.009 | .314 | −0.019 | **.047** |
| | Excluding *HLA-C*06:02* | −0.020 | .066 | 0.015 | .141 |

Abbreviation: GWS, genome-wide significant.

A psoriasis polygenic risk score was derived from independent loci from GWAS meta-analysis (Dand et al, 2025) with and without *HLA-C*06:02*. Interaction was examined in unrelated White British subset of UK Biobank participants. Adiposity measures were standardized and adjusted for age and sex. Statistically significant results ($P < .05$) are shown in bold.

However, Mendelian randomization analysis found no significant differences in the causal effect of central adiposity on psoriasis risk between these subgroups, likely reflecting collider bias rather than a true biological interaction (Holmberg and Andersen, 2022). This suggests that both *HLA-C*06:02* and adiposity independently influence psoriasis risk without modifying each other's effects. These findings, together with the absence of differences in association or adiposity's causal effects across increasing psoriasis PRS, reinforce the importance of optimizing weight management strategies to reduce psoriasis risk and improving outcomes across all profiles of psoriasis genetic risk. Furthermore, these results suggest the possibility of previously unreported adiposity-related biological mechanisms contributing to psoriasis pathogenesis, independent of established genetic pathways, warranting further investigation. The lack of significant interaction between percentage body fat compared with waist-to-hip ratio and *HLA-C*06:02* may reflect differences in measurement precision rather than differences in biological relevance of central adiposity in psoriasis risk.

These findings have important translational implications for both clinical practice and public health. The strong association between central adiposity and psoriasis, independent of genetic risk, suggests that waist-to-hip ratio could serve as a useful marker for identifying individuals at higher risk of psoriasis, including those at risk of more severe disease. The independence of adiposity from psoriasis genetic risk supports the potential integration of adiposity measures into risk stratification models to improve the prediction of disease development, progression, severity, and associated comorbidities. In addition, the observed links between central adiposity and psoriasis underscore the need for further research into underlying biological mechanisms, including inflammatory pathways and gut microbiome alterations, to better understand the role of central adiposity in psoriasis pathogenesis.

## DATA AVAILABILITY STATEMENT

The UK Biobank resource is available to bona fide researchers for health-related research in the public interest (https://www.ukbiobank.ac.uk/enable-your-research). All data supporting the findings of this study are presented within the manuscript and the supplementary materials. Additional details are available from the corresponding author (catherine.smith@kcl.ac.uk) upon reasonable request.

## KEYWORDS

Adiposity; *HLA-C*06:02*; Mendelian randomization; Polygenic risk score; Psoriasis

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## CONFLICT OF INTEREST

SKM reports departmental funding but no personal payments from AbbVie, Almirall, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB, outside the submitted work. JNB has received honoraria and/or research grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, LEO Pharma, Lilly, Novartis, Samsung, and Sun Pharma. CHS reports grants from an MRC-funded stratified medicine consortium with multiple industry partners; grants from IMI (Horizon 2020)-funded European consortium with multiple industry partners; and others from AbbVie, Novartis, Pfizer, Sanofi, Boehringer Ingelheim, and SOBI, outside the submitted work. CHS is Chair of UK guidelines on biologic therapy in psoriasis. The remaining authors state no conflict of interest.

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## Disclaimer

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## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2025.03.024.

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## SUPPLEMENTARY RESULTS

### Measures of central adiposity are strongly associated with psoriasis

To refine the understanding of the association between adiposity and psoriasis, we used measures of adipose tissue volume and distribution derived from bioelectric impendence; imaging techniques, including magnetic resonance imaging and dual-energy X-ray absorptiometry; alongside routine anthropometric measures of adiposity. Adiposity measures were standardized to aid comparisons. In total, the association of 25 adiposity measures with psoriasis was evaluated, and the resulting relationships were examined to infer how differences in the distribution of adipose depots contribute to psoriasis risk and whether these relationships vary by sex and genetic predisposition.

Anthropometric measures of total body fat and central adiposity were found to be strongly associated with psoriasis (Supplementary Table S1), consistent with previous findings (Snekvik et al, 2017). Interrogation of measures of adiposity distribution showed that 4 of the 5 adiposity measures with the largest effect sizes were related to measures of central adiposity (abdominal fat ratio, total abdominal adipose tissue index, waist circumference, and waist-to-hip ratio), aligning with the well-established link between central obesity and cardiometabolic traits (Dutheil et al, 2018). Leg fat ratio was the only measure significantly inversely associated with psoriasis risk (OR = 0.92, $P$ = 3.22e-04), with the stronger effects observed in females.

Among the measures of total body fat, percentage body fat (OR = 1.29, $P$ = 3.77e-69) showed the largest effect size, highlighting the advantage of bioelectric impedance as a modality to estimate total body fat composition compared with body mass index. Among the measures of body fat distribution, waist-to-hip ratio (OR = 1.26, $P$ = 8.74e-65) had the strongest association with psoriasis.

### The association between central adiposity and psoriasis is strongest in women and those with more severe disease

Larger effect sizes for associations between measures of central adiposity and psoriasis were observed in females than in males across anthropometric, impedance, and imaging measures (Supplementary Table S1). This effect was most prominent for visceral adipose tissue mass (interaction with sex $P$ = 6.70e-03) and visceral fat volume (interaction with sex $P$ = .03).

To explore the influence of disease severity on the observed associations, we compared an alternative definition of psoriasis that did and did not include cases ascertained through primary care data alongside hospital episode statistics. This approach was taken because the use of therapies only accessible in specialist settings (eg, systemic treatments) serves as a proxy for more severe disease, because these treatments are not available in United Kingdom primary care settings (Ramessur et al, 2024). Effect sizes for associations between adiposity measures and psoriasis were larger when this more stringent psoriasis case definition was used, suggesting that disease severity may amplify the relationship between adiposity and psoriasis (Supplementary Table S2).

### Larger effect sizes for the association between adiposity measures and psoriasis in *HLA-C*06:02*−negative versus *HLA-C*06:02*−positive participants

Using the measures most strongly associated with psoriasis risk, we investigated whether body fat percentage and waist-to-hip ratio contribute differently to psoriasis susceptibility in genetically distinct subgroups. Previous studies have reported higher levels of body weight, body mass index, and waist circumference in individuals with *HLA-C*06:02*−negative psoriasis than in those with *HLA-C*06:02*−positive psoriasis (Douroudis et al, 2022). To build on this evidence, we examined the association between adiposity and psoriasis risk in subgroups stratified by *HLA-C*06:02* status.

Consistent with this previous observation, a stronger association was observed between waist-to-hip ratio and psoriasis in *HLA-C*06:02*−negative than in *HLA-C*06:02*−positive participants (interaction beta = −0.088, $P$ = 4.35e-05) (Supplementary Tables S3 and S4). However, differences in the association between percentage body fat and psoriasis between *HLA-C*06:02* subgroups were not statistically significant using the psoriasis definition including (interaction $P$ = .385) and excluding cases defined using primary care data (Supplementary Tables S3 and S4−6).

### There is no significant interaction between psoriasis polygenic risk and measures of adiposity on psoriasis risk, beyond the effect of *HLA-C*06:02*

To establish whether the observed associations are independent of known psoriasis genetic risk factors, we explored the interaction between adiposity measures and psoriasis polygenic risk (either including or excluding *HLA-C*06:02*) through interaction testing.

A significant interaction was observed between a full psoriasis polygenic risk score (PRS) and waist-to-hip ratio (beta = −0.019, standard error = 0.01, $P$ = .047) on psoriasis risk (Supplementary Table S7). However, the interaction effect was no longer significant when *HLA-C*06:02* was excluded from the PRS (beta = 0.015, standard error = 0.01, $P$ = .141), suggesting that the presence of *HLA-C*06:02* has a major contribution to the significant interaction effect observed with the full psoriasis PRS. No significant interaction was found between the full psoriasis PRS and percentage body fat on psoriasis risk ($P$ = .314).

To explore whether these relationships might be influenced by disease severity, these interactions were also examined using the psoriasis definition that excluded primary care data (Supplementary Table S8). The interaction between the effects of the full psoriasis PRS and waist-to-hip ratio on psoriasis risk had a larger effect size (than a psoriasis definition that included primary care data) and was also no longer significant when *HLA-C*06:02* was excluded from the PRS.

### Risk-increasing Mendelian randomization effects of central adiposity on psoriasis risk observed, irrespective of psoriasis genetic risk

Assessing differences in the causal effect of central adiposity on psoriasis risk across subgroups with varying genetic susceptibility is important for understanding whether certain individuals with psoriasis are more susceptible to

the effects of adiposity. Identifying these differences could help inform personalized prevention strategies, such as targeted weight management interventions, for individuals at different genetic risk for psoriasis.

Therefore, we investigated whether the observed stronger association between waist-to-hip ratio and psoriasis in *HLA-C*06:02*−negative participants could be explained by the presence of a stronger causal effect of waist-to-hip ratio on psoriasis in *HLA-C*06:02*−negative participants.

The causal effect of waist-to-hip ratio on psoriasis risk did not differ significantly between *HLA-C*06:02*−positive and −negative subgroups or across quartiles of psoriasis polygenic risk (Supplementary Tables S9 and S10).

## SUPPLEMENTARY MATERIALS AND METHODS

### Study design overview

This investigation was conducted in individuals of European ancestry in the UK Biobank, a large population-based cohort. The following key steps of the study are outlined

1. To refine the understanding of how differences in the distribution of adipose depots contribute to psoriasis risk, the strength of association between 25 measures of adiposity and psoriasis was examined. First, this was performed using both anthropometric measures and bioelectric impedance measures, which are available for nearly all UK Biobank participants. Second, dual-energy X-ray absorptiometry and magnetic resonance imaging measures of adiposity were then examined, which are available in a smaller subset (∼8%) of the of total cohort. To investigate sex-specific differences in the association between measures of adiposity and psoriasis, analyses were also stratified by sex
2. Genetic analyses focused on percentage body fat and waist-to-hip ratio because, of total body fat and body fat distribution measures examined, these measures of adiposity showed the strongest associations with psoriasis. To examine potential differences in the strength of association between adiposity and psoriasis between *HLA-C*06:02*−stratified subgroups, the association between these measures of adiposity and psoriasis was examined in *HLA-C*06:02*−positive (participants with 1 or 2 copies of the *HLA-C*06:02* allele) and *HLA-C*06:02*−negative (participants lacking the *HLA-C*06:02* allele) participants.
3. To explore the interplay between known psoriasis genetic risk and the association between measures of adiposity (percentage body fat and waist-to-hip ratio) and psoriasis, interaction testing was performed using a psoriasis PRS score both including and excluding the lead variant for the primary susceptibility allele, *HLA-C*06:02*.
4. To establish whether the causal effect of adiposity measures on psoriasis differed in subgroups of psoriasis genetic risk, the Mendelian randomization (MR) causal estimate was examined between genetic predictors of waist-to-hip ratio and psoriasis (i) between *HLA-C*06:02*−stratified subgroups and (ii) across increasing quartiles of psoriasis PRS scores excluding *HLA-C*06:02*.

Subsequent methods description follows STrengthening the REporting of Genetic Association Studies, United Kingdom guidelines (Little et al, 2009).

### Setting

UK Biobank is a population-based prospective study of 502,682 volunteer participants with biological sample collection and longitudinal follow-up (Sudlow et al, 2015). It includes genotypic data, a wide range of detailed phenotypic data, and linkage to electronic health records. Participants aged 40−69 years were recruited in 2006−2010 and provided electronically written informed consent (REC reference 11/NW/0382, https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Consent.pdf). UK Biobank has approval from the Northwest Multicentre Research Ethics Committee. Data were downloaded on December 6, 2016 (UK Biobank project number 15147). Participants aged 40−69 years were recruited in 2006−2010 and provided electronically written informed consent (REC reference 11/NW/0382, https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Consent.pdf).

### Participants

UK Biobank analysis included 9305 participants with psoriasis who were determined to be of White British genetic ancestry by the UK Biobank core team (Bycroft et al, 2018). Psoriasis was indicated by participant self-report at baseline assessment (through touchscreen questionnaire and structured interview) and/or a primary or secondary diagnosis in linked in-patient hospital episode statistics (International Classification of Diseases, Revision 10 codes L400, L401, L402, L403, L404, L408, and L409, chosen to best reflect a diagnosis of psoriasis) and/or diagnosis of psoriasis based on linked primary care data (Seminara et al, 2011). Results for all analyses corresponding to a psoriasis definition excluding cases defined using primary care data as a data source are presented in results tables. This was performed to explore whether relationships might be influenced by disease severity.

### Variables

The primary exposure variables for association testing were measures of adiposity, recorded as continuous variables and psoriasis PRSs. Adiposity measurements were taken at baseline at UK Biobank assessment center visits (Sudlow et al, 2015). For bioelectrical impedance analysis measurements, the Tanita BC418MA body composition analyser was used in UK Biobank enrollment centers. Magnetic resonance imaging was performed at a single site using Siemens 1.5T MAGNETOM Aera. Dual-energy X-ray absorptiometry was performed using Lunar iDXA (GE Healthcare) with proprietary body composition analysis in a single UK Biobank imaging center. Numerical values were exported to the UK Biobank server without further processing. Missing imaging data were handled using a complete-case analysis, and no imputation was performed.

The 109 genome-wide significant variants from a psoriasis susceptibility meta-analysis (Dand et al, 2025) were assigned to linkage disequilibrium−independent blocks, and the lead variants from each genome-wide significant block was

incorporated into the PRS and weighted according to its effect size estimate. A full psoriasis PRS used in analyses included all 109 genome-wide significant variants. A sensitivity analysis was performed with the PRS constructed without major histocompatibility complex locus variants, giving a further score without *HLA-C*06:02*. The psoriasis PRS and adiposity measures were standardized to aid a comparative assessment across a range of adiposity measures with different base units.

**Data sources/measurement**

Genome-wide genotyping array data were generated for UK Biobank participants by Affymetrix using the Applied Biosystems UK BiLEVE Axiom Array or the Applied Biosystems UK Biobank Axiom Array (Applied Biosystems, Waltham, MA), as described elsewhere (Bycroft et al, 2018). Additional quality control steps were applied using PLINK (Purcell et al, 2007): cases were excluded on the basis of discordant sex information, genotyping rate $< 99\%$, relatedness (identity by descent $> 0.1875$), excess heterozygosity rate (mean $\pm$ 3 SD), or non-European ancestry. Variants (for use in the calculation of ancestry principal components) were excluded on the basis of missing genotyping rate $> 1\%$, minor allele frequency $< 1\%$, or departure from Hardy–Weinberg equilibrium ($P < 1 \times 10^{-5}$). Genome-wide imputation was undertaken by the UK Biobank central team using IMPUTE2 software and the UK10K haplotype reference panel merged with the 1000 Genomes phase 3 reference panel (Howie et al, 2009). Imputed variants with an imputation $r^2 > 0.7$ and minor allele frequency $> 0.5\%$ were included in further analyses.

For *HLA-C*06:02* stratification, *HLA* alleles were imputed centrally by the UK Biobank core team using the *HLA*IMP:02* algorithm with a multi-population reference panel (Dilthey et al, 2013). *HLA-C*06:02* status was inferred as negative (0 copies) or positive (1 or 2 copies) where the imputed allele dosage was exactly 0, 1, or 2; participants with imprecise imputed allele count were excluded.

A genetic instrument for waist-to-hip ratio comprising of 39 genome-wide significant variants was derived from the GIANT consortium GWAS meta-analysis for MR (Shungin et al, 2015).

**Bias**

Potential confounders of age and sex were established a priori by a subgroup of study investigators comprising expert clinicians and analysts. Confounders were controlled for during statistical analysis to allow estimation of the direct effect between measures of adiposity and psoriasis. Lifestyle-related confounders such as smoking, alcohol consumption, or physical activity were not adjusted for in analyses. Although these factors can influence both adiposity and psoriasis risk, this study aimed to assess the direct association between adiposity measures and psoriasis without overadjustment that could potentially obscure true relationships.

The F-statistic in 1-sample MR for waist-to-hip ratio was 64.3. An F-statistic $\geq 10$ indicates sufficient instrument strength to avoid weak instrument bias (Burgess and Thompson, 2011).

**Study size**

The primary UK Biobank analyses included 9305 participants with psoriasis and 327,501 controls. A secondary analysis using a psoriasis definition excluding cases defined using primary care data was also performed (5194 psoriasis cases and 331,612 controls).

**Statistical methods**

The following methods were employed in statistical analysis:

1. Logistic regression was used to assess the association between measures of adiposity (exposure) and psoriasis (outcome). To aid comparison of the strength of associations with psoriasis, standardized ORs are reported for each adiposity measure. The OR per SD in the exposure after adjustment for age and sex (full cohort) or age only (sex-stratified analyses) is presented.
2. A logistic regression model was used to assess the association between measures of adiposity (percentage body fat and waist-to-hip ratio) and psoriasis in *HLA-C*06:02*–stratified subgroups. A second model was generated where *HLA-C*06:02* status was converted into a binary variable (*HLA-C*06:02* positive = 1, *HLA-C*06:02* negative = 0) added as a dependent variable in a multivariable regression model.
3. A logistic regression model was first used to assess the association between measures of adiposity (percentage body fat and waist-to-hip ratio) and psoriasis. The psoriasis PRS was then added as a dependent variable in a multivariable regression model, and the interaction results are reported.
4. MR is a powerful genetic tool that helps to overcome issues of unmeasured confounding and reverse causation found in observational studies, providing supportive evidence for causality (Burgess et al, 2019). One-sample MR was used to examine the causal relationship between waist-to-hip ratio (exposure) and psoriasis (outcome) using individual-level data in the UK Biobank. The statistical method for evaluating causal effects was the inverse-variance–weighted MR. For each outcome, we report the inverse-variance–weighted causal effect with corresponding *P*-values. Psoriasis PRS quartiles were generated for both PRSs used to enable assessment across quartiles of psoriasis genetic risk (Q1, lowest psoriasis genetic risk, Q4, highest psoriasis genetic risk).

**Software**

Analyses were performed using R (version 4.1.2) (R Foundation for Statistical Computing, Vienna, Austria). All MR analyses were performed using the "MendelianRandomization" R package (Hemani et al, 2018).

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## Supplementary Table S1. Association between Standardized Measures of Adiposity and Psoriasis

| Measure of Adiposity | | | Association with Psoriasis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Both Sexes (n = 336,806) | | Males (n = 155,775) | | Females (n = 180,714) | |
| | | | Standardized OR | *P*-Value | Standardized OR | *P*-Value | Standardized OR | *P*-Value |
| Total body fat measures | Anthropometric measures | Body mass index (n = 335,626) | 1.18 | **3.60e-65** | 1.19 | **3.00e-30** | 1.17 | **5.37e-37** |
| | | Body weight (n = 335,745) | 1.17 | **4.36e-47** | 1.16 | **2.22e-22** | 1.18 | **9.33e-27** |
| | Impedance measures | Percentage body fat (n = 330,638) | 1.29 | **3.77e-69** | 1.34 | **1.452e-37** | 1.26 | **3.89e-34** |
| | | Whole body fat mass (n = 330,284) | 1.19 | **7.31e-66** | 1.22 | **5.41e-35** | 1.17 | **2.36e-33** |
| | | Whole body fat-free mass (n = 330,810) | 1.13 | **7.08e-11** | 1.10 | **1.34e-05** | 1.20 | **6.39e-08** |
| | Abdominal MRI measures | Subcutaneous fat volume (n = 27,173) | 1.18 | **2.88e-06** | 1.07 | .052 | 1.21 | **8.75e-15** |
| | | Abdominal subcutaneous adipose tissue volume (n = 27,963) | 1.19 | **9.80e-07** | 1.10 | **.027** | 1.25 | **.0001** |
| | DEXA measures | Total fat mass (n = 27,686) | 1.12 | **6.65e-05** | 1.00 | .15 | 1.19 | **.0002** |
| | | Total tissue fat percentage (n = 33,021) | 1.18 | **8.82e-07** | 1.05 | **.012** | 1.13 | **1.65e-05** |
| Body-fat distribution measures | Anthropometric measures | Waist circumference[1] (n = 336,158) | 1.23 | **1.43e-75** | 1.23 | **3.82e-35** | 1.23 | **2.34e-42** |
| | | Waist-to-hip ratio[1] (n = 336,087) | 1.26 | **8.74e-65** | 1.25 | **9.55e-30** | 1.27 | **8.09e-37** |
| | Impedance measures | Arm fat ratio (n = 330,130) | 1.08 | **4.52e-16** | 0.99 | .583 | 1.15 | **2.17e-28** |
| | | Leg fat ratio (n = 330,241) | 0.93 | **3.22e-04** | 1.04 | .172 | 0.85 | **8.46e-09** |
| | | Trunk fat ratio (n = 330,060) | 1.01 | .70 | 0.97 | .267 | 1.04 | .161 |
| | Abdominal MRI measures | Abdominal fat ratio[1] (n = 27,421) | 1.24 | **4.70e-08** | 1.19 | **.002** | 1.30 | **4.29e-06** |
| | | Total thigh fat-free muscle volume (n = 27,448) | 1.02 | .814 | 0.98 | .825 | 1.10 | .381 |
| | | Total trunk fat volume (n = 27,904) | 1.19 | **1.16e-07** | 1.13 | **.007** | 1.23 | **1.78e-06** |
| | | Total abdominal adipose tissue index[1] (n = 27,904) | 1.22 | **3.68e-08** | 1.15 | **.006** | 1.22 | **1.12e-06** |
| | | Visceral fat volume[1] (n = 27,173) | 1.20 | **2.71e-06** | 1.13 | **.006** | 1.35 | **1.03e-05** |
| | | Visceral adipose tissue volume[1] (n = 27,971) | 1.20 | **8.31e-07** | 1.14 | **.003** | 1.36 | **3.89e-06** |
| | DEXA measures | Android fat mass[1] (n = 27,686) | 1.15 | **2.11e-05** | 1.09 | .054 | 1.23 | **2.11e-05** |
| | | Android tissue fat percentage[1] (n = 33,021) | 1.18 | **9.44e-07** | 1.12 | **.016** | 1.23 | **8.79e-06** |
| | | Arms fat mass (n = 27,686) | 1.13 | **4.49e-04** | 1.07 | .214 | 1.16 | **.0004** |
| | | Arms tissue fat percentage (n = 33,021) | 1.21 | **1.62e-05** | 1.15 | .076 | 1.32 | **3.39e-05** |
| | | Gynoid fat mass (n = 27,686) | 1.12 | **.001** | 1.06 | .266 | 1.17 | **.001** |
| | | Gynoid tissue fat percentage (n = 33,021) | 1.19 | **2.02e-04** | 1.12 | .096 | 1.26 | **3.58e-04** |
| | | Legs fat mass (n = 27,686) | 1.10 | **.009** | 1.04 | .569 | 1.14 | **.005** |
| | | Legs tissue fat percentage (n = 33,021) | 1.17 | **.003** | 1.10 | .243 | 1.23 | **.003** |
| | | Trunk fat mass[1] (n = 27,686) | 1.15 | **1.46e-05** | 1.09 | .053 | 1.23 | **1.73e-05** |
| | | Trunk tissue fat percentage[1] (n = 33,021) | 1.19 | **3.56e-07** | 1.13 | .0125 | 1.24 | **3.47e-06** |
| | | Visceral adipose tissue mass[1] (n = 27,530) | 1.16 | **4.02e-05** | 1.10 | .034 | 1.39 | **4.45e-06** |
| | | Visceral adipose tissue volume[1] (n = 27,530) | 1.16 | **4.02e-05** | 1.10 | .034 | 1.39 | **4.44e-06** |

(*continued*)

## Supplementary Table S1. Continued

| Measure of Adiposity | | | Association with Psoriasis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Both Sexes (n = 336,806) | | Males (n = 155,775) | | Females (n = 180,714) | |
| | | | Standardized OR | *P*-Value | Standardized OR | *P*-Value | Standardized OR | *P*-Value |
| Other | Abdominal MRI measures | Weight to muscle ratio (n = 27,448) | 1.21 | **2.61e-06** | 1.18 | .030 | 1.22 | **2.71e-05** |
| | | Muscle fat infiltration (n = 27,399) | 1.17 | **5.52e-06** | 1.00 | .030 | 1.21 | **2.85e-05** |

Abbreviations: DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.

The table presents association between measures of adiposity and psoriasis (9305 cases, defined using self-reported questionnaire, hospital episode summary, and primary care coding data) in unrelated White British subset of UK Biobank participants in (i) both sexes (standardized OR adjusted for age and sex as covariates), (ii) males (standardized OR adjusted for age as a covariate), and (iii) females (standardized OR adjusted for age as a covariate). Standardized OR is reported as per 1 SD change in the exposure (adiposity measure). Statistically significant results ($P < .05$) are shown in bold.

[1]Central adiposity measures.

**Supplementary Table S2. Association between Standardized Measures of Adiposity and Psoriasis (Psoriasis Definition Excluding Cases Defined Using Primary Care Data as a Data Source)**

| Measure of Adiposity | | | Association with Psoriasis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Both Sexes (n = 336,806) | | Males (n = 155,775) | | Females (n = 180,714) | |
| | | | Standardized OR | *P*-Value | Standardized OR | *P*-Value | Standardized OR | *P*-Value |
| Total body fat measures | Anthropometric measures | Body mass index (n = 335,626) | 1.23 | **2.58e-60** | 1.04 | **3.54e-23** | 1.24 | **2.80e-39** |
| | | Body weight (n = 335,745) | 1.22 | **9.60e-43** | 1.17 | **8.68e-15** | 1.28 | **1.62e-32** |
| | Impendance measures | Percentage body fat (n = 330,638) | 1.40 | **3.03e-64** | 1.41 | **1.29e-32** | 1.38 | **1.75e-33** |
| | | Whole body fat mass (n = 330,284) | 1.25 | **1.48e-63** | 1.25 | **9.38e-29** | 1.25 | **1.53e-36** |
| | | Whole body fat-free mass (n = 330,810) | 1.15 | **2.68e-08** | 1.07 | **.026** | 1.39 | **9.84e-13** |
| | Abdominal MRI measures | Subcutaneous fat volume (n = 27,173) | 1.19 | **1.79e-05** | 1.14 | .052 | 1.22 | **9.62e-05** |
| | | Abdominal subcutaneous adipose tissue volume (n = 27,963) | 1.19 | **1.05e-05** | 1.16 | **.027** | 1.21 | **1.25e-04** |
| | DEXA measures | Total fat mass (n = 27,686) | 1.15 | **2.76e-04** | 1.09 | .154 | 1.22 | **2.27e-04** |
| | | Total tissue fat percentage (n = 33,021) | 1.25 | **1.27e-06** | 1.18 | **.012** | 1.33 | **1.71e-05** |
| Body-fat distribution measures | Anthropometric measures | Waist circumference[1] (n = 336,158) | 1.30 | **7.28e-70** | 1.26 | **3.20e-28** | 1.33 | **3.02e-44** |
| | | Waist-to-hip ratio[1] (n = 336,087) | 1.32 | **3.76e-55** | 1.30 | **3.92e-25** | 1.35 | **8.97e-32** |
| | Impendance measures | Arm fat ratio (n = 330,130) | 1.10 | **8.97e-15** | 0.97 | .232 | 1.22 | **6.62e-30** |
| | | Leg fat ratio (n = 330,241) | 0.88 | **7.34e-06** | 0.99 | .846 | 0.80 | **5.10e-09** |
| | | Trunk fat ratio (n = 330,060) | 1.03 | .203 | 1.02 | .605 | 1.05 | .211 |
| | Abdominal MRI measures | Abdominal fat ratio[1] (n = 27,421) | 1.26 | **1.89e-06** | 1.22 | **.003** | 1.29 | **1.50e-04** |
| | | Total thigh fat-free muscle volume (n = 27,448) | 1.01 | .934 | 0.94 | .521 | 1.18 | .217 |
| | | Total trunk fat volume (n = 27,904) | 1.20 | **1.38e-06** | 1.15 | **.011** | 1.25 | **2.20e-05** |
| | | Total abdominal adipose tissue index[1] (n = 27,904) | 1.22 | **1.63e-07** | 1.19 | **.005** | 1.25 | **7.47e-06** |
| | | Visceral fat volume[1] (n = 27,173) | 1.22 | **8.50e-06** | 1.14 | **.017** | 1.44 | **5.79e-06** |
| | | Visceral adipose tissue volume[1] (n = 27,971) | 1.22 | **4.07e-06** | 1.15 | **.008** | 1.42 | **7.78e-06** |
| | DEXA measures | Android fat mass[1] (n = 27,686) | 1.17 | **9.31e-05** | 1.10 | .079 | 1.26 | **8.64e-05** |
| | | Android tissue fat percentage[1] (n = 33,021) | 1.22 | **1.40e-06** | 1.16 | **.011** | 1.27 | **2.28e-05** |
| | | Arms fat mass (n = 27,686) | 1.15 | **5.34e-04** | 1.08 | .254 | 1.20 | **4.11e-04** |
| | | Arms tissue fat percentage (n = 33,021) | 1.31 | **1.04e-05** | 1.21 | **.036** | 1.39 | **6.28e-05** |
| | | Gynoid fat mass (n = 27,686) | 1.12 | **.007** | 1.07 | .315 | 1.16 | **.007** |
| | | Gynoid tissue fat percentage (n = 33,021) | 1.23 | **2.77e-04** | 1.18 | **.041** | 1.28 | **.002** |
| | | Legs fat mass (n = 27,686) | 1.10 | **.036** | 1.03 | .686 | 1.14 | **.020** |
| | | Legs tissue fat percentage (n = 33,021) | 1.19 | **.007** | 1.13 | .179 | 1.23 | **.015** |
| | | Trunk fat mass[1] (n = 27,686) | 1.17 | **5.47e-05** | 1.10 | **.080** | 1.26 | **5.16e-05** |
| | | Trunk tissue fat percentage[1] (n = 33,021) | 1.23 | **3.76e-07** | 1.17 | **.008** | 1.30 | **6.63e-06** |
| | | Visceral adipose tissue mass[1] (n = 27,530) | 1.19 | **5.99e-05** | 1.11 | **.049** | 1.47 | **3.00e-06** |
| | | Visceral adipose tissue volume[1] (n = 27,530) | 1.19 | **5.98e-05** | 1.11 | **.049** | 1.47 | **2.99e-06** |

(*continued*)

## Supplementary Table S2. Continued

| Measure of Adiposity | | | Association with Psoriasis: Both Sexes (n = 336,806) Standardized OR | *P*-Value | Males (n = 155,775) Standardized OR | *P*-Value | Females (n = 180,714) Standardized OR | *P*-Value |
|---|---|---|---|---|---|---|---|---|
| Other | Abdominal MRI measures | Weight to muscle ratio (n = 27,448) | 1.22 | **2.20e-05** | 1.22 | **.029** | 1.23 | **2.78e-04** |
| | | Muscle fat infiltration (n = 27,399) | 1.18 | **2.57e-05** | 1.12 | .073 | 1.24 | **4.52e-05** |

Abbreviations: DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.

Presented is association between measures of adiposity and psoriasis (5186 cases, defined using self-reported questionnaire and hospital episode summary data) in unrelated White British subset of UK Biobank participants in (i) both sexes (standardized OR adjusted for age and sex as covariates), (ii) males (standardized OR adjusted for age as a covariate), and (iii) females (standardized OR adjusted for age as a covariate). Standardized OR is reported as per 1 SD change in the exposure (adiposity measure). Statistically significant results ($P < .05$) are shown in bold.

[1]Central adiposity measures.

## Supplementary Table S3. Associations between Standardized Adiposity Measures and Psoriasis Risk

| Subgroup | Measures of Total Body Fat: Percentage Body Fat OR | *P*-Value | Measures of Body Fat Distribution: Waist-to-Hip Ratio OR | *P*-Value |
|---|---|---|---|---|
| HLA-C*06:02 positive (n = 57,527) | 1.25 | **4.01e-21** | 1.23 | **6.76e-21** |
| HLA-C*06:02 negative (n = 278,962) | 1.32 | **2.51e-48** | 1.28 | **4.43e-46** |

Participants carrying 1 or more *HLA-C*06:02* allele were classified as *HLA-C*06:02* positive, and participants with no copies were classified as *HLA-C*06:02* negative. Associations were examined in unrelated White British subset of UK Biobank participants, after standardization of adiposity measures and adjustment for age and sex. Statistically significant results ($P < .05$) are shown in bold.

**Supplementary Table S4. Interaction between HLA-C*06:02 Status and Standardized Adiposity Measures on Psoriasis Risk (Psoriasis Definition Including Cases Defined Using Primary Care Data as a Data Source)**

| | Measures of Total Body Fat | | Measures of Body Fat Distribution | |
|---|---|---|---|---|
| | Percentage Body Fat | | Waist-to-Hip Ratio | |
| Interaction Term | Beta | *P*-Value | Beta | *P*-Value |
| HLA-C*06:02 status | 0.019 | .385 | −0.088 | **4.35e-05** |

Participants carrying 1 or more *HLA-C*06:02* allele were classified as *HLA-C*06:02* positive, and those with no copies were classified as *HLA-C*06:02* negative. Interaction was examined in unrelated White British subset of UK Biobank participants, after standardization of adiposity measures and adjustment for age and sex. Statistically significant results ($P < .05$) are shown in bold.

**Supplementary Table S5. Interaction between HLA-C*06:02 Status and Standardised Adiposity Measures on Psoriasis Risk (Psoriasis Definition Excluding Cases Defined Using Primary Care Data as a Data Source)**

| | Measures of Total Body Fat | | Measures of Body Fat Distribution | |
|---|---|---|---|---|
| | Percentage Body Fat | | Waist-to-Hip Ratio | |
| Interaction Term | Beta | *P*-Value | Beta | *P*-Value |
| HLA-C*06:02 status | 0.053 | .065 | −0.138 | 6.73e-07 |

Participants carrying 1 or more *HLA-C*06:02* allele were classified as *HLA-C*06:02* positive, and those with no copies were classified as *HLA-C*06:02* negative. Interaction was examined in unrelated White British subset of UK Biobank participants (5186 cases, defined using self-reported questionnaire and hospital episode summary data), after standardization of adiposity measures and adjustment for age and sex. Statistically significant results ($P < .05$) are shown in bold.

**Supplementary Table S6. Associations between Standardized Adiposity Measures and Psoriasis Risk (Psoriasis Definition Excluding Cases Defined Using Primary Care Data as a Data Source)**

| | Measures of Total Body Fat | | Measures of Body Fat Distribution | |
|---|---|---|---|---|
| | Percentage Body Fat | | Waist-to-Hip Ratio | |
| Subgroup | OR | *P*-Value | OR | *P*-Value |
| HLA-C*06:02 positive | 1.33 | **1.10e-22** | 1.29 | **1.77e-20** |
| HLA-C*06:02 negative | 1.44 | **4.22e-42** | 1.36 | **1.07e-36** |

Participants carrying 1 or more *HLA-C*06:02* allele were classified as *HLA-C*06:02* positive, and those with no copies were classified as *HLA-C*06:02* negative. Associations were examined in unrelated White British subset of UK Biobank participants (5186 cases, defined using self-reported questionnaire and hospital episode summary data), after standardization of adiposity measures and adjustment for age and sex. Statistically significant results ($P < .05$) are shown in bold.

**Supplementary Table S7. Interaction between Psoriasis Polygenic Risk and Standardized Adiposity Measures on Psoriasis Risk**

| | | Measures of Total Body Fat | | Measures of Body Fat Distribution | |
|---|---|---|---|---|---|
| | | Percentage Body Fat | | Waist-to-Hip Ratio | |
| Interaction Term | | Beta | *P*-Value | Beta | *P*-Value |
| Psoriasis polygenic risk score (GWS) | Including HLA-C*06:02 | −0.009 | .314 | −0.019 | **.047** |
| | Excluding HLA-C*06:02 | −0.020 | .066 | 0.015 | .141 |

Abbreviation: GWS, genome-wide significant.

A psoriasis polygenic risk score was derived from independent loci from GWAS meta-analysis (Dand et al, 2025) with and without *HLA-C*06:02*. Interaction was examined in unrelated White British subset of UK Biobank participants. Adiposity measures were standardized and adjusted for age and sex. Statistically significant results ($P < .05$) are shown in bold.

**Supplementary Table S8. Interaction between Psoriasis Polygenic Risk and Standardized Adiposity Measures on Psoriasis Risk (Psoriasis Definition Excluding Cases Defined Using Primary Care Data as a Data Source)**

| | | Measures of Total Body Fat | | Measures of Body Fat Distribution | |
|---|---|---|---|---|---|
| | | Percentage Body Fat | | Waist-to-Hip Ratio | |
| Interaction Term | | Beta | *P*-Value | Beta | *P*-Value |
| Psoriasis polygenic risk score (GWS) | Including HLA-C*06:02 | −0.003 | .829 | −0.041 | **.001** |
| | Excluding HLA-C*06:02 | −0.027 | .058 | 0.003 | .828 |

Abbreviation: GWS, genome-wide significant.

Psoriasis polygenic risk score was derived from independent loci from GWAS meta-analysis (Dand et al, 2025) with and without *HLA-C*06:02*. Interaction was examined in unrelated White British subset of UK Biobank participants (5186 cases, defined using self-reported questionnaire and hospital episode summary data), after standardization of adiposity measures and adjustment for age and sex. Statistically significant results ($P < .05$) are shown in bold.

**Supplementary Table S9. MR Examining the Causal Relationship between Waist-to-Hip Ratio and Psoriasis in *HLA-C*06:02*—Stratified Subgroups and PRS Quartiles**

| Cohort | Analysis | Waist-to-Hip Ratio |
|---|---|---|
| (A) Whole cohort | IVW estimate | 0.211 |
| | *P*-value | **.011** |
| (Bi) HLA-C*06:02 positive | IVW estimate | 0.301 |
| | *P*-value | .12 |
| (Bii) A*06:02 negative | IVW estimate | 0.127 |
| | *P*-value | .351 |
| (Ci) Q1 PRS | IVW estimate | 0.415 |
| | *P*-value | .242 |
| (Cii) Q2 PRS | IVW estimate | 0.115 |
| | *P*-value | .702 |
| (Ciii) Q3 PRS | IVW estimate | 0.151 |
| | *P*-value | .601 |
| (Civ) Q4 PRS | IVW estimate | 0.231 |
| | *P*-value | .192 |

Abbreviations: IVW, inverse-variance–weighted; MR, Mendelian randomization; PRS, polygenic risk score.

Presented are 1-sample MR IVW causal estimates for the effect of genetic predictors of waist-to-hip ratio on psoriasis in (i) full cohort (n = 336,806, psoriasis cases = 5194), (ii) *HLA-C*06:02*–positive participants, (iii) *HLA-C*06:02*–negative participants, and (iv) PRS quartiles excluding *HLA-C*06:02* (Q1, lowest psoriasis genetic risk; Q4, highest psoriasis genetic risk). The genetic instrument for waist to hip ratio was derived from a published GWAS meta-analyses from the GIANT consortium (Shungin et al, 2015). Participants carrying 1 or more *HLA-C*06:02* allele were classified as *HLA-C*06:02* positive, and those with no copies were classified as *HLA-C*06:02* negative. Statistically significant results ($P < .05$) are shown in bold.

## Supplementary Table S10. MR Examining the Causal Relationship between Waist-to-Hip Ratio and Psoriasis (Definition Excluding Cases Defined Using Primary Care Data as a Data Source) in HLA-C*06:02−Stratified Subgroups and PRS Quartiles

| Cohort | Analysis | Waist-to-Hip Ratio |
|---|---|---|
| Whole cohort | IVW estimate | 0.401 |
| | *P*-value | **.022** |
| HLA*06:02 positive | IVW estimate | 0.511 |
| | *P*-value | **.019** |
| HLA*06:02 negative | IVW estimate | 0.261 |
| | *P*-value | .29 |
| Q1 PRS | IVW estimate | 0.46 |
| | *P*-value | .301 |
| Q2 PRS | IVW estimate | 0.102 |
| | *P*-value | .57 |
| Q3 PRS | IVW estimate | 0.598 |
| | *P*-value | .052 |
| Q4 PRS | IVW estimate | 0.276 |
| | *P*-value | .258 |

Abbreviations: IVW, inverse-variance−weighted; MR, Mendelian Randomization; PRS, polygenic risk score.

Table presents a 1-sample MR IVW causal estimates for the effect of genetic predictors of waist-to-hip ratio on psoriasis in (i) full cohort (n = 336,806, psoriasis cases = 5194), (ii) HLA-C*06:02−positive participants, (iii) HLA-C*06:02−negative participants, (iv) PRS quartiles (Q1, lowest psoriasis genetic risk; Q4, highest psoriasis genetic risk). The genetic instrument for waist-to-hip ratio was derived from a published GWAS meta-analyses from the GIANT consortium (Shungin et al, 2015). Participants carrying 1 or more HLA-C*06:02 allele were classified as HLA-C*06:02 positive, and those with no copies were classified as HLA-C*06:02 negative. Statistically significant results ($P < .05$) are shown in bold.