Associations between High Blood Pressure and DNA Methylation

Abstract

Background: High blood pressure is one of the major risk factors for cardiovascular disease and is influenced by both environmental and genetic factors. Epigenetic processes such as DNA methylation potentially mediate the relationship between genetic factors, the environment and cardiovascular disease. Despite an increased risk of cardiovascular disease in South Asians, it is not clear whether associations between blood pressure and DNA methylation differ between Europeans and South Asians.

Methods and Findings: In this study, we performed an epigenome-wide association study and differentially methylated region analysis to identify DNA methylation sites and regions that were associated with systolic blood pressure, diastolic blood pressure and hypertension. We analyzed samples from 364 European and 348 South Asian men from the Southall and Brent REvisited cohort, measuring DNA methylation from blood using the Illumina Infinium® HumanMethylation450 BeadChip. One CpG site was found to be associated with DBP in trans-ancestry analyses (i.e. both ethnic groups combined), while in Europeans seven CpG sites were associated with DBP. No associations were identified between DNA methylation and either SBP or hypertension. Comparison of effect sizes between South Asian and European EWAS for DBP, SBP and hypertension revealed little agreement between analyses. DMR analysis identified several DMRs including regions with known relationships with CVD and its risk factors.

Conclusion: This study identified differentially methylated sites and regions associated with blood pressure and revealed ethnic differences in these associations. These findings may uncover new molecular pathways which may explain differences in disease risk experienced by South Asians.

Keywords: Cardiovascular disease; DNA methylation; Epigenetics; Hypertension; Trans-ancestry

Introduction

High blood pressure (BP) results from abnormalities in the control systems that normally regulate blood pressure [1]. It is one of the strongest risk factors for cardiovascular disease (CVD) which is the leading cause of death worldwide [2,3]. People of South Asian descent have increased risk of CVD compared to Europeans [4,5]. For example, in South Asians living in the United Kingdom, death rate from stroke is between 20% and 25% greater than the rest of the population [6]. It is also established that associations between SBP or DBP and stroke are stronger in South Asians than Europeans [4]. DNA methylation is an example of an environmentally responsive, mitotically stable, epigenetic mark that is associated with biological processes leading to high blood pressure and stroke [7-9]. Candidate gene analysis in cell-line and animal studies has demonstrated a role of DNA methylation in the
pathogenesis of hypertension [10-14]. For one of these genes, HSD11B2, methylation has also been associated with hypertension in humans [15]. One recent study found associations between systolic and diastolic BP and DNA methylation among participants of European, Hispanic and African American decent [16]. We aimed to identify DNA methylation associated with SBP, DBP and hypertension in peripheral blood of European and South Asian men in data collected using the Infinium HumanMethylation450 (HM450) BeadChip. We planned to analyse all samples together in a trans-ancestry analysis, then to conduct analysis in each ethnic group separately. We hypothesised that BP associated epigenetic marks would differ between South Asian and European groups, highlighting potential mechanisms explaining the disparity in CVD and stroke risk between the two ethnicities.

Methods

Participant’s information

SABRE (Southall and Brent REvisited) is a population-based cohort including 4857 people of European, South Asian and African Caribbean origin aged 40 to 69 living in West London, UK [17]. Peripheral blood samples were collected from the Southall participants at baseline (1988-91) for DNA extraction.

In the current analysis, 800 (400 European and 400 South Asian) samples from the SABRE cohort were randomly selected from available baseline samples of good DNA quality. We lost some samples during quality control procedures and some samples were discarded due to missing information. After exclusion, we remained with 712 (364 European and 348 South Asian) individuals. These individuals did not have known diabetes or coronary heart disease at baseline and were stratified by four-year age group and ethnicity. All individuals were male. The SABRE study predominantly focused on the recruitment of men [17], for that reason epigenetic analyses were restricted to male participants.

Ethnicity in the SABRE cohort was assigned based on grand-parental origins from participant questionnaire. Blood pressure was measured on one occasion (the average of 2 consecutive readings) in the baseline research clinic as described previously [17].

All participants gave written informed consent. Approval for the baseline study was obtained from Ealing, Hounslow and Spelthorne, Parkside and University College London research ethics committees. Characteristics of participants are shown in Table 1.

Traits of interest

We investigated SBP, DBP and hypertension as our traits of interest. Hypertension was defined as occurrence of SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg, or receiving medication for hypertension as described previously [17]. The BP protocol was based on the INTERSALT study protocol [18] and was followed very carefully.

Covariates

Models were adjusted for age (years), body mass index (BMI) (kg/m²), ethnicity (European or South Asian for trans-ancestry analyses), smoking status (never or ever smoking) and social class (manual or non-manual occupation). Age, ethnicity, smoking status and social class of participants were collected from questionnaires. BMI was calculated from clinic measures of height and weight.

DNA methylation and pre-processing

DNA was bisulfite converted using the Zymo EZ DNA Methylation™ kit (Zymo, Irvine, CA). Following conversion, DNA methylation was measured using the HM450 BeadChip in line with standard protocols at the University of Bristol, UK [19].

Samples failing QC (average probe detection p value ≥ 0.01) were repeated and if unsuccessful excluded from further analysis. BeadChip intensity data were converted to β-values using the minfi package [20] in the R statistical programming language.

Methylation beta values range from 0 (no cytosine methylation) to 1 (completely cytosine methylated). Raw beta values were normalised using the Functional Normalisation method of the minfi package [21]. We excluded control probes (n=65), any probes with a detection p-value > 0.05 in more than 5% samples, non-CpG probes, polymorphic probes (defined as SNP-overlapping probes, probes with a SNP at the target CpG site, or probes with a SNP at the base next to the target CpG) and probes with a minor-allele frequency (MAF) ≥ 5%; based on UCSC common SNPs track for dbSNP build 137. We further excluded probes that are considered as cross-hybridizing [22]. We applied this stringent CpG filtering because polymorphic and cross-hybridizing probes can interfere with accurate detection of methylation levels. After excluding these features, 402,331 probes remained for the analysis.

Estimation of cell counts

Cell count estimates were derived using the reference-based Houseman method [23] in the R minfi package [20] using the Reinius et al. dataset as reference [24]. This method estimates the relative proportions of six white blood cell subtypes (CD4+ T-lymphocytes, CD8+ T-lymphocytes, CD8+ T-lymphocytes and NK (natural killer) cells, B-lymphocytes, monocytes and granulocytes).

Statistical Analyses

Epigenome-wide association study (EWAS) analysis

We considered a trans-ancestry analysis as the primary model because this provided maximal statistical power by enabling us to include all participants. Our primary hypothesis was that the potential epigenetic mechanisms of elevated blood pressure would be different across these two ethnicities. However, we postulated that these differences may be in the magnitude of effect at key loci, rather than being completely different loci.

Three sets of EWAS analyses were run to identify CpG sites associated with SBP, DBP or hypertension. Normalised, untransformed beta-values, which are on a scale of 0 (completely unmethylated) to 1 (completely methylated) were utilised. Multiple linear regression models were run to evaluate the association between traits of interest and DNA methylation. Analyses were run for each ethnic subgroup and with all samples combined in a trans-ancestry analysis. To remove potential
batch effects, principal components (PCs) were generated from methylation beta values using Principal Component Analysis (PCA) [25–27]. The first four PCs were included as covariates in each of the EWAS. These PCs were not associated with exposure and captured 27% of the variance.

Two models were run for each trait of interest: i) an unadjusted model and ii) a model adjusted for confounders (age, BMI, ethnicity (where appropriate), smoking status, social class), estimated cell counts and PCs.

The genomic inflation factor (lambda) was computed and Manhattan plots were generated to compare the genome wide distribution of p-values in EWAS. Multiple testing was accounted for using the false discovery rate (FDR) procedure by Benjamini and Hochberg (BH) [21]. CpG sites with FDR-corrected p-value<0.05 were considered to be associated with the trait of interest. We considered the fully adjusted trans-ancestry models as the primary analysis models.

Differentially methylated region analysis

In addition to EWAS analyses, differentially methylated region (DMR) analyses in relation to SBP, DBP and hypertension were conducted separately using the R package DMRcate [28]. In the DMR analysis, normalised, untransformed beta values were used and the models were adjusted for confounders, estimated cell counts and PCs. DMRcate groups associated probes into separate DMRs if the gap between nucleotides is ≥1000 base pairs. P-values of associations were adjusted for multiple testing using the BH method.

Data availability

Data used in these analyses are available from SABRE on request.

Results

Trans-ancestry EWAS analyses

SBP: In the unadjusted EWAS investigating the association between DNA methylation and SBP we identified eight CpG sites with FDR corrected p-value<0.05 (Supplementary Table S1). These CpG sites were cg00669320 near FHL2, cg06192883 in the gene body of MYOSC, cg16867657 near ELOVL2, cg14361627 and cg08097417 near KLF14, cg00494544 in the gene body of PPP1R2, cg24590708 in the gene body of MYOSC and cg22454769 near FHL2. Higher SBP was associated with higher methylation levels at these eight CpG sites. Amongst associated CpG sites, the difference in methylation per unit SBP was 0.03% to 0.08%. After adjustment for potential confounders these associations were markedly attenuated and no longer associated when observing an FDR corrected p-value<0.05 (Supplementary Table S2).

DBP: In the unadjusted EWAS investigating the association between DNA methylation and DBP we identified six CpG sites, with FDR corrected p-value<0.05 (Supplementary Table S3). These sites were cg05575921 in the gene body of AHRR, cg12803068 and cg22132788 in the gene body of MYO1G, cg03636183 in the gene body of F2RL3, cg09935388 in the gene body of GFI1 and cg06355652 near CD59. DBP was associated with both higher and lower methylation levels at these CpG sites and the absolute difference in methylation per unit DBP was 0.01% to 0.26%. After adjustment for potential confounders, the associations identified in the unadjusted EWAS were markedly attenuated and no longer associated when observing an FDR corrected p-value<0.05. However, one additional CpG site (cg07598370 near OR5AP2) was identified in the adjusted EWAS, with FDR corrected p-value<0.05 (Figure 1 and Supplementary Table S4). DBP was associated with lower methylation at this CpG site; 0.1% decrease in DNA methylation per 1 mmHg increase in DBP.

Hypertension: In the unadjusted EWAS investigating the association between DNA methylation and hypertension, we identified three CpG sites, with FDR corrected p-value<0.05 (Supplementary Table S5). These CpG sites are cg00494544 in the gene body of PPP1R2, cg18120259 in the gene body of LOC285548 and cg10461004 near LOC285548. Hypertension was associated with both higher and lower methylation levels at these CpG sites and the absolute difference in methylation was 0.3% to 2.9% between cases and controls. After adjustment for potential confounders, the associations identified in the unadjusted EWAS were markedly attenuated and no longer associated when observing an FDR corrected p-value<0.05 (Supplementary Table S6).

European EWAS

SBP: In both unadjusted and fully adjusted EWAS investigating
the association between SBP and DNA methylation, no CpG sites were associated with SBP after correction for multiple testing (Supplementary Tables S7 and S8).

**DBP:** In the unadjusted EWAS investigating the association between DNA methylation and DBP, we identified eleven CpG sites with FDR corrected p-value<0.05 (Supplementary Table S9). These CpG sites are cg16241714 near CEBPD, cg05575921 in the gene body of AHRR, cg00006122 near C12orf44, cg04751533 in the gene body of AFAP1, cg13799986 in the gene body of TMEM141, cg06726740 in the gene body of CACNA1C, cg05284742 in the gene body of ITPK1, cg06355652 near CDS59, cg04202002 in an intragenic region, cg13691892 near PNPLA7/MRPL41 and cg25648203 in the gene body of AHRR. DBP was associated with both higher and lower methylation levels at these CpG sites and the absolute difference in methylation per unit DBP was 0.02% to 0.4%. In the fully adjusted EWAS, six of the eleven CpG sites: cg16241714, cg00006122, cg04751533, cg13691892, cg13799986 and cg06355652 were identified with FDR corrected p-value<0.05 (Supplementary Table S10). Their direction of association was consistent with the unadjusted EWAS. In addition to these six CpG sites, cg18901940 near MYPN was found with FDR corrected p-value<0.05. DBP was associated with lower methylation at this CpG site; 0.08% decrease in DNA methylation per 1 mmHg increase in DBP (Figures 2, 3 and Supplementary Table S10).

**Hypertension:** In both unadjusted and fully adjusted EWAS investigating the association between hypertension and DNA methylation, no CpG sites were associated with hypertension after correction for multiple testing (Supplementary Tables S11 and S12).

**South Asian EWAS**

**SBP:** In the unadjusted EWAS investigating the association between DNA methylation and SBP, we identified one CpG site (cg07963349 in the gene body of GALR2), with FDR corrected p-value<0.05 (Supplementary Table S13). In the fully adjusted EWAS, this CpG site was no longer associated after multiple corrections but the direction of association was consistent between models (Supplementary Table S14).

**DBP:** In both unadjusted and fully adjusted EWAS investigating the association between DBP and DNA methylation, no CpG site was associated following correction for multiple testing (Supplementary Tables S15 and S16).

**Hypertension:** In both unadjusted and fully adjusted EWAS investigating the association between hypertension and DNA methylation, no CpG site was associated following correction for multiple testing (Supplementary Tables S17 and S18).

The genomic inflation factor, lambda, for all fully adjusted models is provided in Table 2.
Comparison of Effect Sizes between Trans-Ancestry, European and South Asian EWAS

We directly compared the direction and magnitude of associations from the fully adjusted EWAS of SBP, DBP and hypertension between trans-ancestry, Europeans and South Asians in a pairwise comparison. We found moderate consistency between the trans-ancestry and Europeans EWAS (goodness-of-fit R²=0.46, R²=0.48 and R²=0.50 for SBP, DBP and hypertension respectively (Supplementary Figure S1)). The goodness of fit was improved when we compared EWAS of trans-ancestry with South Asians (goodness-of-fit R²=0.48, R²=0.50 and R²=0.56 for SBP, DBP and hypertension respectively (Supplementary Figure S1)). There was little consistency between the EWAS of Europeans and South Asians (goodness-of-fit R²=0 for SBP, DBP and hypertension (Supplementary Figure S1)).

Differentially methylated region analysis

DMR analyses were carried out to identify regions of DNA methylation that were associated with SBP, DBP and hypertension. As in the EWAS analyses, DMR analysis was conducted for the full trans-ancestry group and additionally for European and South Asian sub-groups. Trans-ancestry DMR analysis identified 395 regions (mapped to 325 annotated genes) for SBP, 237 regions (mapped to 160 annotated genes) for DBP and 0 DMRs for hypertension using a FDR-corrected p-value<0.05 (Supplementary Tables S19-S24). Twelve DMRs annotated to genes were common between trans-ancestry SBP and trans-ancestry DBP at FDR p-value<0.05 (Table 3). In Europeans, 313 DMRs for SBP, 58 for DBP and 0 for hypertension were identified using a FDR-corrected p-value<0.05. Nine DMRs annotated to genes were common between European SBP and European DBP at FDR p-value<0.05 (Table 3). In South Asians, 60 DMRs for SBP, 88 DBP and 0 hypertension DMRs were identified using a FDR-

Table 2: Confounder and cell counts adjusted levels of genomic inflation (Lambda).

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<thead>
<tr>
<th></th>
<th>DBP</th>
<th>SBP</th>
<th>Hypertension</th>
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<tbody>
<tr>
<td>Trans-ancestry</td>
<td>1.07</td>
<td>0.94</td>
<td>1.12</td>
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<tr>
<td>European</td>
<td>1.08</td>
<td>1.00</td>
<td>0.92</td>
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<tr>
<td>South Asian</td>
<td>1.00</td>
<td>0.94</td>
<td>0.99</td>
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Table 3: Overlap of DMRs between fully adjusted DMR analysis of SBP and DBP for trans-ancestry, Europeans and South Asians respectively.

<table>
<thead>
<tr>
<th>Overlap for trans-ancestry</th>
<th>Overlap for Europeans</th>
<th>Overlap for South Asians</th>
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<tbody>
<tr>
<td>PRRT1</td>
<td>ARHGEF3</td>
<td>ELL2</td>
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<td>ZNF783</td>
<td>BBS1</td>
<td>PURG,WRN</td>
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<td>TFAP2D</td>
<td>BCORL1</td>
<td>MSR83</td>
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<td>HLX</td>
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<td>ZNF77</td>
<td>SLMO1</td>
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<td>BBS1</td>
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<td>CYFIP1</td>
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<td>BCORL1</td>
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<td>SLMO1</td>
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<td>ARPP-21</td>
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<td>ATP5G3</td>
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<td></td>
<td>CHD4</td>
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<td>TRPS1</td>
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corrected p-value<0.05. Thirty-five DMRs annotated to genes were common between South Asian SBP and South Asian DBP at FDR p-value<0.05 (Table 3).

Known genetic variants in DMRs

Two of the twelve DMRs common in trans-ancestry SBP and DBP analysis, TFAP2D and HLX, contain SNPs previously associated with blood pressure [29,30]. The genetic variant in the PDZD2 DMR was associated with myocardial infarction [30]. HLX was also identified in DMR analysis of SBP and DBP in Europeans (Table 6). PRDM16 was found to be common to SBP and DBP in Europeans its genetic variants were previously associated with dilated cardiomyopathy [31], PRKAG2 was found to be common to SBP and DBP in South Asians, and has been previously associated with hypertrophic cardiomyopathy [32] and chronic kidney disease [33]. Other identified genes previously reported in association to CVD-related GWAS were ELL2 (GWAS of BP [29], insulin [34] and glucose [34]), TRPS1 (GWAS of BP [29]), P1DI (GWAS of stroke [35], lung function [36] and chronic obstructive pulmonary disease [37]) and WIPF1 (GWAS of resting heart rate [38]).

Discussion

We investigated the association between SBP, DBP and hypertension and DNA methylation measured in peripheral blood of European and South Asian men combined and then across individual ethnicities using the HM450 BeadChip array. In the trans-ancestry fully adjusted EWAS, we found DBP was associated with methylation at one CpG site (cg07598370 near ORSAP2) at FDR-corrected p-value<0.05. The genetic variant near the olfactory receptor, family S, subfamily AP, member 2 (ORSAP2) has been reported associated with hematological phenotypes [39] and olfactory receptors regulate blood pressure by the kidney via renal expression [40]. SBP and hypertension were not associated with DNA methylation after adjustment for confounders, estimated cell counts and PCs. EWAS were also conducted in European and South Asian groups separately. In Europeans fully adjusted EWAS, seven CpG sites were associated with DBP with FDR-corrected p-value<0.05. In South Asians fully adjusted EWAS, SBP, DBP and hypertension were not associated with DNA methylation after multiple testing corrections. Several of the initial associations observed in the unadjusted model of DBP were noted to be documented loci responsive to tobacco smoking CpG sites, for example, (cg05575921 [41], cg12803068 [42], cg03636183 [43], cg22132788 [44] and cg09935388 [45]), hence their attenuation on adjustment for smoking was predictable. This highlights the capacity of DNA methylation to index exposure to relevant risk factors.

We found seven CpG sites associated with DBP in Europeans. One CpG site (cg04751533) was in the gene body of AFAP (actin filament-associated protein), AFAP an action-binding and crosslinking protein is enriched in SRC and phorbol ester induced podosomes [46]. Podosomes are specialized plasma-membrane actin-based microdomains and have been suggested to play a role in arterial vessel remodeling [47]. C12orf44 (cg00006122) encodes autophagy-related protein 101 that is also known as ATG101. ATG101 is a newly found important autophagy related protein likewise many other proteins. Autophagy plays a key role in pulmonary vascular remodeling via regulation of apoptosis and hyperproliferation of pulmonary arterial endothelial cells [48]. ATG101 is an essential gene for the initiation of autophagy and may be involved in endothelial cell growth through regulation of autophagy in pulmonary hypertension [48]. CEBPD (cg16241714) encodes CCAAT/enhancer binding protein delta. CEBPD is involved in regulation of apoptosis and cell proliferation and probably acts as tumour suppressor [49]. CD59 (CD59, molecule (CD59 blood group); cg06355652) has been associated with paroxysmal nocturnal hemoglobinuria [50]. Blood coagulation and cell surface receptor signalling are among its biological pathways [51,52]. In apolipoprotein E knockout mice, CD59, slowed down the development of atherosclerotic vulnerable plaque and retarded the progress of atherosclerosis [53]. Component of the sarcomere protein, MYBP (myopalladin; cg18901940), chains together nebulin (skeletal muscle) and nebulette (cardiac muscle) to alpha-actinin, at the Z lines [54]. It has been associated with dilated cardiomyopathy [55,56].

A large EWAS study of SBP and DBP was recently conducted in amongst individuals of European, African American and Hispanic/Latino ancestry (n=17,101) [16]. The study reported 31 associations of DNA methylation with SBP or DBP. Of these, cg19693031 (near TNIP) and cg18120259 (in gene body...
LOC100132354), found within the top hundred CpG sites of the trans-ancestry EWAS of SBP in our analyses, were among the 31 previously reported associations [16]. The direction of effect was consistent with the previous analysis and the magnitude of association was slightly larger in our study. The above reported cg18120259 was also the top CpG site in our trans-ancestry EWAS of hypertension, the direction of effect was consistent but the magnitude of association was stronger in our study. One additional CpG site, cg06690548 (in gene body SLC7A11, among top 100 CpG sites in our study), was found in common between the trans-ancestry EWAS of hypertension and the previous study with same direction of effect and the magnitude of association was stronger in the current study. These three CpG sites were also replicated previously [16]. Although the current study is smaller in size, we found evidence of some overlap between our results and a recent EWAS of blood pressure [16]. Our study is the first blood pressure EWAS to our knowledge that has included South Asians, offering the chance to compare results from European and South Asian individuals.

There was no consistency in the magnitude and direction of associations comparing Europeans to South Asians, suggesting that peripheral blood DNA methylation patterns may differ between Europeans and South Asians in relation to blood pressure. This may reflect the fact that DNA methylation could index exposure to a different suite of risk factors in the two ethnic groups, or that different mechanisms contribute to the pathogenesis of hypertension and its related phenotypic traits. Of note, the South Asian participants in the SABRE study are first generation migrants, arriving in the UK as young adults. The potential early life and developmental antecedents of hypertension and blood pressure will therefore be considerably different between the two ethnic groups. This may explain to some extent the lack of consistency in methylation variable loci observed between the two ethnic groups. However, the study has limited statistical power due to the relatively modest sample size for these analyses.

Where associations were observed, the effect sizes were modest in size between cases and controls at the identified CpG sites. Such differences are unlikely to have profound biological consequences but may in turn exert a polygenic-like effect, altering disease risk or trait characteristics by small amounts. Further work is required to understand the functional consequences of such subtle shifts in DNA methylation.

We carried out DMR analysis and identified a large number of DMRs for SBP and DBP in the trans-ancestry, European and South Asian sub groups. The analyses found support for some of the DMRs for CVD related traits in the literature including BP [29], myocardial infarction [30], dilated cardiomyopathy [31] and stroke [35].

The strengths of this study include the study design where participants were from two different ethnicities; European and South Asian that were analyzed collectively and individually using robust statistical methods. Additionally, the utilization of HM450 arrays provided good coverage of the genome in terms of known annotated genes (although in total only covers <2% of all CpGs). The relatively modest sample size and the utilization of only male participants are among the limitations of this work.

Conclusion

In conclusion, we identified associations between methylation and DBP across trans-ancestry and European-specific analyses. Lack of associations identified in South Asian specific analyses indicates that the associations between methylation and blood pressure may be different between European and South Asian populations.

Funding

The SABRE study was funded at baseline by the Medical Research Council, Diabetes UK, and the British Heart Foundation. At follow-up the study was funded by the Wellcome Trust and the British Heart Foundation. Methylation analysis in the SABRE cohort was supported by a Wellcome Trust Enhancement grant (082464/2/07/C). AH and NC received support from the Medical Research Council (Programme Code MC_UU_12019/1) and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The SABRE study team also acknowledges the support of the National Institute of Health Research Clinical Research Network (NIHR CRN). NK, HRE, TRG and CLR are supported by the Medical Research Council Integrative Epidemiology Unit at the University of Bristol (MC_UU_12013/2 and MC_UU_12013/8).

Competing Interests

The authors declare that they have no competing interests. TRG receives funding from GlaxoSmithKline, Biogen and Sanofi for research unrelated to the work presented here. The SABRE study team also acknowledges the support of the National Institute of Health Research Clinical Research Network (NIHR CRN).

Ethics Approval and Consent to Participate

All participants gave written informed consent. Approval for the baseline study was obtained from Ealing, Hounslow and Spelthorne, Parkside and University College London research ethics committees.

Consent for Publication

Not applicable.

Availability of Data and Materials

Data used in these analyses are available from SABRE on request.

Authors’ Contributions

NK, HRE, NC and CLR designed the study. NK conducted the statistical analysis and wrote the manuscript with input from all authors. Correspondence and material requests should be addressed to NK (nabila.kazmi@bristol.ac.uk). All authors read and approved the final manuscript.
References


