Evidence for a major role of genetic factors in the determination of body mass index (BMI) comes from studies of related individuals. Despite consistent evidence for a heritable component of BMI, estimates of BMI heritability vary widely between studies and the reasons for this remain unclear. While some variation is natural due to differences between populations and settings, study design factors may also explain some of the heterogeneity. We performed a systematic review that identified 88 independent estimates of BMI heritability from twin studies (total 140,525 twins) and 27 estimates from family studies (42,968 family members). BMI heritability estimates from twin studies ranged from 0.47 to 0.90 (5th/50th/95th centiles: 0.58/0.75/0.87) and were generally higher than those from family studies (range: 0.24–0.81; 5th/50th/95th centiles: 0.25/0.46/0.68). Meta-regression of the results from twin studies showed that BMI heritability estimates were 0.07 (P = 0.001) higher in children than in adults; estimates increased with mean age among childhood studies (+0.012/year, P = 0.002), but decreased with mean age in adult studies (−0.002/year, P = 0.002). Heritability estimates derived from AE twin models (which assume no contribution of shared environment) were 0.12 higher than those from ACE models (P < 0.001), whilst lower estimates were associated with self reported versus DNA-based determination of zygosity (−0.04, P = 0.02), and with self reported versus measured BMI (−0.05, P = 0.03). Although the observed differences in heritability according to aspects of study design are relatively small, together, the above factors explained 47% of the heterogeneity in estimates of BMI heritability from twin studies. In summary, while some variation in BMI heritability is expected due to population-level differences, study design factors explained nearly half the heterogeneity reported in twin studies. The genetic contribution to BMI appears to vary with age and may have a greater influence during childhood than adult life.

**Keywords:** body mass index, twin study, family study, heritability

**INTRODUCTION**

Studies of twins and families have quantified the contribution of genetic variation to inter-individual differences in body mass index (BMI). In the last comprehensive review of BMI heritability, Maes et al. (1997) reported that the proportion of phenotypic variance (V_P) that can be attributed to genetic factors (h^2) ranged from 0.40 to 0.90 in twin studies and 0.20 to 0.50 in family studies, demonstrating the wide variation in the magnitude of BMI heritability observed both within and between these study designs (Maes et al., 1997). Genome-wide association studies (GWAS) have so far identified 32 loci robustly associated with adult BMI (Frayling et al., 2007; Loos et al., 2008; Thorleifsson et al., 2009; Willer et al., 2009; Speliotes et al., 2010). Despite highly statistically significant associations, these 32 loci account for less than 2% of the total V_P in BMI. Sub-genome-wide significant variants may be able to explain a substantial portion of the unexplained genetic variance of complex traits. However, even when considering such genetic variance explained remains lower than estimates of heritability (Yang et al., 2011) and much attention has been focused on finding the so-called “missing heritability” (Manolio et al., 2009).

Twin studies are used to quantify genetic and environmental contributions to variation in BMI by comparing intra-pair concordance between monozygotic (MZ) twins and dizygotic (DZ) twins. Assignment of zygosity (MZ or DZ) to twin pairs is achieved either using questionnaires or more accurate DNA-based methods. Twin studies model the V_P to be the composite of up to four components: (A) additive genetic factors; (D) non-additive or dominant genetic factors; (C) shared environmental factors; and (E) non-shared environmental factors (Neale and Cardon, 1992; Rijsdijk and Sham, 2002). Heritability is usually reported as the proportion of overall V_P that can be attributed to additive genetic factors (h^2 = A/V_P), as dominant genetic factors (D) are confounded with shared environmental factors (C) and cannot be estimated in the same model. The “best estimate” of heritability is calculated from the statistically best fitting and most parsimonious combination of the three remaining variance components (A, C, and E), determined by sequentially removing components from
the model and testing for deterioration in fit in structural equation modeling (Rijksdijk and Sham, 2002; Figure A1 in Appendix).

Quantitative genetic analysis in family studies also allows variance in BMI to be partitioned into genetic and environmental components. Estimates of familiality indicate to what extent members of the same family share traits (representing the A, D, and C components of Vp combined) to infer an inherited component. Heritability estimates can be estimated by maximum likelihood variance decomposition (Almasy and Blangero, 1998) or by regressing offspring phenotype onto mean parental phenotype (Lawlor and Mishra, 2009). However, it should be noted that family studies cannot explain to what extent this familial similarity arises from genetic relatedness as opposed to shared environmental factors.

We aimed to identify papers that have estimated the heritability of BMI, and to identify and quantify by meta-regression the effects of demographic and methodological factors that contribute to the heterogeneity between estimates.

MATERIALS AND METHODS

LITERATURE SEARCH

Papers that reported BMI heritability were identified on PubMed. A search was performed in February 2010 with the term “heritability,” combined with the MeSH term “body mass index,” limited to human studies reported in the English language, and this generated 209 papers. Titles and abstracts were assessed for their relevance; inclusion criteria were twin or family studies reporting a quantitative estimate for BMI heritability (h2) as a measure of additive genetic factors (N = 64 papers). Supplementary searches (for example, using the term “genetic contribution” rather than heritability) were performed together with cross-referencing to identify further studies that had not been captured by the original search. For papers duplicating estimates from the same populations, either the study reporting a secondary analysis or using a smaller subset of the dataset was excluded (N = 10). One study was excluded because it reported the heritability of maximal lifetime BMI. To enable a quantitative meta-analysis, measures of uncertainty for the heritability estimates were required. For twin study papers not reporting SE or confidence intervals, heritability, and confidence intervals were calculated directly. This calculation was not possible if twin studies also did not report MZ/DZ correlations (N = 6), mean BMI by zygosity (N = 4), or SD of mean BMI by zygosity (N = 2). Family studies not reporting SE or confidence intervals for BMI heritability were also excluded (N = 6). In total, 31 papers reporting twin studies and 25 papers reporting family studies were eligible for inclusion (Figure A2 in Appendix); many of these papers reported estimates from more than one study.

DATA EXTRACTION AND CLASSIFICATION

Estimates of BMI heritability as a measure of additive genetic components were extracted from each paper, where possible by independent subgroup based on sex, age group, ethnicity, or setting, the source study and, in twin studies, whether twins were raised apart or together. Information was also obtained on the location of the study, the study to which the twins or family members were recruited (where relevant) and the mean age, age range, and number of participants in each study. Twin studies were categorized according to: whether they were conducted in adults (>18 years) or children (≤18 years); the variance component model used to derive the best heritability estimates (ACE versus AE); the method used to assign zygosity (DNA or biological versus questionnaire); and whether BMI was calculated from objective measurements or self-reported body size. Where studies had used mixed strategies to determine twin zygosity, for example if they DNA tested uncertain cases, they were categorized as using a DNA-based/biological strategy.

STATISTICAL ANALYSIS

For studies that did not report measures of uncertainty around BMI heritability, heritability estimates, and their confidence intervals were re-calculated using OpenMx (Boker et al., 2011). Firstly, datasets were simulated based on the reported number of MZ and DZ twins in each study and the mean and SD of BMI in each class of twins. Structural equation modeling was then used to decompose the variance in BMI into additive genetic, shared environmental and unique environmental components based on intra-class correlations of BMI in MZ and DZ twin pairs. In studies that reported heritability from AE models, we also excluded the C component in our re-calculation. To make this analysis more robust, a bootstrapping approach was applied, whereby twin pairs were sampled 1,000 times for each heritability estimate. Re-calculated estimates were highly correlated with originally reported estimates (r = 0.91).

A meta-analysis of the reported or re-calculated estimates of heritability from each study was performed separately for twin and family studies using metan in Stata (Version 11.0). A random effects model was used which accounts for inter-study heterogeneity. Where possible, estimates from men and women were included separately in the twin study meta-analysis, and subgroup estimates by sex were calculated. In longitudinal studies, the baseline heritability or the estimate based on the measurement with largest number of twins was selected. To investigate potential explanations for heterogeneity in estimates across twin studies, random effects meta-regression analyses were conducted using the metareg (Sharp, 1998; Harbord and Steichen, 2004) command in Stata. In these analyses, weights are assigned according to the inverse of the total variance, comprising the individual study variance and the residual between study variance. The influence of sex, age, setting (populations of white compared with East Asian descent), publication year, sample size, choice of variance component model, method used to determine zygosity and method used to determine BMI were quantified. To test for effects of age on BMI heritability, twin study estimates from adults versus children were compared. Secondly, as we have observed biphasic patterns of age modification of genetic effects of FTO and MCHR on BMI and body weight (Hardy et al., 2010), a meta-regression of mean age (or, when this was not reported, the mid-point of the age range as a proxy) was performed in childhood and adulthood studies separately. A similar meta-regression was performed on family study estimates to test for any detectable effects of sample size, mean, or mid age of participants, publication year, and setting of the study (US or European versus East Asian).

The overall heterogeneity in BMI estimates explained by all significant factors was calculated as the proportion of the $\tau^2$ statistic, which measures between study variance (Thompson and
Sharp, 1999), that is accounted for when including these covariates in a meta-regression model. This analysis was based on 70 heritability estimates which could be categorized into adulthood or childhood, AE or ACE models, biological or questionnaire-based zygosity determination and self report or objective BMI assessment.

RESULTS

TWIN STUDIES

A total of 88 independent estimates of BMI heritability from twin studies were identified from 31 papers (Stunkard et al., 1986, 1990; Hewitt et al., 1991; Korkeila et al., 1991; Neale and Cardon, 1992; Carmichael and McGue, 1995; Forbes et al., 1995; Harris et al., 1995; Herskind et al., 1996; Austin et al., 1997; Faith et al., 1999; Knoblach et al., 1999; Narkiewicz et al., 1999; Peliartiainen et al., 1999; Vinck et al., 1999; Baird et al., 2001; Poulsen et al., 2001; Schousboe et al., 2003, 2004; Nelson et al., 2006; Cornes et al., 2007; Hur, 2007; Ordonana et al., 2007; Silventoinen et al., 2007a,b; Souren et al., 2007; Hur et al., 2008; Warde et al., 2008; Lajunen et al., 2009; Watson et al., 2010; Table 1; Figure A2 in Appendix). Reported estimates ranged from 0.47 to 0.90 (5th/50th/95th centiles: 0.58/0.75/0.87; Figure 1). In some papers, estimates were reported separately by sex, age subgroup, or geographical location. The overall sample represented a total

Table 1 | Details of the 31 papers reporting BMI heritability from twin studies.

| Reference | Location | Source | N  | Mean age (range) | Zygosity determinant | BMI measure | Best fitting model | Heritability estimate |
|-----------|----------|--------|----|------------------|----------------------|-------------|-------------------|----------------------|
| Watson et al. (2010) | USA | University of Washington Twin Registry | 1,224 | 36.9 (18–18) | Questionnaire | Self report | ACE | 0.76 (m/f) 0.54, 0.80 |
| Lajunen et al. (2009) | Finland | FinnTwin12 Study | 4,650 | 11.4 (11–12) | Questionnaire | Self report | ACE | 0.69 (m) 0.56, 0.84 |
| Hur et al. (2008) | Australia (A), Finland (F), Netherlands (N), USA (U) | Study of melanoma risk factors, FinnTwin12, Netherlands Twin Registry, Minnesota Twin Family Study | 7,470 | 14.1 (13–15) | Questionnaire; DNA-based in uncertain cases/same sex pairs | Clinical (A, U, C, J); Self report (F, N, J, K, T) | ACE | 0.81 (m) 0.70, 0.90 |
| China (C), Japan (J), South Korea (K), Taiwan (T) | Guangzhou Twin Registry, Tokyo TWIN Cohort, South Korean TWIN Registry, Taiwan Adolescent Twin/Sibling Family Study | 3,168 | 14.0 (13–15) | DNA (C, T), Questionnaire (J, K; uncertain cases excluded) | Clinical (C, J); Self report (J, K, T) | ACE | 0.74 (m) 0.56, 0.93 |
| Liu et al. (2008) | Taiwan | Twin/Sibling Study of Insulin Resistance | 396 | 14.1 (12–18) | DNA-based | Clinical | AE | 0.89 (m/f) 0.85, 0.92 |
| Wardle et al. (2008) | UK | Twin’s Early Development Study | 10,184 | 9.9 (8–11) | Questionnaire; DNA-based in uncertain cases | Self report | ACE | 0.80 (m) 0.72, 0.84 |
| Cornes et al. (2007) | Australia | Schools in Brisbane area, media appeals | 1,812 | 12 | Questionnaire; DNA confirmation in DZ/same sex pairs | Clinical | ADE | 0.77 (m) 0.52, 0.91 |
| Hur (2007) | South Korea | South Korean Twin Registry (SKTR) | 1,776 | 15.6 (13–19) | Questionnaire | Self report | AE | 0.82 (m) 0.72, 0.95 |
| Ordonana et al. (2007) | Netherlands, Spain | Netherlands and Murcia Twin Registers | 1,324 | 41–67 | DNA-based | Self report | AE | 0.77 (m/f) 0.77, 0.99 |
| Silventoinen et al. (2007a) | Netherlands | Netherlands Twin Register | 15,510 | 3 | Questionnaire | Self report | ACE | 0.70 (m) 0.62, 0.77 |
| Silventoinen et al. (2007b) | Sweden | Swedish Young Male Twins Study | 678 | 18 | Questionnaire; DNA-based in uncertain cases | Clinical | AE | 0.84 (m) 0.81, 0.88 |
| Souren et al. (2007) | Belgium | East Flanders Prospective Twin Survey | 756 | 25.3 (18–34) | Questionnaire; DNA-based | Clinical | AE | 0.85 (m) 0.79, 0.89 |

(Continued)
| Reference                              | Location | Source                                      | N    | Mean age (range) | Zygosity determinant | BMI measure | Best fitting model | Heritability estimate | Sex | 95% CI         |
|----------------------------------------|----------|---------------------------------------------|------|------------------|----------------------|-------------|--------------------|-----------------------|-----|----------------|
| Nelson et al. (2006)                   | USA      | Carolina African American Twin Study of Aging | 434  | 470 (22–88)      | Questionnaire        | Clinical    | AE                 | 0.74 (m)              | 0.61, 0.88 |
| Schousboe et al. (2004)                | Denmark  | GEMINAKAR Study                             | 1,248 | 378 (18–67)      | DNA-based            | Clinical    | ACE                | 0.63 (m)              | 0.36, 0.90 |
| Schousboe et al. (2003)                | Australia| Australian Twin Register                    | 5,000 | 20–29            | Questions; blood groups; DNA-based | Self report | AE                 | 0.74 (f)              | 0.71, 0.76 |
|                                        |          |                                             | 2,832 | 30–39            |                      |             |                    | 0.77 (m)              | 0.72, 0.82 |
|                                        | Denmark  | Danish Twin Registry                        | 11,096 | 20–29            | Questionnaire        | Self report | AE                 | 0.75 (m)              | 0.72, 0.78 |
|                                        |          |                                             | 8,094 | 30–39            |                      |             |                    | 0.73 (f)              | 0.71, 0.76 |
|                                        | Finland  | Finnish Twin Cohort Study and FinnTwin16    | 3,976 | 20–29            | Questionnaire        | Self report | AE                 | 0.74 (m)              | 0.69, 0.80 |
|                                        |          |                                             | 11,564 | 30–39            |                      |             |                    | 0.80 (f)              | 0.77, 0.84 |
|                                        | Italy    | National Twin Registry                      | 820   | 20–29            | Questionnaire        | Self report | AE                 | 0.73 (m)              | 0.71, 0.76 |
|                                        |          |                                             | 1,096 | 30–39            |                      |             |                    | 0.66 (f)              | 0.63, 0.70 |
|                                        | Netherlands| Netherlands Twin Registry            | 3,696 | 20–29            | Questionnaire; DNA in subset of 538 twins | Self report | AE                 | 0.79 (m)              | 0.66, 0.92 |
|                                        |          |                                             | 582   | 30–39            |                      |             |                    | 0.67 (f)              | 0.58, 0.67 |
|                                        | Norway   | Norwegian Institute of Public Health Twin Study | 6,782 | 20–29            | Questionnaire        | Self report | ACE AE             | 0.73 (f)              | 0.70, 0.76 |
|                                        |          |                                             | 1,148 | 30–39            |                      |             |                    | 0.78 (m)              | 0.70, 0.87 |
|                                        | Sweden   | Swedish Twin Registry                       | 9,518 | 20–29            | Questionnaire        | Self report | AE                 | 0.74 (f)              | 0.72, 0.77 |
|                                        |          |                                             | 7,300 | 30–39            |                      |             |                    | 0.72 (m)              | 0.69, 0.75 |
|                                        | UK       | St Thomas’ UK Adult Twin Registry           | 328   | 20–29            | Questionnaire; DNA in 50% | Self report | AE                 | 0.75 (f)              | 0.72, 0.78 |
|                                        |          |                                             | 622   | 30–39            |                      |             |                    | 0.75 (f)              | 0.64, 0.81 |
|                                        |          | Birmingham birth registry                   | 396   | 43.7             | Questionnaire        | Clinical   | AE                 | 0.81 (f)              | 0.77, 0.86 |
|                                        | Denmark  | Danish Twin Register                        | 606   | 670 (55–74)      | Questionnaire        | Clinical    | Conb               | 0.58 (m)              | 0.40, 0.76 |
|                                        |          |                                             | 622   | 11.0 (3–17)      |                      |             |                    | 0.90 (f)              | 0.59, 1.00 |
|                                        | USA      | Ohio twin fair                              | 132   | 11.0 (3–17)      | Questionnaire; blood testing | Clinical   | AE                 | 0.88 (m/f)            | 0.82, 0.95 |
|                                        | Germany  | Studies of cardiovascular phenotypes and blood pressure regulation | 444   | 34.0             | DNA-based            | Clinical   | AE                 | 0.86 (m/f)            | 0.59, 1.00 |
|                                        | Poland   | Twins reared together and apart             | 66    | 20.9 (SD = 5)   | DNA-based            | Clinical    | ACE                | 0.76 (f)              | 0.28, 1.00 |
|                                        | Finland  | FinnTwin16                                  | 4,884 | 16.2             | Questionnaire; photographs; DNA-based | Self report | AE                 | 0.82 (m)              | 0.79, 0.86 |
|                                        |          |                                             |       |                  |                      |             |                    | 0.88 (f)              | 0.86, 0.90 |
|                                        | Belgium  | East Flanders Prospective Twin Survey, town registers | 182   | 22.0 (17–38)    |                       | Clinical   | AE                 | 0.85 (m)              | 0.64, 1.00 |

(Continued)
Table 1 | Continued

| Reference          | Location | Source                                      | N   | Mean age (range) | Zygosity determinant | BMI measure | Best fitting model | Heritability estimate |
|--------------------|----------|---------------------------------------------|-----|------------------|----------------------|-------------|--------------------|-----------------------|
| Austin et al. (1997) | USA      | Kaiser Permanente Women’s Twin Study        | 630 | 18–85            | DNA-based            | Clinical    | AE                 | 0.83 (f) 0.79, 0.87   |
| Herskind et al. (1996) | Denmark  | Danish Twin Register                        | 1,602 | 46–59          | Questionnaire; unknown cases excluded | Self report | AE                 | 0.47 (m) 0.37, 0.57   |
| Carmichael and McGue (1995) | USA      | Minnesota Twin Registry and Twin Study of Adult Development | 1,475 | 31.8 (18–38) | Questionnaire | Self report | AE                 | 0.82 (m/f) 0.78, 0.86   |
| Forbes et al. (1995) | USA      | Newspaper advertisement                     | 174  | 7–68             | DNA-based            | Clinical    | Cor\(^b\)          | 0.75 (m/f) 0.57, 0.93   |
| Harris et al. (1995) | Norway   | New Norwegian Twin Panel                    | 4,508 | 18–25           | Questionnaire        | Self report | AE                 | 0.72 (m) 0.67, 0.77   |
| Korkeila et al. (1991) | Finland  | Finnish Twin Cohort                         | 4,988 | 18–24          | Questionnaire; unknown cases excluded | Self report | AE                 | 0.74 (m) 0.70, 0.78   |
| Neale and Cardon (1992) | Australia | Australian NH and MRC study                 | 3,522 | 18–30           | Questionnaire        | Self report | ADE\(^c\)          | 0.76 (m) 0.71, 0.81   |
| Hewitt et al. (1991) | UK       | Birmingham Family Study Register            | 160  | 19.3 (16–24)    | Questionnaire        | Clinical    | AE                 | 0.75 (m) 0.71, 0.80   |
| Stunkard et al. (1990) | Sweden   | Swedish Adoption/Twin Study of Aging (SATSA) | 1,346 | 58.6            | Questionnaire        | Self report; clinical subset | ADE\(^c\) | 0.70\(^i\) (m) 0.53, 0.88 |
| Stunkard et al. (1986) | USA      | National Academy of Sciences-National Research Council Twin Registry Panel | 8,142 | 20.0 (15–28) | Questions; blood groups; DNA-based | Clinical    | Cor\(^b\)          | 0.77 (m) 0.69, 0.84   |

\(^a\)Twins reared together; \(^b\)twins reared apart.
\(^c\)Studies estimating heritability with equations based on correlations.
\(^d\)Heritability calculated directly using OpenMx under AE model.

of 171,227 twins and, allowing for a maximum potential overlap of 30,702 twins between the study samples, the pooled analysis comprised at least 140,525 independent twins. Between study heterogeneity across these estimates was substantial (\(I^2 = 86.1\%, P < 0.001\); Figure 2).

**DEMOGRAPHIC FACTORS**

In estimates from twin studies, there were similar overall heritability estimates for men (0.73; 95% CI: 0.71–0.76) and women (0.75; 95% CI: 0.73–0.77; Figure 2). This was confirmed by meta-regression, which found no effect of sex on the heritability estimate (Table 2). Nineteen of the 88 heritability estimates from twin studies were from children and adolescents (≤18 years), whilst 67 were in adulthood (two estimates were from populations that included participants spanning both childhood and adulthood). Meta-regression showed that, on average, BMI heritability in childhood was 0.07 higher (95% CI: 0.03–0.11, \(P = 0.001\)) than in adulthood (Table 2). Heritability estimates rose by 0.012/year throughout childhood (age ≤18 years; 95% CI: 0.005–0.019, \(P = 0.002\)), but decreased by −0.002/year in
The AE model was chosen as the best fitting model for 61 estimates. Frontiers in Endocrinology.

Sample size was unrelated to BMI heritability estimates ranging from 66 to 8,142 individuals. In meta-regression models, sample size was not nominally associated with heritability in meta-regression analyses (0.003/1 year, P = 0.055). However, this association was attenuated after adjustment for age category (child versus adult studies; P = 0.405).

**METHODOLOGICAL FACTORS**

The number of twins included in each estimate of BMI heritability ranged from 66 to 8,142 individuals. In meta-regression models, sample size was unrelated to BMI heritability estimates (P = 0.202, adjusted for age category). Fifteen of the best estimates of BMI heritability from twin studies were derived from the three-component ACE model, while the more parsimonious AE model was chosen as the best fitting model for 61 estimates. Eight estimates were derived from the ADE model and four estimates were obtained by direct comparisons of the within-pair correlations in monozygotic and dizygotic twins. Best estimates from AE variance component models were on average 0.12 higher than those from ACE models (P = 0.005), adjusted for age category (Table 3). When stratified into childhood or adult studies, this difference was of similar magnitude in children (0.11, 95% CI: 0.06–0.17, P = 0.001) and adults (0.13, 95% CI: 0.008–0.26, P = 0.038).

A total of 33 of the 88 twin study estimates used DNA or biological (blood typing or fingerprints) assignment of zygosity; the remaining 55 relied completely on questionnaire-based methods. Reliance on questionnaires to determine zygosity (compared with DNA or other biological methods) was associated with a 0.04 lower heritability estimate (P = 0.02), when adjusted for age category. Similarly, the heritability was on average 0.05 lower (P = 0.03) in studies that calculated BMI based on self-reported height and weight (N = 59 estimates) compared with studies (N = 21 estimates) that objectively assessed BMI. Eight study estimates based on a combination of both methods were excluded from this meta-regression analysis.

Together, age category, type of variance component model, method of zygosity assignment and BMI measurement, explained 46.7% of the between study heterogeneity in BMI heritability.

**FAMILY STUDIES**

A total of 28 independent estimates of BMI heritability were reported in 25 family study papers retrieved comprising 42,968 family members (Table 4; Longini et al., 1984; Hunt et al., 1989; Moll et al., 1991; Vogler et al., 1995; Bijkerk et al., 1999; Abney et al., 2001; Luke et al., 2001; Treuth et al., 2001; Arya et al., 2002; Coady et al., 2002; See et al., 2002; Henkin et al., 2003; Wu et al., 2003; Sale et al., 2005; Butte et al., 2006; Deng et al., 2006; Li et al., 2006; Bastarrachea et al., 2007; Bayoumi et al., 2007; Bogaert et al., 2008; de Oliveira et al., 2008; Patel et al., 2008; Friedlander et al., 2009; Zabaneh et al., 2009; Figure 1). Reported BMI heritability estimates ranged from 0.24 to 0.81 (5th/50th/95th centiles: 0.25/0.46/0.68), with substantial heterogeneity across estimates (I² = 90.4%, P < 0.001; Figure 4). Meta-regression found no significant effect of sample size, age, setting, or publication year on heritability estimates in family studies (Table 5).

**DISCUSSION**

In a large meta-analysis of more than 140,525 twins and 42,968 family members, we observed that estimates of BMI heritability remain broadly in line with results from the earlier review by Maes et al. (1997). A substantial amount of the variation between estimates from twin studies could be explained by considering demographic and methodological factors. Estimates from twin studies suggest that the influence of genetic factors on BMI is relatively higher in children than in adults. In addition, we have identified and quantified the likely effects of three potential methodological biases in twin studies; these are the choice of final variance component model, and the use of subjective methods to assess both zygosity and BMI. Together these factors explained nearly half of the wide heterogeneity in BMI heritability estimates between studies.

Our finding of a biphasic change in the heritability of BMI with age, increasing with age in children and adolescents and decreasing with age adults, is entirely consistent with studies using specific genetic variants. Hardy et al. (2010) reported that the effect size of the rs9939609 single nucleotide polymorphism (SNP) in FTO on BMI rises until around age 20 years, before gradually attenuating into adulthood. We acknowledge limitations in our analysis.

**TABLE 3**

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including the lack of longitudinal information and reliance on the mean or mid-point of age used in meta-regression analyses. However, in support of our findings, the heritability of BMI has previously been shown to increase over childhood (Haworth et al., 2008) and decrease with age in adults (Korkela et al., 1991) in twin studies with longitudinal data.

We found no difference in BMI heritability estimates between men and women. Individual studies have been inconsistent; some...
Table 2 | Results of meta-regression analyses to identify study-level demographic factors associated with reported BMI heritability estimates in twin studies.

| Covariate | Co-efficient (SE) | P-value | Heritability estimate for reference group | 95% CI |
|-----------|------------------|--------|------------------------------------------|-------|
| Sex (male = 0, female = 1) | 0.019 (0.02) | 0.287 | 0.73 | 0.71, 0.76 |
| Age category (childhood = 0, adulthood = 1) | −0.07 (0.02) | 0.001 | 0.80 | 0.77, 0.84 |
| Age in childhood<sup>b</sup> (per +1 year from age 10) | 0.012 (0.003) | 0.002 | 0.77 | 0.74, 0.81 |
| Age in adulthood<sup>b</sup> (per +1 year) | −0.002 (0.001) | 0.002 | 0.77 | 0.74, 0.79 |
| Setting (Europe/USA = 0, East Asian = 1) | 0.105 (0.04) | <sup>0.006</sup><sup>a</sup> | 0.74 | 0.73, 0.76 |
| Publication year (per +1 year from 1986 to 2010) | 0.003 (0.001) | 0.055 | 0.71 | 0.67, 0.75 |

Three estimates excluded from meta-regression for age as age range >20 years and no mean age reported.

Bold represents P < 0.05.

<sup>a</sup>Becomes non-significant when adjusting for age category (P = 0.12).

<sup>b</sup>Assessed as mean age where possible or mid-point of age range when age range >20 years.

have reported higher BMI heritability estimates in women (Allison et al., 1994; Harris et al., 1995; Estourgie-van Burk et al., 2006), whilst others have reported the opposite finding (Stunkard et al., 1990; Korkela et al., 1991). Other studies have found no difference or reported a pooled heritability estimate for men and women combined. BMI heritability does not differentiate fat and fat-free mass heritability, and given the differences in body composition between sexes, it is plausible that genetic contributions to the variation in BMI may operate differently in men and women.

Hur et al. (2008) reported that heritability estimates for weight, height, and BMI were consistently higher in Caucasian compared with East Asian populations. However, in that study the observed differences were small and confidence intervals were overlapping. In this study, no significant difference was found in the magnitude of BMI heritability from European and East Asian settings after accounting for whether the studies were in childhood or adulthood; however there were only a few studies in East Asians.

The majority of studies reported estimates of BMI heritability from the more parsimonious AE variance component model, rather than from the more complete ACE model. Not surprisingly, heritability (variance attributed to the A component) was higher in studies reporting the AE model, presumably because the variance that would have been attributed to C is re-allocated to components A and E in these analyses. Silventoinen et al. (2010) reported that the C component was relevant to BMI variation only in children up to age 13 years old. However, we found that exclusion of the C component had a similar magnitude of effect on higher heritability estimates in both children and adults. While omission of the C component is statistically best fitting in some analyses, smaller twin studies are often underpowered to identify a significant contribution of this component (Visscher et al., 2008a). These findings suggest that it may be inappropriate to simply ignore any contribution relating to common environmental factors.

The twin study design relies on the accurate identification of MZ and DZ twin pairs. The "gold standard" method is by DNA typing of all twins but, before genotyping technologies became widespread and cost-effective, questionnaire-based methods were common and were used to generate more than half of the BMI heritability estimates that we identified. Such questionnaires are based on subjective assessment of physical resemblance and, although some have been validated against genetic and biological methods (Sarna et al., 1978; Ooki et al., 1993), any non-differential misclassification error would inflate the E component and reduce the additive genetic component. Similarly, non-differential errors in self-reported height and weight to calculate BMI would also inflate the unique environment component. These findings are consistent with those of Macgregor et al. (2006), who showed that heritability estimates for self reported height were lower than for objectively measured height.

Heritability estimates from twin studies are considerably higher than estimates from family studies. Twin studies are generally thought to provide a more robust discrimination between environmental and genetic contributions due to the more precise estimation of shared genetic factors and the automatic matching for age, prenatal environment, and birth cohort. However, it
Table 3 | Results of meta-regression analyses to identify study-level methodological factors associated with reported BMI heritability estimates in twin studies.

| Covariate(s) Added                                                                 | Co-efficient (SE) | P-value | Heritability estimate for reference group | 95% CI | Percentage of between study variance explained* |
|-----------------------------------------------------------------------------------|-------------------|---------|------------------------------------------|--------|-----------------------------------------------|
| Sample size (per participant)                                                     | −0.000 (0.00)     | 0.202   | 0.82                                     | 0.77, 0.86 | 4.13                                           |
| Twin model used (ACE = 0, AE = 1)                                                 | 0.118 (0.03)      | <0.001  | 0.74                                     | 0.70, 0.79 | 21.89                                          |
| Zygosity determinant (DNA-based/biological = 0, Questionnaire-based = 1)          | −0.04 (0.02)      | 0.021   | 0.81                                     | 0.78, 0.85 | 8.65                                           |
| BMI measurement method (clinical = 0, self report = 1)                            | −0.048 (0.02)     | 0.027   | 0.83                                     | 0.78, 0.88 | 9.91                                           |

All meta-regression analyses adjusted for age category.

Bold represents P < 0.05.

* $\tau^2$ explained in a model containing significant covariates and age category, compared with a model containing age category alone.

Table 4 | Details of the 25 papers reporting BMI heritability from family studies.

| References                        | Location          | Study                                                                 | N    | Mean age (range) | BMI heritability | 95% CI   |
|-----------------------------------|-------------------|----------------------------------------------------------------------|------|------------------|------------------|----------|
| Friedlander et al. (2009)         | Israel            | Kibbutzim Family Study, Israel                                       | 476  | NS               | 0.64             | 0.42, 0.86|
| Zabaneh et al. (2009)             | UK                | Asian Indian families living in UK                                   | 1,634| 39.4 (25–50)     | 0.30             | 0.24, 0.36|
| de Oliveira et al. (2008)         | Brazil            | Baependi Heart Study                                                 | 1,666| 44.0             | 0.51             | 0.42, 0.60|
| Bogaert et al. (2008)             | Belgium           | Semi-rural communities in Ghent                                       | 674  | 25–45            | 0.81             | 0.61, 1.00|
| Patel et al. (2008)               | USA               | Cleveland Family Study                                               | 1,802| 35.3             | 0.55             | 0.47, 0.63|
| Bastarrachea et al. (2007)        | Mexico            | Genetics of Metabolic Diseases Family Study (GEMMM)                 | 375  | 40.3 (12–90)     | 0.36             | 0.16, 0.56|
| Bayoumi et al. (2007)             | Saudi Arabia      | Oman Family Study                                                    | 1,198| 33.8 (16–80)     | 0.68             | 0.58, 0.78|
| Butte et al. (2006)               | USA               | Viva La Familia Study (Hispanic Population, overweight proband)      | 1,030| 4–19             | 0.39             | 0.23, 0.55|
| Deng et al. (2006)                | China             | Local Shanghai population (Chinese Han ethnic group)                 | 1,031| (20–45, offspring)| 0.49             | 0.35, 0.63|
| Li et al. (2006)                  | USA               | Mexican-American Coronary Artery Disease (MACAD) project             | 478  | 34.4             | 0.59             | 0.35, 0.83|
| Sale et al. (2005)                | USA               | African American families with T2D affected members                   | 580  | 58.0 > 18        | 0.64             | 0.44, 0.84|
| Henkin et al. (2003)              | USA               | Insulin Resistance and Atherosclerosis Study (IRAS)                   | 1,032| 43.1             | 0.54             | 0.38, 0.70|
| Wu et al. (2003)                  | Taiwan            | Follow up of Mei-Jo Health Screening Programme                        | 1,724| 9–81             | 0.39             | 0.31, 0.47|
| Arya et al. (2002)                | India             | Nutrition and Growth of Certain Population Groups of Visakhapatnam    | 1,903| 21.5 (6–72)      | 0.25             | 0.15, 0.35|
| Coady et al. (2002)               | USA               | Framingham Heart Study Families                                      | 1,051| 35.3* (35–55)    | 0.37             | 0.21, 0.53|
| Hunt et al. (2002)                | Canada            | Canada Fitness Survey                                                | 1,315| 29.6 (7–69)      | 0.39             | 0.27, 0.51|
| Jee et al. (2002)                 | Korea             | Korea Medical Insurance Corporation (KMIC) family study               | 7589 | 59.8 (40–85)     | 0.26             | 0.24, 0.28|
| Abney et al. (2001)               | USA               | Hutterites of South Dakota                                           | 666  | >5               | 0.54             | 0.40, 0.68|
| Luke et al. (2001)                | Nigeria           | International Collaborative Study on Hypertension in Blacks           | 1,815| 38.8 (0–100)     | 0.49             | 0.39, 0.59|
|                                   | Jamaica           |                                                                      | 614  | 39.5 (0–100)     | 0.53             | 0.35, 0.71|
|                                   | USA               |                                                                      | 2,097| 375 (0–100)      | 0.57             | 0.47, 0.67|
| Treuth et al. (2001)              | USA               | Houston area                                                         | 303  | 28.7 (8–9, offspring)| 0.35             | 0.02, 0.68|
| Bijkerk et al. (1999)             | Netherlands       | Rotterdam Study                                                      | 1,583| 63.1 (65–70)     | 0.53             | 0.34, 0.75|
| Vogler et al. (1995)              | Denmark           | Danish Adoption Register                                              | 2,476| 42.0             | 0.34             | 0.28, 0.40|
| Moll et al. (1991)                | USA               | The Muscantine Ponderosity Study                                     | 1,580| 29.4 (4–67)      | 0.58             | 0.46, 0.70|
| Hunt et al. (1989)                | USA               | Utah pedigrees                                                       | 1,102| 35.5             | 0.24             | 0.14, 0.34|
| Longini et al. (1984)             | USA               | Tecumseh population                                                  | 5,174| 6–74             | 0.35             | 0.23, 0.47|

N, number of study participants; NS, not stated; **at entry to study.
is suggested that the twin study design overestimates heritability because of its over-reliance on critical assumptions (Kyvik, 2000). The most commonly highlighted assumption is that of equal common environments in identical and non-identical twin pairs. In reality, MZ twin pairs may share a common environment to a larger extent than DZ pairs, which would lead to an overestimation of heritability (Hettema et al., 1995; Guo, 2001). This can be overcome by studying twin pairs who were separated at birth (Stunkard et al., 1990), a natural experiment whereby individuals are genetically identical but environmentally different. However, such twins are rare and difficult to study, as adoption data is not easy to obtain. Family studies do not invoke some of the problems of the twin study design. For example, questions of equal environments and accurate zygosity recording are eliminated and singletons are more representative of the general population than twins (Estourgie-van Burk et al., 2006). However, the family study design does not permit the differentiation of familial similarity arising from genetics as opposed to shared environmental conditions. In addition, in family studies, parents and children are usually measured at very different ages, often across generations, and lack of consideration of age–genotype interactions will lead to under-estimation of heritability. This might explain why heritability estimates are generally lower in family studies despite the fact that they do not distinguish between genetic and shared environmental variance components.

A limitation of this study was the inability to distinguish effects of demographic and methodological factors from other correlated factors.
study characteristics. For example, studies on children are likely to be over-representative of individuals from more recent birth years, making it difficult to separate effects of age and era. Genetic factors may have been relatively more important before the onset of the obesogenic environment, but others have suggested that these conditions may amplify the effects of obesity susceptibility loci (Andreasen et al., 2008). Era effects were difficult to assess in this study and the separation of birth cohort and age effects on BMI heritability requires confirmation by longitudinal data from large twin cohort studies spanning wide eras.

It should be noted that the models used to calculate heritability are often based on the unlikely assumption that there is no synergistic interaction between genes. Although the study designs discussed here do not usually permit their determination because of confounding with effects of the common environment, non-additive genetic factors may also play an important role (Segal and Allison, 2002). Furthermore, gene–environment interaction is not accounted for in these studies, and any such contribution is allocated to the A component (Visscher et al., 2008b). This work was supported by the Medical Research Council.

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**CONCLUSION**

In conclusion, while many studies in the current GWAS era report estimates from heritability studies as a rationale to look for specific genetic factors for complex traits, it should be emphasized that “missing” heritability is difficult to quantify given the wide heterogeneity in these estimates due to both natural variation and differences in study design. Given the higher heritability estimates in childhood and adolescence, focusing on periods of growth and development to study the genetic etiology of obesity risk is justified.

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FIGURE A1 | Modeling heritability in twin studies. This diagram shows how twin studies can model variance components, based on the path diagram proposed by Neale and Cardon (1992). The lines adjoining variance components indicate the degree of correlation ($r$), shown for both monozygotic (MZ) and dizygotic (DZ) twins. Additive genetic variance (A) is 100% correlated for MZ twin pairs and 50% correlated for DZ twin pairs. Common environment is shared (C) 100% by both types of twin. E represents a unique environmental component, and hence there is no correlation. Statistical modeling allows phenotypic variance to be quantitatively decomposed into A, C, and E subcomponents (the ACE model). The estimate of A gives a measure of the heritability of the trait. In a more parsimonious AE model, the C component would be missing from this diagram.
PubMed Search (February 2010) using Terms:
("body mass index"[Mesh])
AND
("heritability")
Limits: Humans, English language

209 studies

145 studies excluded as quantitative estimates of BMI heritability were not reported

64 studies reporting BMI heritability ($h^2$)

Excluded studies:
- Studies using repeats of the same populations (n=10, study with max N included)
- 1 study reporting heritability of maximum BMI
- Twin studies not reporting either SE/95% CI for BMI $h^2$, or intraclass correlations, mean and SD of BMI in MZ and DZ twins (n=12)
- Family studies reporting BMI $h^2$ with no SE/95% CI (n=6)

Supplementary searches/cross-referencing:

18 twin studies reporting BMI $h^2$ estimates with SE/95%CI
13 twin studies reporting BMI $h^2$ without SE/95%CI, but with intraclass correlations, mean and SD of BMI in MZ and DZ twins
25 family studies reporting BMI $h^2$ estimates with SE/95%CI

31 twin studies for inclusion in meta-analysis
25 family studies for inclusion in meta-analysis

FIGURE A2 | Flow chart of identification of relevant literature.