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# A population-based cross-sectional study of the association between facial morphology and cardiometabolic risk factors in adolescence

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## ABSTRACT

**Objective:** To determine whether facial morphology is associated with fasting insulin, glucose and lipids independent of body mass index (BMI) in adolescents.
**Design:** Population-based cross-sectional study.
**Setting:** Avon Longitudinal Study of Parents and Children (ALSPAC), South West of England.
**Participants:** From the ALSPAC database of 4747 three-dimensional facial laser scans, collected during a follow-up clinic at the age of 15, 2348 white British adolescents (1127 males and 1221 females) were selected on the basis of complete data on cardiometabolic parameters, BMI and Tanner's pubertal stage.
**Main outcome measures:** Fasting insulin, glucose and lipids (triglycerides, high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc)).
**Results:** On the basis of the collection of 63 x, y and z coordinates of 21 anthropometric landmarks, 14 facial principal components (PCs) were identified. These components explained 82% of the variation in facial morphology and were used as exposure variables. With adjustment for age, gender and pubertal stage, seven PCs were associated with fasting insulin, none with glucose, three with triglycerides, three with HDLc and four with LDLc. After additional adjustment for BMI, four PCs remained associated with fasting insulin, one with triglycerides and two with LDLc. None of these associations withstood adjustment for multiple comparisons.
**Conclusions:** These initial hypotheses generating analyses provide no evidence that facial morphology is importantly related to cardiometabolic outcomes. Further examination might be warranted. Facial morphology assessment may have value in identifying other areas of disease risk.

## ARTICLE SUMMARY

### Article focus

- Three-dimensional imaging opens up a new chapter in investigations of facial morphology. Previous research revealed associations of facial morphology with obesity in adolescents, but whether facial morphology can be used to identify those at future risk of adverse cardiometabolic outcomes is unknown.

### Key messages

- Our results suggest that facial morphology is not strongly or consistently associated with fasting insulin, glucose or lipids, particularly after adjustment for body mass index, in white British adolescents. Facial morphology is therefore unlikely to be useful in identifying white British adolescents at future risk of adverse cardiometabolic outcomes.
- A suggested methodology can be used in future studies to explore the associations between facial parameters and other health outcomes. It might provide valuable insights into how facial morphology can be indicative of health.

### Strengths and limitations of this study

- The strengths of this study are a large sample size and the homogeneity of the sample: all participants were of white origin, born and brought up in the same region of the UK. A non-invasive, accurate and reliable method was used for capturing details of facial soft tissue morphology. A comprehensive statistical analysis was undertaken to extract principal components of facial morphology.
- The study has some limitations. First of all, the study is ethnic-specific. Second, a face could not be easily represented as a single exposure due to the complexity of its morphology and the vast amount of data captured by the laser scanning system. Therefore, some data reduction was necessary prior to the analysis. Furthermore, it was not possible to control all the confounding factors in a cross-sectional study design. Since faces of adolescents are still developing, changing their shape and size, future studies might have to investigate the relationship between these changes and cardiometabolic characteristics over time.

## INTRODUCTION

Recent technological advancements in imaging methods marked a transition from a two-dimensional to three-dimensional (3D) approach in craniofacial research, thus opening a new era. A special emphasis has been placed on the development and application of non-invasive methods to capture the human face accurately and reliably.[1 2] Among these, laser surface scanning and stereophotogrammetry have gained wide acceptance of the research community.[3] So far, a large spectrum of medical disciplines have utilised these methods in the investigations of facial growth, facial dysmorphology, craniofacial identification, as well as the influence of different medical conditions on facial phenotype.[4–12] Therefore, an exciting opportunity has occurred to explore whether facial characteristics can serve as new diagnostic measures of illnesses.

Childhood obesity is becoming an epidemic health problem.[13] It is evident from many studies that it is associated with an increased risk of type 2 diabetes and cardiovascular disease later in life.[14–16] Despite this fact, the relation between obesity and craniofacial development has been rarely investigated. Bimaxillary prognathism (overdeveloped jaws in the sagittal direction) and increased transverse facial dimensions seem to indicate the difference between obese adolescents and their normal-weighted peers.[17–19] However, the association between metabolic phenotype and facial form has not been addressed previously.

In order to investigate this problem, a large sample and a comprehensive 3D approach to facial measurements are needed. In this cross-sectional study, which can be considered to be hypothesis generating, we examined the associations of facial soft tissue morphology with metabolic phenotype (fasting insulin, glucose, triglycerides, high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc)) in a large general population cohort of adolescents using an existing database of 3D facial laser scans.

## MATERIAL AND METHODS

### Sample

We used the data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK-based longitudinal birth cohort study designed to explore genetic and environmental influences on health and well-being.[20 21] All pregnant women were eligible to participate in ALSPAC if their estimated delivery date fell between 1 April 1991 and 31 December 1992, inclusive. In total, 14 541 pregnant women were recruited, and from these women there were 14 676 live-born infants. Since age 7, surviving offspring have been invited to regular follow-up clinics.

The current study was approved by the ALSPAC Law and Ethics Committee and the Local Research Ethics Committee and informed consent was obtained from children and their parents or guardians. The data collected during an annual follow-up clinic at the age of 15, which was attended by 5235 adolescents, were examined. On that occasion, facial laser scanning was performed, and after a dropout of 488 individuals due to the low quality of the scans or some sort of facial dysmorphology, a database of 4747 individuals (2233 males and 2514 females) was formed.[22] Out of these, we selected 2348 white adolescents (1127 males and 1221 females), with complete data related to the outcome and confounding variables (see below), as facial laser scans were used to derive exposure variables. The flow chart diagram (figure 1) shows a gradual selection of individuals who comprised the final sample. In order to make sure that there was no selection bias, we first compared facial principal components (PCs; ie, exposure variables; see below) of the study sample (2348 adolescents) with those of 4747 adolescents forming a 3D facial database[22] and concluded that there was no reason to believe that selected individuals were significantly different in terms of facial morphology. Second, we compared observed values for outcomes and confounding variables in the study sample (2348 adolescents) with imputed variables in the eligible sample of the follow-up clinic (5235 adolescents), which were published as supplementary online material of the previous study.[23] The distributions in imputed datasets were very similar to those observed, providing some evidence that the missing data were missing at random.

### Measures

#### Exposure variables

Facial laser scans were used to derive PCs of facial morphology, which served as the exposure variables. This is explained in detail in the section on statistical analysis. Prior to this, it was necessary to perform three steps, which will be described here. First of all, facial scans were processed. The validity and reliability of the laser scanning procedure, as well as the processing stages of the scans, have been previously investigated.[24–27] Second, 21 anthropometric landmarks were manually identified on facial scans by one experienced examiner (figure 2), according to their respective definitions by Farkas,[28] and their x, y and z coordinates were saved for the subsequent analysis. Previous research showed that these landmarks are clinically reliable.[29 30] Finally, facial scans were initially normalised according to the natural head position, with the origin of the coordinate system set at the point halfway between the inner corners of the eyes (mid-endocanthion). The x-axis was pointing left, from the right eye to the left eye, the y-axis was pointing vertically upwards from the chin to the forehead and the z-axis was pointing outwards, in the nose direction. The coronal, sagittal and transverse planes were taken as the xy, yz and xz planes, respectively.[1 2 8 22 29]

#### Outcome variables

Fasting insulin, fasting glucose, triglycerides, HDLc and LDLc were taken as the outcome variables. Full details of their assessment have been previously reported.[23]

#### Confounding variables

Since this study is exploratory (being the first to examine these associations) and our main motivation

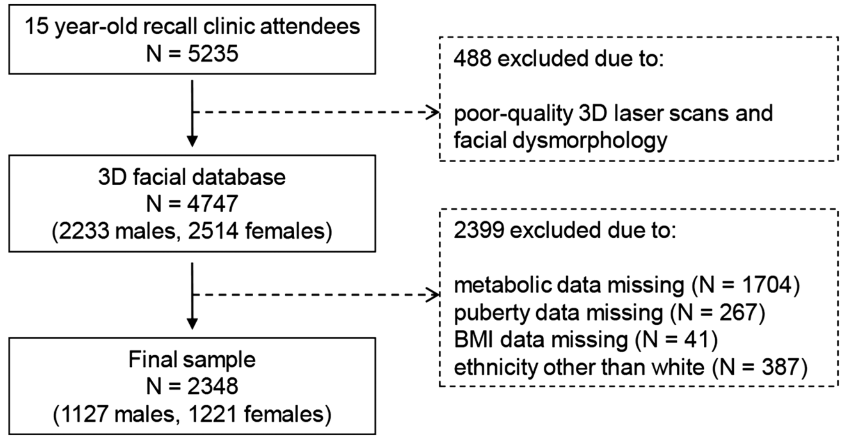


**Figure 1** Flow chart showing the selection of a study sample from a 15+ year follow-up clinic of the Avon Longitudinal Study of Parents and Children. All analyses presented in this paper are based on 2348 participants with complete data on facial soft tissue morphology (exposure), blood-based indicators of insulin resistance and associated cardiometabolic risk factors (outcomes) and body mass index and pubertal stage (covariables).

was to understand whether facial morphology might be able to predict those at risk of cardiometabolic disease over and above simple measurement of adiposity, we did not adjust for a wide range of confounding variables. However, we adjusted for age, pubertal stage and body mass index (BMI), as these are potentially important predictors of cardiometabolic risk and we would want to be clear that facial morphology predicted outcome over and above these. The age of the participants was recorded in months as they arrived at the clinic. Pubertal status was assessed on participants' self report with Tanner's questionnaires.

## Statistical analyses

Participant characteristics were summarised with means (SD) for continuous, approximately normally distributed variables, median (IQR) for continuous right skewed variables, and the number (%) of categorical variables.

Generalised Procrustes Analysis (GPA) was performed on landmark configurations (each consisting of 63 x, y and z coordinates of 21 facial landmarks) in order to remove differences in landmark positions attributable to translation and rotation.[31–33] Scaling was not performed in order to preserve facial size. Principal Component Analysis (PCA) was used to reduce the set of 63 coordinates into a smaller number of independent components of facial morphology. According to the 'Kaiser-Guttman criterion', PCs with eigenvalues greater than the average eigenvalue value were retained[34–36] and saved as new exposure variables. The rotation method used for PCA was varimax with Kaiser normalisation.[37] GPA was performed in the open source software R project and PCA in SPSS V.17.0 (SPSS Inc, Chicago, Illinois, USA).

While this is a cross-sectional study, in all our analyses we examined the association of PCs of facial morphology (as exposures) with fasting insulin, glucose, triglycerides, HDLc and LDLc (as outcomes) using multivariable linear regression models. No evidence was found for any gender interactions (all p values ≥0.1), and therefore analyses are presented with both genders combined. In the first model, we adjusted for age, gender and

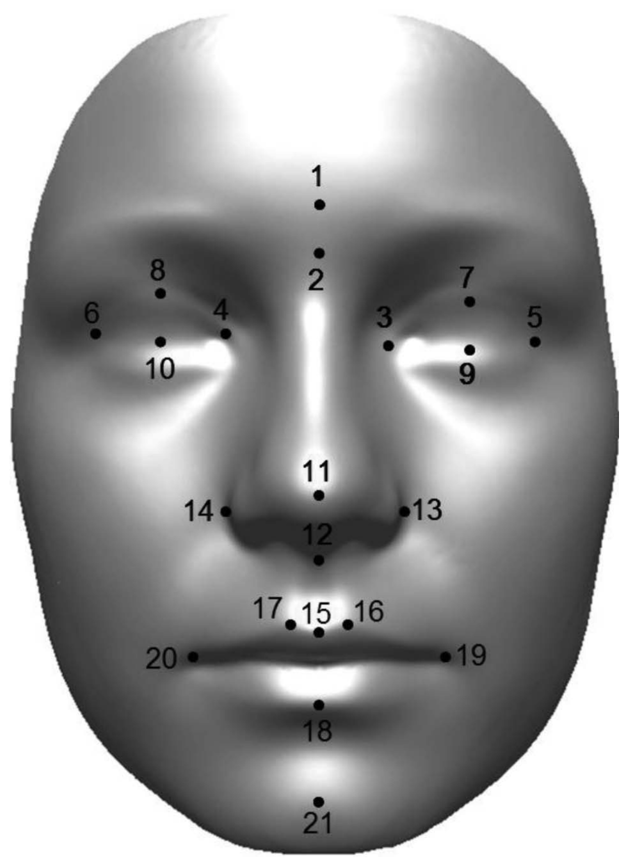


**Figure 2** Twenty-one anthropometric landmarks which were identified on facial laser scans of participants. (1) Glabella (g); (2) Nasion (n); (3) Endocanthion left (enl); (4) Endocanthion right (enr); (5) Exocanthion left (exl); (6) Exocanthion right (exr); (7) Palpebrale superius left (psl); (8) Palpebrale superius right (psr); (9) Palpebrale inferius left (pil); (10) Palpebrale inferius right (pir); (11) Pronasale (prn); (12) Subnasale (sn); (13) Alare left (all); (14) Alare right (alr); (15) Labiale superius (ls); (16) Crista philtri left (cphl); (17) Crista philtri right (cphr); (18) Labiale inferius (li); (19) Cheilion left (chl); (20) Cheilion right (chr); (21) Pogonion (pg). Definitions by Farkas[28] were used. Reprinted from the author's previous publication with permission from 'John Wiley and Sons'.

pubertal stage. In the second model, we adjusted for age, gender, pubertal stage and BMI and examined how much this reduced any associations of facial PCs with the outcomes. Fasting insulin and triglyceride levels were right (positively) skewed and their logged values were used in the linear regression models, which ensured that the model residuals were approximately normally distributed. The resultant regression coefficients with 95%CI are presented.

In these multivariable analyses, 140 comparisons were made (14 exposures with 5 outcomes and 2 models). In initial analyses, we considered the conventional 0.05 level of statistical significance. We then adjusted for multiple comparisons using a Bonferroni correction by dividing 0.05 by 140; thus, for these corrected analyses, a p value of 0.0004 would be considered to be statistically significant at the 0.05 level. All statistical analyses were performed in SPSS V.17.0 (SPSS Inc).

## RESULTS

Table 1 shows the characteristics of the study participants. The PCA identified 14 PCs of facial morphology (table 2). Each PC consisted of a number of coordinates of anthropometric landmarks. For example, the first PC (PC 1) comprised 17 *y* coordinates of landmarks located in the upper and lower thirds of the face. These coordinates represented facial height (size). In order to facilitate the understanding and interpretation of individual PCs, they are presented graphically in figure 3. The first three PCs (facial size, inter-eye distance and prominence of the nose and lower lip) accounted for almost half of the total variation (45.7%). The other 11 PCs contributed to facial variation to a much lesser extent (between 1.6 and 5%), but marked those subtle features which make the faces unique.

The multivariable associations of the 14 PCs with cardiometabolic outcomes are shown in tables 3–7. With adjustment for age, gender and pubertal stage (model 1), seven PCs were associated with fasting insulin, none with fasting glucose, three PCs with triglycerides and HDLc and four PCs with LDLc. After additional adjustment for BMI (model 2), four PCs remained associated with fasting insulin, none with glucose, one with triglycerides, none with HDLc and two with LDLc. However, none of these associations withstood adjustment for multiple comparisons.

## DISCUSSION

Laser surface scanning is a non-invasive technology which enables the accurate and precise analysis of facial morphology.[1 2 24–26] Owing to its portability, easy application and relatively low cost, this technique is very suitable for epidemiological field studies. The vast amount of data captured by the system (more than 40 000 points, each consisting of x, y and z coordinates) is a testimony to the complexity of facial surfaces. For this reason, the face cannot be easily represented as a single exposure.

Therefore, it was necessary to make some facial data-reduction prior to its meaningful use. First of all,

**Table 1** Characteristics of the study sample

| Categories/units | Males N=1127 | Females N=1221 | All N=2348 |
|---|---|---|---|
| Age | | | |
| Mean (months) | 184.8 (3.0) | 184.9 (3.2) | 184.9 (3.1) |
| Tanner's pubertal stages | | | |
| Stage I n (%) | 0 | 0 | 0 |
| Stage II n (%) | 8 (0.7) | 6 (0.5) | 14 (0.6) |
| Stage III n (%) | 64 (5.7) | 118 (9.7) | 182 (7.8) |
| Stage IV n (%) | 552 (49) | 632 (51.8) | 1184 (50.4) |
| Stage V n (%) | 503 (44.6) | 465 (38.1) | 968 (41.2) |
| BMI | | | |
| Median (kg/m$^2$) | 20.4 (18.9, 22.3) | 21.2 (19.5, 23.4) | 20.8 (19.1, 23.0) |
| Fasting insulin | | | |
| Median (IU/l) | 8.2 (5.9, 10.9) | 9.7 (7.4, 13.0) | 9.0 (6.6, 12.0) |
| Fasting glucose | | | |
| Mean (mmol/l) | 5.3 (0.4) | 5.1 (0.3) | 5.2 (0.4) |
| Total cholesterol | | | |
| Mean (mmol/l) | 3.6 (0.6) | 3.9 (0.6) | 3.8 (0.6) |
| Triglycerides | | | |
| Median (mmol/l) | 0.7 (0.6, 1.0) | 0.8 (0.6, 1.0) | 0.7 (0.6, 1.0) |
| HDLc | | | |
| Mean (mmol/l) | 1.2 (0.3) | 1.4 (0.3) | 1.3 (0.3) |
| LDLc | | | |
| Mean (mmol/l) | 2.0 (0.5) | 2.2 (0.6) | 2.1 (0.6) |

Number (%) for categorical variables, mean (SD) or median (IQR) for continuously distributed variables are presented.
BMI, body mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

**Table 2** The results of the principal component analysis showing partial correlation coefficients between coordinates of anthropometric landmarks and facial principal components

| | Facial principal components | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Coordinates** | **PC1** | **PC2** | **PC3** | **PC4** | **PC5** | **PC6** | **PC7** | **PC8** | **PC9** | **PC10** | **PC11** | **PC12** | **PC13** | **PC14** |
| Ls (y) | −0.84 | | | | | | | | | | | | | |
| Enl (y) | 0.84 | | | | | | | | | | | | | |
| Cphr (y) | −0.84 | | | | | | | | | | | | | |
| Cphl (y) | −0.83 | | | | | | | | | | | | | |
| Enr (y) | 0.83 | | | | | | | | | | | | | |
| Pg (y) | −0.82 | | | | | | | | | | | | | |
| Chr (y) | −0.82 | | | | | | | | | | | | | |
| Pil (y) | 0.81 | | | | | | | | | | | | | |
| Chl (y) | −0.81 | | | | | | | | | | | | | |
| Pir (y) | 0.81 | | | | | | | | | | | | | |
| Psl (y) | 0.79 | | | | | | | | | | | | | |
| Li (y) | −0.78 | | | | | | | | | | | | | |
| Psr (y) | 0.78 | | | | | | | | | | | | | |
| Exr (y) | 0.75 | | | | | | | | | | | | | |
| Exl (y) | 0.74 | | | | | | | | | | | | | |
| G (y) | 0.64 | | | | | | | | | | | | | |
| N (y) | 0.62 | | | | | | | | | | | | | |
| Psl (x) | | 0.94 | | | | | | | | | | | | |
| Psr (x) | | −0.93 | | | | | | | | | | | | |
| Pil (x) | | 0.93 | | | | | | | | | | | | |
| Pir (x) | | −0.92 | | | | | | | | | | | | |
| Enr (x) | | −0.83 | | | | | | | | | | | | |
| Enl (x) | | 0.83 | | | | | | | | | | | | |
| Exr (x) | | −0.79 | | | | | | | | | | | | |
| Exl (x) | | 0.75 | | | | | | | | | | | | |
| All (z) | | | −0.80 | | | | | | | | | | | |
| Alr (z) | | | −0.79 | | | | | | | | | | | |
| Sn (z) | | | −0.79 | | | | | | | | | | | |
| Prn (z) | | | −0.68 | | | | | | | | | | | |
| Li (z) | | | 0.56 | | | | | | | | | | | |
| Ls (z) | | | | 0.87 | | | | | | | | | | |
| Cphl (z) | | | | 0.86 | | | | | | | | | | |
| Cphr (z) | | | | 0.86 | | | | | | | | | | |
| Pg (z) | | | | −0.78 | | | | | | | | | | |
| G (z) | | | | | −0.86 | | | | | | | | | |
| N (z) | | | | | −0.82 | | | | | | | | | |
| Pir (z) | | | | | 0.65 | | | | | | | | | |
| Pil (z) | | | | | 0.64 | | | | | | | | | |
| Prn (y) | | | | | | 0.82 | | | | | | | | |
| All (y) | | | | | | 0.79 | | | | | | | | |
| Alr (y) | | | | | | 0.77 | | | | | | | | |
| Sn (y) | | | | | | 0.72 | | | | | | | | |
| Chr (x) | | | | | | | 0.82 | | | | | | | |
| Chl (x) | | | | | | | −0.82 | | | | | | | |
| Chl (z) | | | | | | | 0.80 | | | | | | | |
| Chr (z) | | | | | | | 0.80 | | | | | | | |
| Sn (x) | | | | | | | | 0.94 | | | | | | |
| Prn (x) | | | | | | | | 0.90 | | | | | | |
| G (x) | | | | | | | | | 0.97 | | | | | |
| N (x) | | | | | | | | | 0.97 | | | | | |
| Exl (z) | | | | | | | | | | −0.62 | | | | |
| Exr (z) | | | | | | | | | | −0.60 | | | | |
| Psl (z) | | | | | | | | | | | 0.80 | | | |
| Psr (z) | | | | | | | | | | | 0.79 | | | |
| Ls (x) | | | | | | | | | | | | 0.92 | | |
| Cphr (x) | | | | | | | | | | | | | 0.82 | |
| Cphl (x) | | | | | | | | | | | | | −0.78 | |
| Pg (x) | | | | | | | | | | | | | | 0.91 |
| Li (x) | | | | | | | | | | | | | | 0.76 |

Only major landmarks contributing to each principal component (PC) are shown (coefficients with absolute values above 0.5). Anthropometric landmarks are explained in figure 2 and the principal components in figure 3.

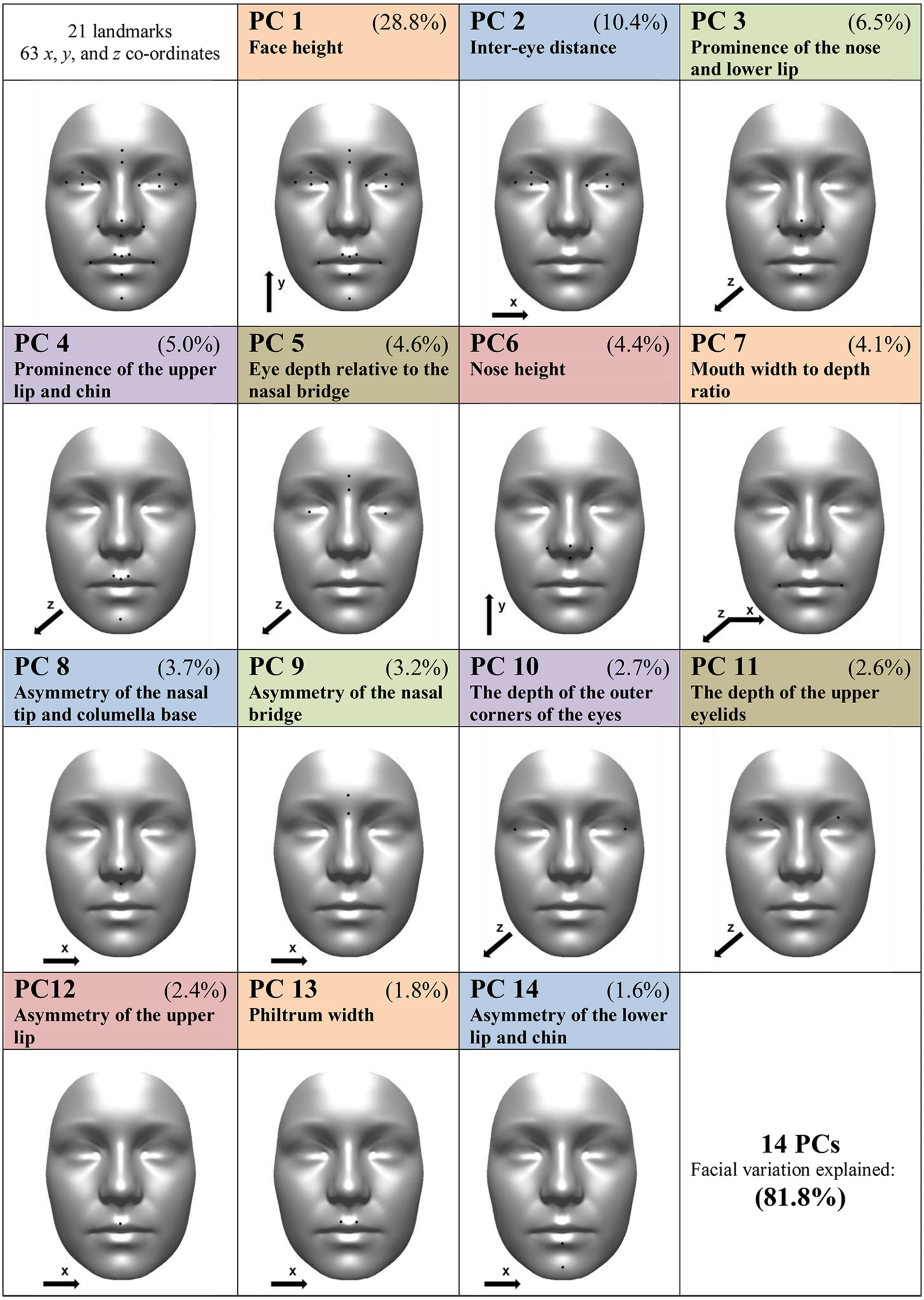


**Figure 3** Facial principal components (PCs). Numbers indicate percentages of normal facial variation explained by the given principal component. Coordinates which constitute each principal component are marked on the face (refer to table 2), and arrows indicate the x, y and z directions.

GPA (a widely established method in statistical shape analysis) was used to place landmark coordinates in the same space reducing confounding errors (rotation and translation). Second, PCA was applied on the set of coordinates and 14 facial PCs were identified, which accounted for almost 82% of the total variation in

**Table 3** Multivariable association of 14 facial principal components (exposures) with fasting insulin as an outcome

| PC | Model 1 B | Model 1 (95% CI) | Model 1 p Value | Model 2 B | Model 2 (95% CI) | Model 2 p Value |
|---|---|---|---|---|---|---|
| PC1 | 0.004 | (−0.006 to 0.014) | 0.397 | *−0.011* | *(−0.021 to −0.001)* | *0.026* |
| PC2 | *0.011* | *(0.002 to 0.019)* | *0.011* | −0.003 | (−0.011 to 0.005) | 0.419 |
| PC3 | *0.010* | *(0.002 to 0.019)* | *0.015* | 0.002 | (−0.006 to 0.010) | 0.681 |
| PC4 | −0.001 | (−0.009 to 0.007) | 0.803 | 0.002 | (−0.005 to 0.010) | 0.538 |
| PC5 | *−0.011* | *(−0.020 to −0.002)* | *0.019* | 0.001 | (−0.008 to 0.010) | 0.802 |
| PC6 | *0.010* | *(0.002 to 0.018)* | *0.013* | 0.001 | (−0.007 to 0.009) | 0.787 |
| PC7 | 0.000 | (−0.008 to 0.008) | 0.935 | 0.005 | (−0.003 to 0.013) | 0.190 |
| PC8 | *−0.017* | *(−0.028 to −0.006)* | *0.003* | *−0.014* | *(−0.024 to −0.004)* | *0.009* |
| PC9 | *0.012* | *(0.003 to 0.020)* | *0.005* | *0.012* | *(0.004 to 0.020)* | *0.002* |
| PC10 | 0.005 | (−0.003 to 0.014) | 0.190 | 0.002 | (−0.006 to 0.010) | 0.601 |
| PC11 | *0.026* | *(0.018 to 0.034)* | *<0.001* | *0.009* | *(0.001 to 0.017)* | *0.029* |
| PC12 | 0.006 | (−0.002 to 0.014) | 0.151 | 0.005 | (−0.002 to 0.013) | 0.172 |
| PC13 | −0.005 | (−0.014 to 0.003) | 0.220 | 0.001 | (−0.007 to 0.009) | 0.867 |
| PC14 | −0.003 | (−0.011 to 0.005) | 0.485 | −0.005 | (−0.012 to 0.003) | 0.236 |

Model 1 is adjusted for age, gender and puberty (adjusted $R^2$=0.07); model 2 is adjusted for age, gender, puberty and body mass index (adjusted $R^2$=0.17). PC, principal component of the face (refer to the text, table 2 and figure 3 for an explanation); B, regression coefficient. Italics indicate statistically significant associations at the level p<0.05 (before Bonferroni corrections).

normal facial form, consisting of size and shape. Normal facial variation was recently analysed on a complete sample of 4747 faces from the ALSPAC database and the same number of PCs was extracted, with an almost identical order of individual PCs and very similar percentages of variation.[22]

The application of this statistical technique is not new. Previously, PCA was performed on two-dimensional data sets, obtained from either lateral skull radiographs or photographs of both children and adults.[38–41] The resultant number of PCs in these studies was between 6 and 8, and these explained up to 90% of the total variance in facial profile, based on linear measurements between anthropometric landmarks, or their coordinates. However, with the introduction of sophisticated 3D imaging techniques, the amount of data entering PCA increased significantly. Therefore, the number of PCs which represent facial variation also increased: between 14 and 16 PCs have been reported to account for between 86% and 92% of the total variation.[10 11 41 42]

Although the first three components in the current study explain almost half of the total variation, other components are also important, since they represent subtle changes that make the face unique. Therefore, a decision was made to keep all of them in the subsequent multivariable analyses. Following adjustment for BMI

**Table 4** Multivariable association of 14 facial principal components (exposures) with fasting glucose as an outcome

| PC | Model 1 B | Model 1 (95% CI) | Model 1 p Value | Model 2 B | Model 2 (95% CI) | Model 2 p Value |
|---|---|---|---|---|---|---|
| PC1 | −0.010 | (−0.028 to 0.008) | 0.286 | −0.017 | (−0.035 to 0.001) | 0.065 |
| PC2 | 0.003 | (−0.011 to 0.018) | 0.674 | −0.003 | (−0.018 to 0.012) | 0.724 |
| PC3 | 0.010 | (−0.005 to 0.025) | 0.197 | 0.006 | (−0.009 to 0.021) | 0.458 |
| PC4 | −0.008 | (−0.023 to 0.007) | 0.310 | −0.006 | (−0.021 to 0.009) | 0.427 |
| PC5 | 0.002 | (−0.014 to 0.019) | 0.769 | 0.007 | (−0.009 to 0.024) | 0.381 |
| PC6 | 0.012 | (−0.003 to 0.026) | 0.115 | 0.009 | (−0.006 to 0.023) | 0.243 |
| PC7 | 0.009 | (−0.006 to 0.023) | 0.226 | 0.011 | (−0.004 to 0.025) | 0.147 |
| PC8 | −0.002 | (−0.016 to 0.013) | 0.808 | −0.001 | (−0.015 to 0.014) | 0.924 |
| PC9 | −0.004 | (−0.018 to 0.011) | 0.613 | −0.003 | (−0.018 to 0.011) | 0.657 |
| PC10 | −0.011 | (−0.026 to 0.003) | 0.124 | −0.013 | (−0.027 to 0.002) | 0.083 |
| PC11 | 0.008 | (−0.007 to 0.023) | 0.301 | 0.002 | (−0.014 to 0.017) | 0.838 |
| PC12 | 0.005 | (−0.010 to 0.019) | 0.535 | 0.005 | (−0.010 to 0.019) | 0.521 |
| PC13 | 0.003 | (−0.013 to 0.018) | 0.730 | 0.004 | (−0.011 to 0.020) | 0.563 |
| PC14 | 0.001 | (−0.013 to 0.016) | 0.866 | 0.002 | (−0.013 to 0.016) | 0.812 |

Model 1 is adjusted for age, gender and puberty (adjusted $R^2$=0.05); model 2 is adjusted for age, gender, puberty and body mass index (adjusted $R^2$=0.06). PC, principal component of the face (refer to the text, table 2 and figure 3 for an explanation); B, regression coefficient.

**Table 5** Multivariable association of 14 facial principal components (exposures) with triglycerides as an outcome

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| PC | B | (95% CI) | p Value | B | (95% CI) | p Value |
| PC1 | 0.010 | (−0.001 to 0.020) | 0.073 | 0.000 | (−0.011 to 0.010) | 0.975 |
| PC2 | 0.004 | (−0.003 to 0.010) | 0.291 | −0.003 | (−0.010 to 0.003) | 0.351 |
| PC3 | *0.008* | *(0.001 to 0.015)* | *0.019* | 0.004 | (−0.003 to 0.010) | 0.287 |
| PC4 | −0.005 | (−0.001 to 0.002) | 0.177 | −0.003 | (−0.009 to 0.004) | 0.397 |
| PC5 | −0.001 | (−0.008 to 0.007) | 0.818 | 0.005 | (−0.002 to 0.012) | 0.193 |
| PC6 | *0.011* | *(0.004 to 0.017)* | *0.001* | *0.007* | *(0.000 to 0.013)* | *0.045* |
| PC7 | 0.000 | (−0.007 to 0.006) | 0.945 | 0.002 | (−0.005 to 0.008) | 0.563 |
| PC8 | −0.005 | (−0.012 to 0.001) | 0.118 | −0.004 | (−0.011 to 0.002) | 0.206 |
| PC9 | 0.005 | (−0.001 to 0.012) | 0.113 | 0.006 | (−0.001 to 0.012) | 0.086 |
| PC10 | 0.005 | (−0.001 to 0.012) | 0.113 | 0.004 | (−0.003 to 0.010) | 0.263 |
| PC11 | *0.008* | *(0.001 to 0.014)* | *0.024* | <0.001 | (−0.007 to 0.007) | 0.988 |
| PC12 | −0.003 | (−0.010 to 0.003) | 0.341 | −0.003 | (−0.010 to 0.003) | 0.317 |
| PC13 | −0.004 | (−0.011 to 0.003) | 0.213 | −0.002 | (−0.009 to 0.005) | 0.601 |
| PC14 | −0.005 | (−0.011 to 0.002) | 0.143 | −0.005 | (−0.012 to 0.001) | 0.118 |

Model 1 is adjusted for age, gender and puberty (adjusted $R^2$=0.03); model 2 is adjusted for age, gender, puberty and body mass index (adjusted $R^2$=0.06). PC, principal component of the face (refer to the text, table 2 and figure 3 for an explanation); B, regression coefficient. Italics indicate statistically significant associations at the level p<0.05 (before Bonferroni corrections).

and taking account of multiple statistical testing, we did not find that any of these PCs were associated with fasting insulin or associated cardiometabolic risk factors, suggesting that facial morphology is unlikely to be a reliable way of predicting young people at future risk of type 2 diabetes or cardiovascular disease. Consistent with other large epidemiological studies conducted in healthy general population samples, we were not able to directly measure insulin resistance using the gold standard euglycaemic hyperinsulinaemic clamp. Fasting insulin has been shown to have modest-to-strong correlations with clamp-assessed insulin resistance (correlation coefficients 0.5–0.9) in children and adolescents.[43 44] Any measurement error is likely to be non-differential and therefore would be expected to bias results towards the null. Since strong associations of these outcomes with BMI have been shown in ALSPAC,[23] any associations with a better measure of insulin resistance are unlikely to be stronger than those of BMI.

The study has some limitations. First of all, it is ethnic-specific, and therefore future studies will have to address the research question in different ethnic groups. Second, facial variation can be affected by many different factors. While it is possible to control the age, gender and ethnicity of the sample, environmental factors present a greater challenge, even with a good

**Table 6** Multivariable association of 14 facial principal components (exposures) with high-density lipoprotein cholesterol as an outcome

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| PC | B | (95% CI) | p Value | B | (95% CI) | p Value |
| PC1 | *−0.028* | *(−0.042 to −0.014)* | *<0.001* | −0.013 | (−0.027 to 0.001) | 0.073 |
| PC2 | −0.005 | (−0.017 to 0.006) | 0.351 | 0.008 | (−0.003 to 0.020) | 0.154 |
| PC3 | −0.006 | (−0.017 to 0.006) | 0.339 | 0.003 | (−0.008 to 0.014) | 0.611 |
| PC4 | 0.007 | (−0.004 to 0.019) | 0.228 | 0.004 | (−0.008 to 0.015) | 0.538 |
| PC5 | 0.007 | (−0.006 to 0.020) | 0.279 | −0.005 | (−0.018 to 0.008) | 0.443 |
| PC6 | *−0.014* | *(−0.025 to −0.003)* | *0.016* | −0.005 | (−0.016 to 0.006) | 0.408 |
| PC7 | 0.003 | (−0.008 to 0.015) | 0.570 | −0.001 | (−0.012 to 0.010) | 0.797 |
| PC8 | 0.009 | (−0.003 to 0.020) | 0.129 | 0.007 | (−0.004 to 0.018) | 0.205 |
| PC9 | 0.001 | (−0.010 to 0.012) | 0.883 | 0.000 | (−0.011 to 0.011) | 0.940 |
| PC10 | −0.010 | (−0.022 to 0.001) | 0.078 | −0.007 | (−0.018 to 0.004) | 0.229 |
| PC11 | *−0.022* | *(−0.034 to −0.011)* | *<0.001* | −0.006 | (−0.017 to 0.006) | 0.340 |
| PC12 | 0.005 | (−0.007 to 0.016) | 0.413 | 0.005 | (−0.006 to 0.016) | 0.348 |
| PC13 | 0.005 | (−0.007 to 0.017) | 0.387 | −0.001 | (−0.012 to 0.011) | 0.905 |
| PC14 | 0.000 | (−0.012 to 0.011) | 0.959 | 0.001 | (−0.010 to 0.012) | 0.798 |

Model 1 is adjusted for age, gender and puberty (adjusted $R^2$=0.08); model 2 is adjusted for age, gender, puberty and body mass index (adjusted $R^2$=0.13). PC, principal component of the face (refer to the text, table 2 and figure 3 for an explanation); B, regression coefficient. Italics indicate statistically significant associations at the level p<0.05 (before Bonferroni corrections).

**Table 7** Multivariable association of 14 facial principal components (exposures) with low-density lipoprotein cholesterol as an outcome

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| PC | B | (95% CI) | p Value | B | (95% CI) | p Value |
| PC1 | 0.004 | (−0.023 to 0.030) | 0.793 | −0.014 | (−0.041 to 0.013) | 0.307 |
| PC2 | −0.004 | (−0.026 to 0.018) | 0.708 | −0.020 | (−0.042 to 0.002) | 0.074 |
| PC3 | *0.038* | *(0.016 to 0.061)* | *0.001* | *0.028* | *(0.006 to 0.050)* | *0.013* |
| PC4 | −0.002 | (−0.025 to 0.020) | 0.855 | 0.002 | (−0.020 to 0.024) | 0.851 |
| PC5 | 0.006 | (−0.019 to 0.031) | 0.621 | 0.021 | (−0.004 to 0.046) | 0.108 |
| PC6 | *0.027* | *(0.005 to 0.049)* | *0.014* | 0.016 | (−0.005 to 0.038) | 0.140 |
| PC7 | 0.012 | (−0.009 to 0.034) | 0.263 | 0.018 | (−0.004 to 0.040) | 0.103 |
| PC8 | *−0.024* | *(−0.045 to −0.002)* | *0.033* | *−0.022* | *(−0.043 to 0.000)* | *0.048* |
| PC9 | −0.014 | (−0.035 to 0.008) | 0.222 | −0.013 | (−0.034 to 0.008) | 0.235 |
| PC10 | 0.006 | (−0.015 to 0.028) | 0.561 | 0.002 | (−0.019 to 0.024) | 0.824 |
| PC11 | *0.031* | *(0.009 to 0.053)* | *0.006* | 0.011 | (−0.011 to 0.034) | 0.322 |
| PC12 | 0.021 | (−0.001 to 0.043) | 0.056 | 0.020 | (−0.001 to 0.042) | 0.061 |
| PC13 | −0.006 | (−0.029 to 0.016) | 0.582 | 0.001 | (−0.022 to 0.023) | 0.961 |
| PC14 | 0.013 | (−0.009 to 0.035) | 0.238 | 0.011 | (−0.010 to 0.033) | 0.315 |

Model 1 is adjusted for age, gender and puberty (adjusted $R^2$=0.05); model 2 is adjusted for age, gender, puberty and body mass index (adjusted $R^2$=0.06). PC, principal component of the face (refer to the text, table 2 and figure 3 for an explanation); B, regression coefficient. Italics indicate statistically significant associations at the level p<0.05 (before Bonferroni corrections).

research strategy, as many of them can be unknown at the time of the study. The face changes throughout life, increasing in size and changing in shape.[1 2 7] This holds true for the present sample consisting of 15-year-old adolescents. The cross-sectional design of the study did not allow us to track these changes and analyse their relationship with metabolic phenotype through time. That may be more important than the assessment of variation among individuals and thus should be considered in future studies.

## CONCLUSION

Our results do not provide strong evidence that facial morphology is robustly and importantly associated with cardiometabolic risk factors. The associations identified were not consistent across outcomes, were weak in magnitude, attenuated with adjustment for BMI, and did not withstand correction for multiple statistical testing. Further study of facial parameters with cardiometabolic and/or other health outcomes might provide valuable insights into how facial morphology can be indicative of health.

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**Contributors** JD, DAL and SR were responsible for the conception and the design of the study. JD and SR initiated the study. JD and AMT collected the data. JD, DAL and RP were responsible for statistical analyses. JD, AMT, AIZ and SR analysed and interpreted the data on facial parameters. JD, DAL and RP analysed and interpreted the data on metabolic parameters. JD and DAL wrote the first draft of the paper. All authors contributed to and approved the final version of the paper.

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