Uterine fibroids show evidence of shared genetic architecture with blood pressure traits

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Uterine leiomyomata (fibroids, UFs) are common, benign tumors in females, having an estimated prevalence of up to 80%. They are fibrous masses growing within the myometrium leading to chronic symptoms like dysmenorrhea, abnormal uterine bleeding, anemia, severe pelvic pain, and infertility. Hypertension (HTN) is a common risk factor for UFs, though less prevalent in premenopausal individuals. While observational studies have indicated strong associations between UFs and HTN, the biological mechanisms linking the two conditions remain unclear. Understanding the relationship between HTN and UFs is crucial because UFs and HTN lead to substantial comorbidities adversely impacting female health. Identifying the common underlying biological mechanisms can improve treatment strategies for both conditions. To clarify the genetic and causal relationships between UFs and BP, we conducted a bidirectional, two-sample Mendelian randomization (MR) analysis and evaluated the genetic correlations across BP traits and UFs. We used data from a multi-ancestry genome-wide association study (GWAS) meta-analysis of UFs (44,205 cases and 356,552 controls), and data from a cross-ancestry GWAS meta-

analysis of BP phenotypes (diastolic BP [DBP], systolic BP [SBP], and pulse pressure [PP], N=447,758). We evaluated genetic correlation of BP phenotypes and UFs with linkage disequilibrium score regression (LDSC). LDSC results indicated a positive genetic correlation between DBP and UFs (R_g=0.132, $p<5.0x10^{-5}$), and SBP and UFs (R_g=0.063, $p<2.5x10^{-2}$). MR using UFs as the exposure and BP traits as outcomes indicated a relationship where UFs increases DBP (odds ratio [OR]=1.20, $p<2.7x10^{-3}$). Having BP traits as exposures and UFs as the outcome showed that DBP and SBP increase risk for UFs (OR =1.04, $p<2.2x10^{-3}$; OR=1.00, $p<4.0x10^{-2}$; respectively). Our results provide evidence of shared genetic architecture and pleiotropy between HTN and UFs, suggesting common biological pathways driving their etiologies. Based on these findings, DBP appears to be a stronger risk factor for UFs compared to SBP and PP.

Keywords: uterine fibroids; hypertension; Mendelian randomization; genetic correlation; women's health

1. Introduction

Uterine leiomyomata (fibroids, UFs) is a highly prevalent and genetically complex disease.[1,2] UFs are the most common benign tumors in premenopausal individuals, having an estimated cumulative prevalence of up to approximately 80%, with Black women being up to three times more likely to develop UFs than White women.[2,3] Black women also experience earlier onset, more severe symptoms, greater challenges in accessing timely and effective treatment, and higher rates of surgical interventions like hysterecomy.[3,4] Uterine fibroids are characterized by the presence of fibrous masses growing in and on the smooth muscle of the uterus. People with UFs present symptoms of dysmenorrhea, heavy or abnormal uterine bleeding, and anemia, and pelvic pain.[2] Uterine fibroid symptoms have substantial overlap with other gynecologic conditions, such as ovarian cysts, endometriosis, and menstrual disorders.[1] Inevitably, the overlap in symptomology between these conditions present challenges for UFs to be accurately and timely diagnosed and treated. Studies report that up to 41% of females with UFs visit two or more providers and experience a three to five year deferment in treatment of UFs.[4,5] Nonsurgical and fertility-preserving interventions for UFs are limited; treatment strategies commonly aim at controlling symptoms or surgeries to remove the affected reproductive tissues/organs altogether. Furthermore, myomectomy surgeries are not 100% effective as reoccurrence of UFs occurs in approximately 59% of patients.[6,7] As a consequence, UFs result in over a $10-billion annual national economic burden due to direct and indirect costs associated with doctors office visits, treatments, hospitalizations, surgeries, and wage losses.[8]

UFs are associated with many comorbidities, including hypertension (HTN), which also disproportionately affects Black women. HTN is a major risk factor associated with increasing risk of UFs. Individuals with UFs are at 1.44 fold increased risk of having HTN.[9] For complex diseases such as UFs and HTN, multiple factors influence their onset, progression, and severity, with health inequities further compounding these risks. The most recent published GWAS estimated single nucleotide polymorphism (SNP)-heritability of UFs to be 13%, which is much lower than pedigree-based heritability estimates ranging between 26 and 69%, suggesting that many factors, including social determinants of health, are involved in UFs development and are not fully captured by GWAS.[10–13]

Although there are many epidemiological studies indicating strong associations between UFs and HTN, the origins and links between the two conditions remain poorly understood. Emerging evidence suggests that females with treated HTN are at a reduced risk of UFs than those with untreated HTN.[14,15] However, these studies are not without limitations, such as collider bias, selection bias, and possible incomplete covariate assessment, reducing their reliability. The limitations of these observational studies underscore the need for more robust methodologies, such as Mendelian randomization, which can better account for confounding factors and help elucidate causal relationships.

Elucidating the shared genetic architecture across UFs and HTN can help capture the biological factors contributing to disease risk. Additionally, further research is needed to determine whether these conditions are causes or consequences of one another, or perhaps arising in part from some common causes. Our study aims to clarify the genetic correlations and pleiotropy of HTN and UFs. To help clarify the potential causal association between UFs and HTN, we conducted a Mendelian randomization analysis and evaluated the genetic correlations using data from two large, multi-ancestry UFs and blood pressure (BP) trait GWAS meta-analyses.

2. Methods

2.1 *Study populations*

We used cross-ancestry, meta-analyzed uterine fibroid GWAS summary statistics from an unpublished study as well as summary statistics from a cross-ancestry GWAS meta-analysis of BP phenotypes (including diastolic BP [DBP], systolic BP [SBP], and pulse pressure[PP], [N = 447,758]).[16–18] The UFs multi-ancestry meta-analysis included diverse cohorts of female participants (with the inclusion of individuals having African/Black, European/White, and Asian ancestry or self-reported race) who were 18 years of age or older from BioVU, eMERGE, All of Us, Coronary Artery Risk Development in Young Adults, Black Women's Health Study, FinnGen, and Biobank Japan[18–25]. The BP multi-ancestry meta-analysis included cohorts of individuals in the Million Veteran Program and UK Biobank. The BP meta-analysis also included people having African/Black, European/White, and Asian ancestry or self-reported race. To ensure independent meta-analysis summary statistics for BP and UFs, summary statistics from UK Biobank were excluded from the UFs meta-analysis to avoid overlapping and 58,832 cases and 295,991 controls samples remained.

2.2 *Linkage disequilibrium score regression analysis*

With the GWAS summary statistics for UFs and BP traits, we conducted Linkage Disequilibrium Score Regression (LDSC) analyses to assess pairwise genetic correlations and estimate heritability.[26] Summary statistics were filtered under the following default parameters: imputation quality > 0.9, minor allele frequency (MAF) between 0.01 and 0, strand ambiguous SNPs, SNPs with duplicated 'rs' numbers, multi-allelic variants, insertion/deletions were removed as determined by the LDSC program. Alleles were merged with the HapMap 3 reference panel and LD scores were precomputed from 1000 Genomes European GWAS data.[27,28]

2.3 *Bidirectional, two-sample mendelian randomization*

Bidirectional, two-sample Mendelian randomization (MR) was performed with the "TwoSampleMR" R package (version 0.5.7).[29] Using the MR approach, we evaluated the relationships between UFs and BP traits. MR uses genetic variants robustly associated with exposures of interest as genetic instrumental variables to estimate the causal and unbiased association between the exposure with the outcome. The MR approach assumes the following: (1) the genetic instrument is strongly associated with the trait; (2) the genetic instrument only affects the outcome via the trait; and (3) the genetic instrument is not associated with confounders of the exposure-outcome association.[30] Bidirectional MR allows users to investigate the direction of the relationship between two phenotypes (e.g., determining if HTN is a cause or a consequence of UFs). The genetic instruments for the analysis were selected from the meta-analyzed summary-level data of BP traits and UFs by linkage disequilibrium clumping of genome-wide significant SNPs ($p<5x10^{-8}$) with an r^2 threshold of 0.01. The inverse variance weighted (IVW) method was utilized to obtain initial estimates of the associations. In addition to the standard IVW Mendelian randomization estimate, we used MR-Egger to detect directional pleiotropy and F-statistics were calculated to assess genetic instrument strength. All F-statistics of genetic instruments used in the analysis were >29.

2.4 *Functional annotation and gene set analysis*

The Functional Mapping and Annotation (FUMA) is a web-based tool that analyzes GWAS summary statistics in various post-GWAS analysis[31]. We used FUMA to conduct pathway analysis of the UFs genetic instruments used for MR. Gene mapping of SNPs present in the genetic instrument was completed using the SNP2GENE process. The UFs GWAS summary statistics were used as the GWAS input file and the UFs genetic instrument file was input as pre-defined independent lead SNPs. We utilized default parameters for SNP2GENE and opted out of the identification of additional independent lead SNPs. After the SNPs were annotated and mapped to their respective genes, we used the GENE2FUNC function, under default parameters, to obtain insight of the biological mechanisms of our prioritized gene set. GENE2FUNC uses biological information from multiple databases for each gene annotated in SNP2GENE to identify biological pathways associated with the gene set.

3. Results

3.1 *Genetic correlation across uterine fibroids and blood pressure traits*

To determine whether UFs and BP associations are due to shared genetic architecture or arise from independent genetic contributions to risk, we first used genetic correlation analysis. LDSC results (Table 1) indicated a positive genetic correlation between DBP and UFs ($R_g = 0.132$, $p < 5.0x10^{-5}$), and SBP and UFs ($R_g = 0.063$, $p < 2.5x10^{-2}$ 0.025). Genetic correlation between pulse pressure and UFs was nonsignificant ($R_g = 0.006$, $p > 0.050$). Ancestry-stratified analysis of European/White cohort displayed a similar trend where significant positive genetic correlations estimated between DBP and UFs (R_g= 0.114, $p < 5.2 \times 10^{-6}$) and SBP and UFs (R_g= 0.08, $p < 1.1 \times 10^{-3}$). Genetic correlations of UFs and BP traits in the African/Black cohort were greatly inflated, had large standard errors, and were therefore inconclusive and omitted.

Table 1: LDSC Results of Uterine Fibroids and Blood Pressure Traits. This table depicts results of genetic correlations of uterine fibroids and blood pressure traits. There were positive genetic correlations between DBP and UFs and SBP and UFs. Multi-Ancestry: includes results from GWAS summary statistics of individuals of African/Black, European/White, and Asian ancestry or self-reported race. European/White: includes results from GWAS summary statistics of individuals of European/White ancestry or self-reported race only. DBP: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.

	Multi-Ancestry		**European/White**	
	Genetic Correlation (R_g)	p-value	Genetic Correlation (R_g)	p-value
DBP	0.132	$5.0x10^{-5}$	0.114	5.2×10^{-6}
SBP	0.063	$2.5x10^{-2}$	0.080	1.1×10^{-3}
PP	0.006	0.830	0.011	0.669

3.2 *Assessment of potential causal associations between uterine fibroids and blood pressure traits using bidirectional, two-sample mendelian randomization*

Having UFs as the exposure variable and BP traits as the outcomes indicated a moderate, positive relationship between UFs and DBP (odds ratio [OR] = 1.20, 95% confidence interval [CI]: 1.08-1.32, $p < 2.7x10^{-3}$) (Table 2). SBP and PP as outcomes and did not provide significant results. Using BP traits as exposure variables and UFs as the outcome showed that DBP increases risk for UFs (OR = 1.04, 95% CI: 1.01-1.06, $p < 2.2x10^{-3}$) (Table 2). With DBP as the exposure, a significant MR Egger

regression p-value ($p < 3.8x10^{-2}$) indicated horizontal pleiotropy in the analysis. Leave-one-out sensitivity analysis depicted that the DBP IVW estimate was largely influenced by a single SNP, rs78378222 with DBP as the exposure. Excluding SNP rs78378222 reduced the IVW OR estimate by 0.08 (OR = 1.12, 95% CI: 1.01-1.22, $p < 4.4x10^{-2}$) with DBP as the outcome (Table 3). A similar change in IVW estimate was observed with excluding SNP rs78378222 (OR=1.02, 95% CI: 1.01-1.04, $p < 2.8x10^{-3}$) with DBP as exposure and UFs as outcome and there was no horizontal pleiotropy (MR egger p=0.52).

Table 2. Bidirectional, Two-Sample Mendelian Randomization Results of Uterine Fibroids and Blood Pressure Traits. There were significant relationships between uterine fibroids and systolic blood pressure with systolic blood pressure as the exposure variable. There was a bidirectional relationship between uterine fibroids and diastolic blood pressure. OR: odds ratio; SE: standard error; Egger p-value: test for horizontal pleiotropy.

Exposure	Outcome	No. of Genetic Instruments	Mendelian Randomization			
			IVW OR	SE	p-value	Egger p-value
Uterine Fibroids	Diastolic Blood Pressure	108	1.20	0.061	$2.7x10^{-3}$	0.180
	Systolic Blood Pressure	110	1.15	0.111	0.220	0.892
	Pulse Pressure	110	0.91	0.089	0.310	0.289
Diastolic Blood Pressure	Uterine Fibroids	99	1.04	0.012	$2.2x10^{-3}$	$3.8x10^{-2}$
Systolic Blood Pressure		407	1.00	0.002	$4.0x10^{-2}$	0.400
Pulse Pressure		411	0.99	0.004	$9.8x10^{-3}$	0.090

Table 3. Changes in Inverse Variance Weighted Estimate After Removing SNP rs78378222 in Genetic Instruments. The IVW estimates decreased for diastolic blood pressure after removing SNP rs78378222 from the genetic instruments. Pleiotropy originally detected by the MR Egger test was eliminated. OR: odds ratio; SE: standard error; Egger p-value: test for horizontal pleiotropy.

Exposure	Outcome	No. of Genetic Instruments	Mendelian Randomization			
			IVW OR	SE	p-value	Egger p-value
Uterine Fibroids	Diastolic Blood Pressure	107	1.12	0.055	$4.4x10^{-2}$	0.433
	Systolic Blood Pressure	109	1.20	0.113	0.098	0.487
	Pulse Pressure	109	1.01	0.082	0.524	0.347
Diastolic Blood Pressure	Uterine Fibroids	98	1.02	0.008	$2.8x10^{-3}$	0.524
Systolic Blood Pressure		407	1.00	0.002	$3.5x10^{-2}$	0.400
Pulse Pressure		410	0.99	0.003	0.061	0.773

3.3 *FUMA pathway analysis*

We used the UFs genetic instruments from the MR analysis as the pre-defined lead SNPs supplementary input file for FUMA. FUMA identified 22 biological pathways, derived from Canonical Pathways, that were associated with our prioritized gene set (Table 4)[32]. There were multiple overlapping genes associated with *TP53* mediation, *P53* regulation and signaling, and cellular senescence dysfunction. Other overlapping genes are present in pathways related to androgen biosynthesis, cell cycle, DNA damage responses, and breast cancer. FUMA also identified genes previously reported from studies present in the GWAS catalog that are associated with DBP, SBP, and PP (Table 5)[33]. There were 19, 35, and 22 genes in our gene list that are significantly associated with DBP, SBP, and PP; respectively.

Table 4. FUMA Results of Biological Pathways Significantly Associated with Our Prioritized Gene List. The gene list was created from the uterine fibroid genetic instruments used for Mendelian randomization. N: number of genes; Adjusted p-value: p-value after correcting for multiple comparisons.

Gene Set	N	Adjusted p-value	Genes
Reactome Regulation of TP53 Activity Through Methylation	5	1.08×10^{-2}	*MDM4, ATM, TP53, CHEK2, EP300*
WP Glioblastoma Signaling Pathways	8	1.55×10^{-2}	*PIK3C2B, MDM4, PDGFRA, CDKN1A, ATM, FOXO1, TP53, EP300*
Biocarta G2 Pathway	5	1.55×10^{-2}	*CDKN1A, ATM, TP53, CHEK2, EP300*
PID HDAC Class III Pathway	5	1.55×10^{-2}	*CDKN1A, SIRT3, FOXO1, TP53, EP300*
WP miRNAs Involved in DNA Damage Response	4	3.46×10^{-2}	*CDKN1A, ATM, RAD52, TP53*
WP Male Infertility	9	3.67×10^{-2}	*PARP1, CLOCK, ESR1, CYP17A1, ATM, YBX2, HORMAD2, TCN2, EP300*
Reactome Sumoylation	10	3.67×10^{-2}	*PARP1, DNMT3A, THRB, ESR1, NCOA2, RAD52, TP53, EP300, L3MBTL2, RANGAP1*
Biocarta BLK3 Pathway	3	3.67×10^{-2}	*ATM, TP53, CHEK2*
PID P53 Regulation Pathway	6	3.67×10^{-2}	*MDM4, ATM, NEDD8, TP53, CHEK2, EP300*
Reactome RHO GTPases Activate PAKs	4	3.67×10^{-2}	*CDC42, MYH11, MYH10, NF2*
Biocarta ATM Pathway	4	3.67×10^{-2}	*CDKN1A, ATM, TP53, CHEK2*
Biocarta P53 Hypoxia Pathway	4	3.67×10^{-2}	*CDKN1A, ATM, TP53, EP300*
WP ATM Signaling Pathway	5	4.43×10^{-2}	*MDM4, CDKN1A, ATM, TP53, CHEK2*
PID ERA Genomic Pathway	6	4.68×10^{-2}	*GREB1, ESR1, NCOA2, NEDD8, XBP1, EP300*

WP Breast Cancer Pathway	9	4.68×10^{-2}	*WNT4, PARP1, KIT, CDKN1A, ESR1, WNT2, FGF8, ATM, TP53*
WP NAD Metabolism in Oncogene Induces Senescence and Mitochondrial Dysfunction Associated Senescence	4	4.68×10^{-2}	*PARP1, SIRT3, SLC2A4, TP53*
Reactome G1 S DNA Damage Checkpoints	6	4.68×10^{-2}	*MDM4, CDKN1A, PSMD13, ATM, TP53, CHEK2*
Reactome Androgen Biosynthesis	3	4.68×10^{-2}	*POMC, SRD5A3, CYP17A1*
Reactome Regulation of FOXO Transcriptional Activity By Acetylation	3	4.68×10^{-2}	*SIRT3, FOXO1, EP300*
KEGG P53 Signaling Pathway	6	4.82×10^{-2}	*MDM4, CDKN1A, SESN1, ATM, TP53, CHEK2*
WP DNA Damage Response	6	4.82×10^{-2}	*CDKN1A, SESN1, ATM, RAD52, TP53, CHEK2*
Reactome Circadian Clock	6	4.82×10^{-2}	*USP46, CLOCK, NCOA2, BTRC, ELOVL3, EP300*

Table 5. FUMA Results of Genes Reported in the GWAS Catalog Significantly Associated with Blood Pressure Traits. The gene list was created from the uterine fibroid genetic instruments used for Mendelian randomization. N: number of genes; Adjusted p-value: p-value after correcting for multiple comparisons.

Gene Set	N	Adjusted p-value	Genes
Diastolic Blood Pressure	19	1.69×10^{-2}	*DNM3, MDM4, OCIAD2, PDLIM5, HSPA4, ESR1, RGS17, PAX2, BTRC, ARL3, CYP17A1, CNNM2, NT5C2, SLK, SORCS3, SLC2A4, TP53, ZNRF3, TNRC6B*
Systolic Blood Pressure	35	2.17×10^{-8}	*RNF207, WNT4, DNM3, MDM4, ITPR1, TEC, SLAIN2, OCIAD1, OCIAD2, PDGFRA, TERT, ESR1, RBPMS, KANK1, PAX2, FGF8, SUFU, ARL3, WBP1L, CYP17A1, AS3MT, CNNM2, NT5C2, RPEL1, SLK, SORCS3, ARL14EP, RAD52, ITGA11, SLC2A4, ZNF208, TTC28, ZNRF3, C22orf31, TNRC6B*
Pulse Pressure	22	2.06×10^{-3}	*RNF207, TEC, SLAIN2, CHIC2, PDGFRA, PDLIM5, CDKN1A, ESR1, TRIM8, ARL3, WBP1L, CYP17A1, CNNM2, NT5C2, RPEL1, SLK, SORCS3, WT1, MYH11, SLC2A4, TP53, TNRC6B*

4. Discussion

Our study utilized summary statistics from the largest multi-ancestry UFs GWAS meta-analysis to date and a BP trait multi-ancestry GWAS meta-analysis with 447,758 individuals.[16,17] Here we report that UFs and BP have significant, positive genetic correlations and there is a bidirectional, causal relationship between UFs and BP traits. We provide evidence that genetic predisposition to UFs increases BP. We also report novel associations between DBP and UFs.

Blood pressure is a modifiable risk factor for cardiovascular disease. Approximately 20% of reproductive-aged female individuals have high BP worldwide.[34,35] HTN is often underdiagnosed in female populations, and less than 25% have this condition under control.[36] Approximately one in five deaths in females is attributed to high BP in the United States.[37] There are notable parallels between the disparities of HTN and UFs. For both conditions, Black women have the highest prevalence, the most severe symptoms, and have the poorest health outcomes.[4,5,34] So far, the epidemiological relationship between UFs and BP has been mainly evaluated by retrospective and observational studies. Some of these studies have identified that individuals being treated for HTN (specifically with angiotensin-converting enzyme [ACE] inhibitors and beta adrenoceptor antagonist [beta blockers]) are at reduced risk of UFs, implicating the renin angiotensin pathway and angiogenic processes in UFs pathology.[14,38] Yet, ACE inhibitors are prescribed less to Black patients due to poor BP responses to treatments.[39] Combination therapies that include ACE inhibitors and a calcium channel agonist or diuretic are highly effective at reducing BP in Black patients.[40] Currently, there is one U.S. Food and Drug Administration (FDA) approved combination therapy for UFs.[41,42] The causal associations identified in our study may aid in discovering new targets for developing more combination therapies for UFs.

In this study, the LDSC indicated a positive genetic correlation between UFs and SBP, UFs and DBP, but not UFs and PP, which is consistent with findings from prior research[9,43]. UFs and DBP were more correlated than SBP and UFs, implying that DBP and UFs have a stronger, common underlying genetic background. A similar trend was also observed in the MR data. In both directions, DBP exhibited a stronger relationship with UFs than SBP. SBP and DBP have differing biological mechanisms driving their pathologies. SBP is largely influenced by arterial stiffening. Elevated and high SBP are indicative of decreased compliance of the arteries, which can be attributed to the aging process or arteriosclerosis[44,45]. Conversely, DBP is a measure of arteriolar peripheral resistance. High DBP is attributed to the thickening of the vascular wall and increased tone of the smooth muscle in the arterioles.[44,46] This causes an increase in the pressure blood exhorts within the arteries the during the diastole. The relationship demonstrated in our results suggests that the shared genetics between UFs, SBP, and DBP are also through different mechanisms.

FUMA provided biological context to this study. Pathways identified by FUMA involve *p53* regulation and signaling, *TP53* mediation, and cellular response to hypoxic stress, all of which are associated with vascular alterations and endothelial dysfunction in hypertension.[47] Furthermore, *TP53* and *p53* are regulators of important cellular processes including DNA repair, cell cycle arrest, cellular senescence, and apoptosis.[48,49] Tumor suppressor genes have been implicated in mediating the induction

of sex hormone-binding globulin and other steroid binding factors and their mutations are associated with increased cancer pathogenesis.[50,51] This suggests that the vascular changes observed in HTN may intersect with the hormonal pathways influencing UFs formation, providing a plausible explanation for the shared genetic mechanisms observed between DBP, SBP, and UFs. Further investigation into the TP53 pathway and its role in both vascular and fibroid pathology could elucidate additional therapeutic targets for managing these conditions.

UFs have been associated with increasing BP in numerous studies.[43,43,52] However, the direction of the relationship remained unclear. Based on the IVW estimate in our study, the causal relationship between BP and UFs is more distinct having UFs as the exposure, suggesting that genetic predisposition to UFs increases risk for HTN. Prior studies showed that individuals with severe and symptomatic fibroids requiring surgical intervention are at higher risk of hypertension.[53] Thus, it is possible that UFs may increase BP over time. UFs depend on uterine arteries for blood supply and uterine angiogenic dysregulation plays an important role in fibroid pathophysiology.[54,55] Genetic alterations, hormonal factors, and hypoxic conditions caused by tumor growth promote angiogenesis within fibroids[56–58]. This vascular remodeling tends to be to be zone specific where more vasculature is present on the superficial layers of fibroids than in deep layers[58]. Similarly, HTN is associated with changes in artery structure and function. The arterial wall is sensitive to changes in tension and stress caused by BP elevation and it is hypothesized that arterial thickening is involved in a positive feedback loop.[59,60] This maladaptation to increased BP may drive subsequent arterial fibrosis and diminishes vascular function. Furthermore, our study demonstrates a positive genetic correlation and causal relationship between DBP and UFs, whereas previous research had only indicated SBP.[61] Interestingly here, the genetic correlation and relationship are stronger between DBP and UFs than SBP. The stronger correlation between DBP and UFs found here suggests that UFs pathophysiology shares more underlying biological mechanisms with DBP than SBP.

This study's major strength is the utilization of highly diverse and large study populations. However, there are some limitations. GWAS of UFs in African and Asian ancestry cohorts are greatly limited. Despite the large overall sample size of our study, the proportion of non-European populations were smaller, limiting the power of ancestry-stratified analyses. Therefore, the ancestry-stratified analysis could not produce reliable results. Future studies should aim to expand GWAS for these groups, particularly given the disparities in HTN and UFs burdens. Also, MR can indicate causal relationships, but results should be validated in larger-scale longitudinal studies and clinical trials. Moreover, future research should also confirm findings by exploring underlying molecular and biological mechanisms. Last, this study relies on GWAS summary statistics from published studies. Other confounding and mediating factors, such as fibroid size and number or oral contraceptive use, could not be taken into consideration.

5. Conclusions

The findings of our study provide evidence for shared genetic architecture across BP traits and UFs risk. Our analysis identified the direction of the relationship between BP and UFs where genetic risk of UFs significantly increases risk for high BP. In addition, risk for UFs influences DBP more than SBP. Clinically, UFs contribute significantly to morbidity and healthcare costs for reproductive-aged females. Accumulating information about the genetic and biological processes driving UFs formation will enhance our understanding of the disease and pave the way for improved therapeutic decisions and personalized treatments.

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Social Determinants of Health and Lifestyle Risk Factors Modulate Genetic Susceptibility for Women's Health Outcomes

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Abstract

Women's health conditions are influenced by both genetic and environmental factors. Understanding these factors individually and their interactions is crucial for implementing preventative, personalized medicine. However, since genetics and environmental exposures, particularly social determinants of health (SDoH), are correlated with race and ancestry, risk models without careful consideration of these measures can exacerbate health disparities. We focused on seven women's health disorders in the All of Us Research Program: breast cancer, cervical cancer, endometriosis, ovarian cancer, preeclampsia, uterine cancer, and uterine fibroids. We computed polygenic risk scores (PRSs) from publicly available weights and tested the effect of the PRSs on their respective phenotypes as well as any effects of genetic risk on age at diagnosis. We next tested the effects of environmental risk factors (BMI, lifestyle measures, and SDoH) on age at diagnosis. Finally, we examined the impact of environmental exposures in modulating genetic risk by stratified logistic regressions for different tertiles of the environment variables, comparing the effect size of the PRS. Of the twelve sets of weights for the seven conditions, nine were significantly and positively associated with their respective phenotypes. None of the PRSs was associated with different ages at diagnoses in the time-to-event analyses. The highest environmental risk group tended to be diagnosed earlier than the low and medium-risk groups. For example, the cases of breast cancer, ovarian cancer, uterine cancer, and uterine fibroids in highest BMI tertile were diagnosed significantly earlier than the low and medium BMI groups, respectively). PRS regression coefficients were often the largest in the highest environment risk groups, showing increased susceptibility to genetic risk. This study's strengths include the diversity of the All of Us study cohort, the consideration of SDoH themes, and the examination of key risk factors and their interrelationships. These elements collectively underscore the importance of integrating genetic and environmental data to develop more precise risk models, enhance personalized medicine, and ultimately reduce health disparities.

Keywords: Polygenic Risk Scores, Social Determinants of Health, Health Disparities, Genetic Risk, Disease Prediction, Women's Health, Breast Cancer, Endometriosis, Ovarian Cancer, Preeclampsia, Uterine Cancer, Uterine Fibroids