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# Body mass index and height and risk of cutaneous melanoma: Mendelian randomization analyses

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## ABSTRACT

**Background:** Height and body mass index (BMI) have both been positively associated with melanoma risk, although findings for BMI have been less consistent than height. It remains unclear, however, whether these associations reflect causality or are due to residual confounding by environmental and lifestyle risk factors. We re-evaluated these associations using a two-sample Mendelian randomization (MR) approach.

**Methods:** We identified single nucleotide polymorphisms (SNPs) for BMI and height from separate genome-wide association study (GWAS) meta-analyses. We obtained melanoma SNPs from the most recent melanoma GWAS meta-analysis comprising 12,874 cases and 23,203 controls. We used the inverse variance-weighted estimator to derive separate causal risk estimates across all SNP instruments for BMI and height.

**Results:** Based on the combined estimate derived from 730 SNPs for BMI, we found no evidence of an association between genetically predicted BMI and melanoma (OR per 1SD [4.6 kg/m$^2$] increase in BMI 1.00, 95% CI: 0.91-1.11). In contrast, we observed a positive association between genetically-predicted height (derived from a pooled estimate of 3,290 SNPs) and melanoma risk (OR 1.08, 95% CI: 1.02-1.13, per 1SD [9.27 cm] increase in height). Sensitivity analyses using two alternative MR methods yielded similar results.

**Conclusions:** These findings provide no evidence for a causal association between higher BMI and melanoma, but support the notion that height is causally associated with melanoma risk. Mechanisms through which height influences melanoma risk remain unclear, and it remains possible that the effect could be mediated through diverse pathways including growth factors and even socioeconomic status.

**Key words:** body mass index; height; body size; skin cancer; melanoma; causality; Mendelian randomization

**Key Messages**

- Observational studies examining the association between BMI and height and melanoma risk have yielded inconsistent findings.
- To resolve this inconsistency, we conducted Mendelian randomization analyses using large GWAS datasets.
- We found no evidence to suggest that the association between higher BMI and melanoma risk is causal but, height was found to be associated with melanoma.
- Mechanisms through which height influences melanoma risk remain unclear; numerous pathways have been proposed.

## INTRODUCTION

Exposure to ultra-violet radiation and having a sun-sensitive phenotype are established risk factors for cutaneous melanoma (hereafter referred to as melanoma) among susceptible people [1, 2]. The associations with other factors are less clear, although some studies suggest a possible link between anthropometric factors and melanoma risk [3-5]. Previous observational studies have reported positive associations with body mass index (BMI) and height, but findings varied across studies. Positive associations between high BMI and melanoma have been reported in some [4, 6] but not all [7-9] cohort studies. With regard to height, most previous observational studies of melanoma have reported an increased risk among taller people [4, 5, 10-13].

It remains unclear whether the reported associations represent true causal relationships or are explained by bias or confounding by other factors simultaneously associated with BMI, height and melanoma risk. For example, some studies have speculated that obesity and height might be causally associated with melanoma through increased body surface area and larger number of target cells at risk [14, 15] or, conversely, that melanoma risk might be decreased among obese people through limited outdoor recreational activities and difference in sun-seeking behaviours compared to their non-obese counterparts. Obesity may also be associated with other unknown or unmeasured lifestyle factors, and the possibility of residual confounding by such factors remains a limitation of all observational studies. Finally, information regarding childhood illness and nutrition status, which are potential modifiable factors of height, have not been assessed in previous studies.

One approach to circumvent some of the threats to validity and limitations found in conventional observational studies is to conduct instrumental variable analyses using genetic variants as proxy markers for risk factors, a technique known as Mendelian randomization (MR) [16]. MR uses genetic

variants associated with an exposure (or a biological intermediate) to estimate its effects on the outcome [17]. Because genetic variants associated with adult BMI and height are randomly assigned from parents to their offspring at conception, MR studies are closer to the random assignment of exposure in a randomized controlled trial, in which known and unknown genetic confounders are randomly distributed across different treatment arms, assuming various MR assumptions are met. We conducted MR analyses of BMI and height in relation to the risk of melanoma using the very large international genome-wide association (GWAS) datasets from the Genetic Investigation of ANthropometric Traits (GIANT) consortium [18] and consortium data from the melanoma GWAS meta-analysis [19].

## METHODS

We applied a two-sample Mendelian randomization approach to evaluate whether genetically predicted BMI and height are risk factors for melanoma using publically available summary data from the meta-analyses of genome-wide association studies (GWAS).

### Instrumental variables

Single nucleotide polymorphisms (SNPs) were identified from the largest 2018 GWAS meta-analysis of measured BMI and height in adulthood from the GIANT consortium [18]. This meta-analysis included data from a total of ~700,000 participants of European descent, comprising ~250,000 participants from the earlier GWAS meta-analyses (conducted in 2014 and 2015) [20, 21], and new GWAS data from ~450,000 participants in the UK Biobank (UKBB). In total, 754 and 3290 independent SNPs known to be associated at $P < 5 \times 10^{-8}$ with BMI and height, respectively, were used as instruments for these analyses. Detailed information regarding sample and SNP selection, summary statistics, quality control and meta-analyses have been reported previously [18].

We extracted data on major and minor alleles for each SNP together with the allele frequencies, beta coefficient, standard error (SE) of the beta coefficient and p-value for the relevant association. We tested the validity of the BMI and height instrumental variables in an independent dataset of 17,965 participants in the QSkin cohort. The QSkin Sun and Health Study is a population based cohort consisting of 43,794 men and women aged between 40-69 years who were randomly sampled from the Queensland population [22]. The study was approved by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute and each participant provided written informed consent. Genome-wide polygenic risk scores (PRS) for BMI and height were calculated for eligible cohort participants who provided a DNA sample (n=17,222). We generated the PRS using summary statistics from the same set of SNPs as used for MR analyses. PRS were generated using the --score function of plink V1.90b6.6 [23].

**Association of BMI and height genetic variants with cutaneous melanoma**

We obtained GWAS summary statistics on melanoma from the largest meta-analysis of GWAS on cutaneous melanoma to date which included 12,874 histologically confirmed cases and 23,203 controls from 11 independent GWAS in people of European ancestry in UK, Australia, USA, Germany, France and Greece [19]. Details regarding GWAS quality control and study samples have been published previously [19]. For each identified BMI or height SNP instrument, we extracted the per allele log odds ratio (OR) for melanoma together with its SE and allele frequencies from the melanoma GWAS meta-analysis. Since the two-sample MR involves combining data from two independently-generated datasets, we harmonised the data by comparing allele frequencies between the BMI, height and melanoma datasets, thereby ensuring that reference alleles for each locus were concordant across the datasets. Palindromic strands with minor allele frequency threshold for alignment above 0.3 are non-inferable and hence were excluded from the analyses.

**Two-sample Mendelian randomization methods**

In contrast to traditional 2-stage least squares MR, whereby individual level genotype and phenotype data are obtained from the same sample, we used a two-sample MR strategy in which the SNP exposure and SNP outcome associations are estimated using summary statistics from independent samples [24]. The two-sample method typically offers greater statistical power than the one-sample method, because one can use large, independent datasets to firstly derive the instruments, and then to test the associations. The association between genetically predicted BMI or height and melanoma risk per SNP was evaluated using a Wald-type ratio estimator [25]. The 95% confidence intervals (95% CIs) were calculated from the SE of each Wald ratio. We combined individual Wald ratio estimates for all SNPs for each trait (i.e. BMI or height) using the inverse variance-weighted method (IVW) to obtain a weighted average of the effect estimates [25]. We tested for heterogeneity in Wald ratios using Cochran's Q statistic [26].

**Sensitivity analyses**

The IVW method assumes that there is no horizontal pleiotropy for all SNPs (that is, that the effect of genetic variants on the outcome operates entirely via the exposure of interest), and that all SNPs are valid instruments. However, because testing the validity of these assumptions is difficult in practice, two additional MR analyses, namely MR-Egger regression [27] and weighted median estimator [28] were conducted to check for robustness of the estimates from IVW [27]. MR-Egger regression is similar to IVW except that the intercept is not constrained to pass through the origin, with a non-zero intercept suggesting possibility of directional pleiotropy. The weighted median estimator method has the advantage that it is possible to estimate the effect as long as at least 50% of the variants in the analysis come from SNPs that satisfy the MR assumptions. While these

techniques address potential concern on the causal estimate due to weak violation of MR assumptions, they require large sample sizes to detect effects.

Because deriving BMI and height instruments from datasets which include patients with melanoma could conceivably induce bias in odds ratios, we performed an additional sensitivity analysis restricted to 390,628 cancer-free white British participants in the UKBB only. For this analysis we used 520 and 2059 independent SNPs that were associated with BMI or height respectively at genome-wide significance as previously described [29, 30]. Cancer-free participants were defined as any individual without cancer, or benign or in situ tumours, recorded in the cancer registry using the International Classification of Disease, 10th edition (ICD10). Prevalent and incident cancer cases in the UK Biobank were identified through linkage to the national cancer registries and hospital in-patients data. To assess whether our estimates were sensitive to the choice of instrument, we also conducted a separate analysis restricted to 97 BMI-associated SNPs and 697 height-associated SNPs identified in earlier published studies in the GIANT consortium only [20, 21]. We used R software (TwoSampleMR package) for Mendelian randomization analyses [31].

## RESULTS

### Mendelian randomization analyses of the association between BMI and melanoma risk

The primary analyses included 754 independent genetic variants obtained from the UKBB and the GIANT consortia as instruments for BMI. Five variants that were not available in the melanoma GWAS dataset and 19 that were palindromic strands were excluded, leaving 730 variants for analysis [Table 1]. These variants explained approximately 8% of the variance in BMI in the UKBB and GIANT [Table 1]. In an independent cohort (QSkin), a PRS derived from these variants explained ~5% of the variance in BMI (Supplementary Figures 1 and 2).

We estimated the overall odds ratio of developing melanoma per one SD increase in BMI (1 SD=4.6 kg/m$^2$). Based on the combined estimate derived from 730 genetic variants for BMI, we found no evidence of an association between higher genetically predicted BMI and melanoma (OR per 1SD increase in BMI 1.00, 95% CI: 0.91-1.11) [Table 2] [Figure 1].

We performed sensitivity analyses to check whether the null association might have arisen through violations of the MR assumptions. We found no evidence that our risk estimates were influenced by directional pleiotropy, as the average pleiotropic effect of the MR-Egger regression intercept was close to null (MR-Egger intercept: 0.0001, p-value=0.9 [Table 3] . Graphical assessment of bias in the MR funnel plot suggested that the dispersion of individual estimates was symmetrical [Supplementary Figure 3], indicating that our estimates were not driven by individual outliers. Taken together, the sensitivity analyses suggest that the null findings were very unlikely to be due to violating the assumption imposed by the exclusion restriction criterion. Finally, we checked whether our inferences were influenced by the choice of instruments by repeating the analyses using 79 of the 97 BMI-associated variants identified by the GIANT consortium. We also repeated the same analysis using the 495 of the 520 BMI variants identified from the UKBB. The results were essentially the same regardless of the source of instrument [Table 2].

**Mendelian randomization analyses of the association between height and melanoma risk**

We obtained data for a total of 3,290 height-related genetic variants from UKBB and the GIANT consortium as potential instrumental variables. However, 117 of these 3,290 variants were not available in the melanoma GWAS dataset and 10 variants were palindromic, so were excluded from the analysis. The remaining 3163 variants explained ~19% of variance in height in UKBB and

GIANT [Table 1]. A PRS derived from these height variants, explained ~12% of variance in height in the QSkin cohort [Supplementary Figures 4 and 5]. Using the IVW method to pool estimates from individual variants, genetically-predicted height was statistically significant associated with increased melanoma risk (OR 1.08, 95% CI: 1.02-1.13, per 1SD (9.27 cm) increase in height) [Table 2] [Figure 2].

After excluding non-inferable palindromic SNPs and SNPs that could not be obtained from the melanoma GWAS dataset, we performed sensitivity analyses initially using 1810 height-associated SNPs from the UKBB only, and secondly using a restricted list of 360 height-associated SNPs from the earlier GIANT consortium analysis [21]. These analyses made little difference to the main findings [Table 2]. Additional sensitivity analysis using MR-Egger regression to assess whether the causal estimates could have been affected by directional pleiotropy showed no such evidence (intercept=-0.001, p-value=0.6) (Table 3). Visual assessment of directional pleiotropy using a funnel plot showed that variants were symmetrically distributed [Supplementary Figure 6].

We observed evidence of heterogeneity across SNP estimates (Q=937, p<0.0001 for BMI; Q=2757, p<0.0001 for height (Supplementary Table 1)). SNPs that showed strong evidence of heterogeneity (Q>3.84) were removed and the analyses were repeated. The adjusted MR estimates showed no evidence of heterogeneity. However, the effect estimates were generally unchanged.

## DISCUSSION

We conducted two-sample MR analyses using summary statistics from the largest GWAS meta-analyses of BMI, height and melanoma. Overall, we found no evidence that genetically predicted BMI was associated with increased risk of melanoma, but found evidence to suggest that genetically-predicted height conferred increased risk of melanoma.

Investigating a possible causal association between obesity and melanoma is relevant given the heterogeneity observed across previous observational studies, the substantial increase in obesity prevalence worldwide [32], and the rapid increases in melanoma incidence observed in many populations [33]. To our knowledge, this is the first analysis to use MR techniques. While observational studies can identify associations, they cannot always establish whether relationships are causal, notably in instances where confounding is believed to be present but not fully controlled. For example, many epidemiological studies rely on self-reported weight and height measurements [8, 12, 34] which are subject to misclassification [35, 36]. In addition, few studies adjusted for confounding effect of the sun exposure [6, 37], the major risk factor for melanoma.

Our null findings suggest that the increased risk of melanoma among overweight and obese people reported in previous epidemiological studies [3, 4, 38, 39], may be due to other, non-causal explanations such as ascertainment biases, misclassification or residual confounding inherent to observational studies. Earlier experimental studies had suggested that an association between BMI and melanoma might be plausible. For example, there were reports that obese mice exposed to UVB radiation had higher levels of proinflammatory cytokines in their skin than their non-obese counterparts [40]. Those laboratory findings gave some credence to a possible link between obesity and skin cancer, on the basis that inflammatory responses in the skin might increase the risk of neoplasia [41, 42]. Our data

indicate that even if obesity modifies cutaneous responses to sunlight in some animal models, the effects do not necessarily translate into measurable changes in melanoma risk in humans.

In contrast to the lack of association between BMI and melanoma, the MR findings in relation to a positive association between height and melanoma is broadly consistent with the observational literature, albeit a smaller effect size estimate from MR. For instance, the UK Million Women Study, with ~3,500 melanoma cases, reported a 30% increased melanoma risk per 10cm increase in height [5]. Subsequently, in a large population-based cohort in Norway, including more than 3,000 melanoma cases among ~300,000 men and women, a 50% increased melanoma risk was observed for men and women in the fifth versus first quintile of height [4]. Increased risk of melanoma with greater height was also reported in a study conducted in a high ambient sunlight setting (Queensland, Australia), although the estimates lack precision due to low sample size [9]. Finally, the evidence from a pooled analysis including 8 case-control studies provides additional support for an association between height and melanoma in women [11].

The MR findings described in this study in relation to the two-sample MR generally agree with previously reported findings from one-sample MR analyses conducted in the UK Biobank. In those analyses, no association between genetically determined higher BMI and melanoma was found (OR: 0.98, 95% CI: 0.85-1.14)[43], but a 12% increase in melanoma risk was reported per 10 cm increase in genetically predicted height (OR: 1.12, 95% CI: 1.001 - 1.26)[29]. Height has also been reported as a risk factor for other types of cancer in other MR studies, although the effect of height on melanoma reported in our study was relatively lower for some cancer types, but similar for others. For example, previous research has reported that for every 10 cm increase in genetically predicted height, the risk ratio was 1.22 (95% CI: 1.13-1.32) for breast cancer [44], 1.07 (95% CI:

1.01-1.14) for colorectal cancer[45], 1.23 (95% CI 1.06-1.42) for endometrial cancer [29] and 1.12 (95% CI: 1.02-1.23) for ovarian cancer[46].

Adult height is determined by various growth mechanisms, childhood environment, and possibly by epigenetic factors, any of which may influence melanoma risk. Previous investigators have speculated that height is a proxy for the total number of cells (including stem cells) in the body, and that this presumably increases the probability of mutations and hence malignancy [14, 15]. However, this hypothesis does not accord with the higher rates of malignancy observed across species (for example, between mice and humans which differ in volume by orders of magnitude) [47]. The lack of relationship between body size and cancer risk across species, known as Peto's Paradox [48], suggests that larger organisms might have evolved cancer-suppressing mechanisms in order to live longer [49]. For example, a recent study has shown that the genome of an elephant has 20 copies of the P53 tumour suppressor gene whereas humans have only one copy [50]. Thus, body size is an imperfect predictor of cancer risk in an organism across species, but body size and cancer risk are positively correlated within members of the same species [7-10]. While BMI is a reliable measure of body size, mature adipocytes do not undergo mitoses as they are fully differentiated cell type and thus, provide fewer targets for oncogenic mutations.

An earlier study also reported a positive association between the number of naevi and height but not weight [51]. The study argued that both naevi count and melanoma are associated with longer telomeres. Telomere length has been reported as a genetic marker of reduced senescence and increased growth [52], and is believed to play important roles in carcinogenesis [53]. Various hormones implicated in childhood growth, such as insulin-like growth factor (IGF)-I [54], also regulate cell turnover, apoptosis and tumour progression [55], and thus could be implicated in cancer development.

These mechanisms are presumably largely under genetic control, and the genetic associations between height and melanoma might be mediated through these pathways.

While biological mechanisms to explain the association between height and melanoma have intuitive appeal, it is also possible that height might mediate its effects on melanoma risk through other pathways, at least in some populations. Recently, a Mendelian randomization study conducted within the UK BioBank (using very similar instruments to those that we used) reported that genetically-predicted height was significantly associated with four different measures of socioeconomic status (SES), with strong positive associations observed for job class and annual household income [56]. Previous observational studies, particularly those conducted in settings of low ambient sunlight (such as northern Europe), have reported significantly higher melanoma incidence among people in high SES categories compared to those in low SES categories. In those settings, it has been postulated that greater affluence has given greater access to holidays in sunny locations and sunburns, thereby conferring an increased risk of melanoma [57-59]. Occupational studies from the UK [60] and Sweden [61] corroborate this hypothesis, showing that indoor workers have significantly higher risks of melanoma than outdoor workers in those countries. Thus, at a population-level, genetically determined height is possibly causally associated with melanoma through a pathway of social class and sun exposure.

A limitation common to all MR analyses relates to potential pleiotropy, whereby a genetic variant is independently associated with the outcome, but not through the exposure of interest. We assessed potential pleiotropy using the MR-Egger method and observed no evidence that the exclusion restriction criteria assumption was violated. While it is also possible that some of the variants used in the analysis might be associated with confounders of the height and melanoma association, such

an effect would likely be small because our genetic instrument was generated from more than 3000 variants explaining ~19% of variance in height, which further reduces the likelihood of bias from violating MR assumptions [62]. Our analyses also intrinsically assume a linear relationship between BMI/height and the log(OR) on melanoma. Here, the MR estimates capture a population averaged effect across different strata of exposure, which might differ from the association of BMI/height on melanoma for individuals at extreme ends of the distribution. We argue that this is unlikely a major concern for our analyses given the overall null finding for BMI (except for extreme circumstances where the opposing direction of effect across two ends of a stratum directly cancel out), however a larger sample size will be required to comprehensively evaluate any non-linear relationships between height and melanoma.

In conclusion, these large-scale Mendelian randomization analyses found little evidence to suggest that the association between higher BMI and melanoma risk is causal but, in accord with earlier observational studies, height was found to be associated with melanoma. Mechanisms through which greater height might lead to increased risk of melanoma remain unclear, and it is possible that the effect is mediated through various pathways, ranging from direct hormonal effects through to social class and sun exposure. While the most effective way to reduce cancer risks involves elimination of the causal risk factor, it is not feasible to modify adult height. However, the specific mechanisms (which might be modifiable) underlying this association may provide valuable insights into carcinogenesis. It is also possible that height may contribute to future risk stratification algorithms which could be used to target people for early detection activities.

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**Table 1. The characteristics and source of genetic instruments used in Mendelian randomisation (MR) analyses**

| Instruments from | Body mass index | | | | Height | | | |
|---|---|---|---|---|---|---|---|---|
| | **Sample size** | **Number of SNPs obtained** | **Number of SNPs used** | **Total variance Explained($r^2$)*** | **Sample size** | **Number of SNPs obtained** | **Number of SNPs used** | **Total variance Explained ($r^2$)*** |
| UK Biobank + GIANT | 681,275 | 754 | 730 | 7.8% | 693,529 | 3,290 | 3,163 | 19% |
| GIANT only | 339,224 | 97 | 79 | 2.7% | 253,288 | 697 | 360 | 13% |
| UK Biobank only | 390,628 | 520 | 495 | 7% | 310,793 | 2,059 | 1810 | 17% |

SNP: single-nucleotide polymorphism; GIANT: Genetic Investigation of ANthropometric Traits

*Total variance explained by instrument is computed based on the genetic influence of the BMI or height SNPs instruments on measured BMI or height from the white-British participants from the UK Biobank cohort.

**Table 2. Association between increased BMI and height and risk of melanoma using two-sample Mendelian randomisation (MR)[1]**

| Instruments from | MR method | Body mass index | | | Height | | |
|---|---|---|---|---|---|---|---|
| | | **Odds ratio** | **95% CI** | ***P*-Value** | **Odds ratio** | **95% CI** | ***P*-Value** |
| UK Biobank + GIANT[2] | IVW | 1.00 | 0.91-1.11 | 0.99 | 1.08 | 1.02-1.13 | 0.004 |
| | MR-Egger[5] | 0.99 | 0.74-1.33 | 0.97 | 1.05 | 0.96-1.14 | 0.14 |
| | Weighted Median | 1.01 | 0.86-1.17 | 0.92 | 1.11 | 1.02-1.20 | 0.02 |
| | Simple Mode | 0.85 | 0.51-1.43 | 0.55 | 1.07 | 0.80-1.45 | 0.61 |
| | Weighed Mode | 0.98 | 0.73-1.32 | 0.89 | 1.13 | 0.95-1.36 | 0.15 |
| GIANT only[3] | IVW | 0.96 | 0.80-1.15 | 0.66 | 1.09 | 1.02-1.18 | 0.01 |
| | MR-Egger[5] | 0.99 | 0.56-1.73 | 0.25 | 1.02 | 0.84-1.25 | 0.8 |
| | Weighted Median | 0.86 | 0.66-1.11 | 0.82 | 1.14 | 1.02-1.27 | 0.02 |
| | Simple Mode | 0.78 | 0.45-1.34 | 0.36 | 1.14 | 0.81-1.60 | 0.44 |
| | Weighed Mode | 0.99 | 0.72-1.38 | 0.98 | 1.14 | 0.87-1.49 | 0.34 |
| UK Biobank only[4] | IVW | 1.01 | 0.98-1.03 | 0.76 | 1.07 | 1.01-1.13 | 0.01 |
| | MR-Egger[5] | 1.03 | 0.96-1.11 | 0.31 | 1.04 | 0.87-1.25 | 0.25 |
| | Weighted Median | 1.00 | 0.97-1.04 | 0.81 | 1.07 | 0.99-1.16 | 0.08 |
| | Simple Mode | 0.95 | 0.86-1.07 | 0.45 | 1.03 | 0.97-1.07 | 0.33 |
| | Weighed Mode | 1.01 | 0.93-1.08 | 0.83 | 1.02 | 0.98-1.04 | 0.26 |

SNP: single-nucleotide polymorphism; CI: confidence interval; UKBB: UK Bio-bank; GIANT: Genetic Investigation of ANthropometric Traits; IVW: inverse variance weighted

[1]The estimates are given per one SD increase in BMI (1 SD=4.6 kg/m$^2$) and per one SD increase in height (1SD=9.27 cm)

[2]UKBB + GIANT: Genetic variants obtained from the 2018 BMI and height GWAS meta-analysis in the GIANT consortium

[3]GIANT only: Genetic variants obtained from the 2015 BMI GWAS meta-analysis and from 2014 height GWAS meta-analysis in the GIANT consortium

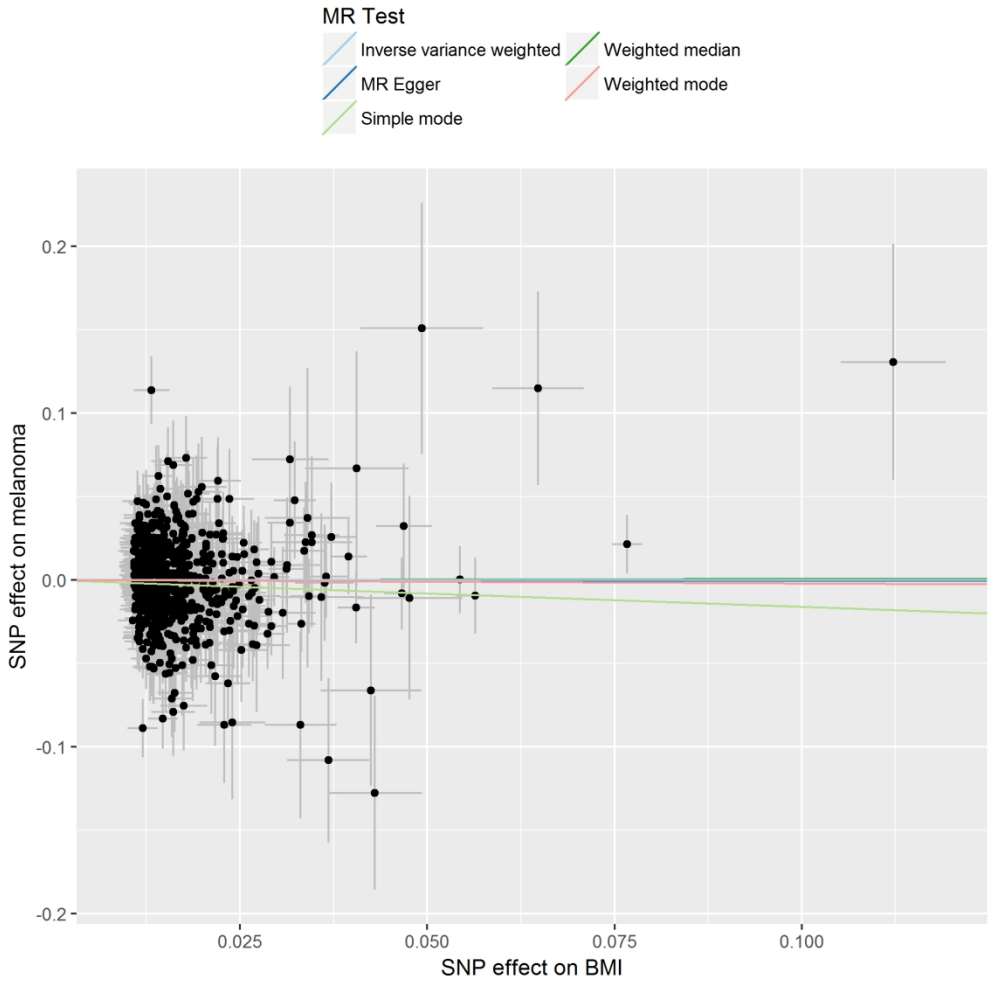
[4]UK Biobank only: BMI and height genetic variants obtained from the UKBB only.

[5]For MR-Egger analyses, the standard error (SE) for each exposure-outcome estimate was obtained by bootstrapping the distributions of the SNP effect estimates for both exposure and outcome 1000 times.

**Table 3. Estimates of Egger intercept to evaluate evidence for directional pleiotropy in MR association**

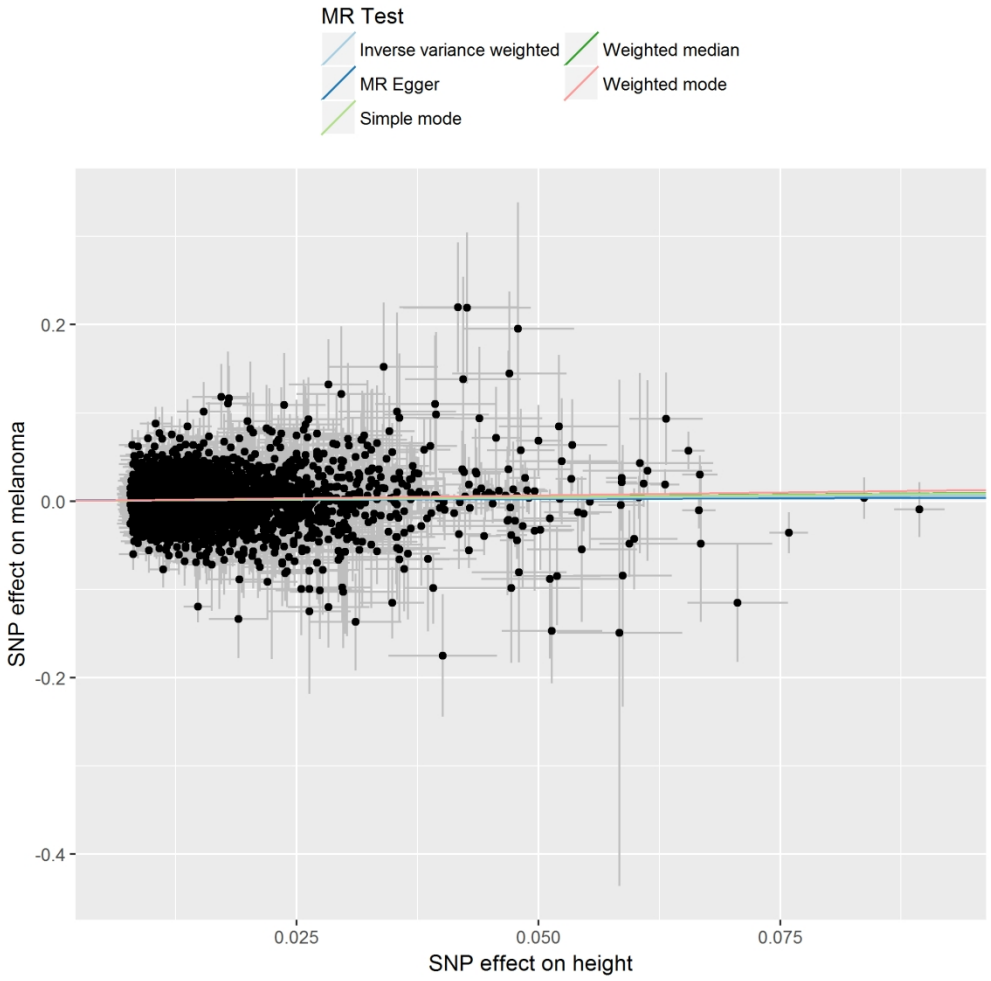
| Instruments from | Body mass index | | | Height | | |
|---|---|---|---|---|---|---|
| | **Egger intercept** | **SE of Egger intercept** | **P-value** | **Egger intercept** | **SE of Egger intercept** | **P-value** |
| UKBB + GIANT | 0.0001 | 0.002 | 0.9 | 0.001 | 0.0008 | 0.6 |
| UKBB only | -0.002 | 0.02 | 0.3 | 0.003 | 0.001 | 0.5 |
| GIANT only | -0.005 | 0.005 | 0.4 | 0.004 | 0.003 | 0.2 |

Here, p-value refers to the p-value of the estimated Egger intercept being null. A significant p-value ($P<0.05$) would present evidence that the MR causal estimates derived via the inverse-variance weighted model were biased by directional pleiotropy.




Association of individual SNPs with BMI and melanoma risk. Instrumental variable estimates were derived from 730 BMI SNP instruments identified in the BMI GWAS meta-analyses using samples from GIANT and the UKBB cohort. Error bars represent 95% confidence intervals. The gradients of regression lines colors correspond to the instrumental variable estimates of the effect of BMI on melanoma risk with different MR methods compared.

177x177mm (300 x 300 DPI)




Association of individual SNPs with height and melanoma risk. Instrumental variable estimates were derived from 3290 height SNP instruments identified in the height GWAS meta-analysis using samples from GIANT and the UKBB cohort. Error bars represent 95% confidence intervals. The gradients of regression lines colors correspond to the instrumental variable estimates of the effect of height on melanoma risk with different MR methods compared.

177x177mm (300 x 300 DPI)