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# Insulin resistance and obesity, and their association with depression in relatively young people

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### Insulin resistance and obesity, and their association with depression in relatively young people: findings from a large UK birth cohort

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#### Abstract

**Background.** Depression frequently co-occurs with disorders of glucose and insulin homeostasis (DGIH) and obesity. Low-grade systemic inflammation and lifestyle factors in childhood may predispose to DGIH, obesity and depression. We aim to investigate the cross-sectional and longitudinal associations among DGIH, obesity and depression, and to examine the effect of demographics, lifestyle factors and antecedent low-grade inflammation on such associations in young people.

**Methods.** Using the Avon Longitudinal Study of Parents and Children birth cohort, we used regression analyses to examine: (1) cross-sectional and (2) longitudinal associations between measures of DGIH [insulin resistance (IR); impaired glucose tolerance] and body mass index (BMI) at ages 9 and 18 years, and depression (depressive symptoms and depressive episode) at age 18 years and (3) whether sociodemographics, lifestyle factors or inflammation [interleukin-6 (IL-6) at age 9 years] confounded any such associations.

**Results.** We included 3208 participants. At age 18 years, IR and BMI were positively associated with depression. These associations may be explained by sociodemographic and lifestyle factors. There were no longitudinal associations between DGIH/BMI and depression, and adjustment for IL-6 and C-reactive protein did not attenuate associations between IR/BMI and depression; however, the longitudinal analyses may have been underpowered.

**Conclusions.** Young people with depression show evidence of DGIH and raised BMI, which may be related to sociodemographic and lifestyle effects such as deprivation, smoking, ethnicity and gender. In future, studies with larger samples are required to confirm this. Preventative strategies for the poorer physical health outcomes associated with depression should focus on malleable lifestyle factors.

#### Introduction

Depression in 10–24 year olds is a leading cause of disease burden throughout the world (Gore *et al.*, 2011). An important aspect of this burden is the co-occurrence of disorders of glucose and insulin homeostasis (DGIH) [type-2 diabetes mellitus (T2DM) and prediabetes] and obesity (Roy and Lloyd, 2012; Vancampfort *et al.*, 2016). This may be a consequence of disease-related factors such as symptomatology [e.g. appetite disturbance and decreased physical activity (Lysy *et al.*, 2008; Vancampfort *et al.*, 2017)], increased rates of smoking (Katon *et al.*, 2004), alcohol use (Tann *et al.*, 2007), an unhealthy diet (Firth *et al.*, 2018) and also sociodemographic risk factors such as either male (Nichols and Brown, 2003; Ali *et al.*, 2006; Ding *et al.*, 2006; Timonen *et al.*, 2006; Perreault *et al.*, 2008; Menke *et al.*, 2014) or female (Anderson *et al.*, 2001; Blazer *et al.*, 2002; Nichols and Brown, 2003; Ali *et al.*, 2008; Lloyd *et al.*, 2018) sex, non-white European race/ethnic group (Blazer *et al.*, 2002; Li *et al.*, 2008; Dagenais *et al.*, 2016; Mangurian *et al.*, 2018) and lower social class or adversity (Everson *et al.*, 2002; Tamayo *et al.*, 2010; Pisto *et al.*, 2014).

Another postulated mechanism is that depression, DGIH and obesity are intrinsically linked beyond the above via common antecedent inflammatory processes. Raised interleukin-6 (IL-6) and tumour necrosis factor alpha are antecedent to insulin resistance (IR) (Pickup, 2004; Belgardt *et al.*, 2010), and subsequently T2DM and obesity (DeFronzo and Ferrannini, 1991; Dandona *et al.*, 2004; Rader, 2007). A recent genome-wide association

study (Milaneschi *et al.*, 2017) found that common genetic variants for body mass index (BMI) and C-reactive protein (CRP) show overlap with gene variants associated with depression. In addition, inflammation may be prospectively linked to depression in young people, with longitudinal cohort-based research finding raised levels of IL-6 during childhood to be associated with future depressive symptoms and diagnosis of depression at age 18 years, which persisted after controlling for BMI, social class, and childhood psychological and behavioural problems preceding IL-6 measurement (Khandaker *et al.*, 2014; Khandaker *et al.*, 2018*a*, 2018*b*). This may relate to antecedent stressful events (Slopen *et al.*, 2013). A recent large meta-analysis has added to these findings, with cytokines including IL-6 marked as part of a potential chemokine/cytokine profile associated with depression (Köhler *et al.*, 2017).

The finding that low-grade systemic inflammation appears antecedent to DGIH, obesity and depression may be evidence of a common biological pathway that begins with an inflammatory response. Research examining the association among DGIH, obesity and depression, particularly longitudinally, in a sample of relatively young people who are less affected by years of illness, is scarce. It is nonetheless an important extension of the current literature as the findings may promote earlier and closer monitoring of metabolic and inflammatory function in young people with depression. It may in addition further our pathophysiological understanding of the multi-systemic nature of depression and suggest possible preventative therapeutic targets (Insel and Charney, 2003).

Using longitudinal population-based data, we tested the hypothesis that even relatively young people with depression may display early signs of DGIH or obesity. We tested cross-sectional (age 18 years) and longitudinal (age 9 and 18 years) associations among DGIH, obesity and depression. We hypothesised that early signs of DGIH might be explained by shared inflammatory processes, or demographic/lifestyle factors. We tested this by assessing for any attenuation (confounding) effect of either demographic, lifestyle or inflammatory measures on associations among DGIH, obesity and depression.

#### Methods

#### Description of cohort and sample selection

The Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort (Boyd *et al.*, 2013; Fraser *et al.*, 2013) comprises 14 062 live births from mothers residing in (former) Avon County, southwest England, with expected dates of delivery between April 1991 and December 1992. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool (http://www. bristol.ac.uk/alspac/researchers/our-data/). Parents completed regular postal questionnaires about all aspects of their child's health and development from birth. From age 7 years, the children attended an annual assessment clinic during which they participated in various face-to-face interviews and physical tests. In an attempt to boost study numbers, further phases of recruitment took place after the age of 7 years, leading to an additional 713 participants recruited by age 18.

We first selected all participants with a measure for the outcome (n = 4563) and removed participants with CRP > 10 (Khandaker *et al.*, 2014), to minimise the potential confounding effect of ongoing or recent inflammatory disease/infection on our results, leaving 3208 participants. For cross-sectional analyses, 2231 participants had complete data on all exposure and confounder variables. For longitudinal analyses, 331 participants had complete data on all exposure and confounder variables. The lower sample with complete data for longitudinal analyses is explained by age 9 glycaemic data being derived from a smaller ALSPAC sub-study (Ong *et al.*, 2004). Complete-case analysis is presented in online Supplementary Tables 1 and 2. See statistical methods for our means of addressing missing data.

The study received ethics approval from the ALSPAC Ethics and Law Committee and local research ethics committees. All participants provided written informed consent.

#### **Outcome measures**

#### Depressive symptoms/episode at age 18 years

Depression was measured using the Clinical Interview Schedule-Revised (CIS-R), a widely used standardised self-assessment tool for measuring depression and anxiety in community samples (Lewis *et al.*, 1992). It includes symptoms of depression based on *International Statistical Classification of Diseases, 10th Revision* (ICD-10) criteria, and gives a total depression score of 0–21 comprising symptom scores for depression, depressive thoughts, fatigue, concentration and sleep problems. Our primary outcome measure was the continuous CIS-R depression score (Khandaker *et al.*, 2014). As a secondary outcome, we created a binary variable 'depressive episode'. This consisted of participants meeting ICD-10 criteria for a depressive episode (mild/moderate/severe) (F32.0/F32.1/F32.2), as has been used previously (Bowes *et al.*, 2015; Davies *et al.*, 2016; Quarini *et al.*, 2016).

#### **Exposures**

#### Fasting plasma glucose, fasting insulin, glucose tolerance

We used the biochemical measurements of fasting plasma glucose (FPG) and fasting insulin (FI) (ages 9 and 18 years), and 2-h glucose tolerance (2hrGT) (age 9 years). The age 9 glycaemic data were derived from a smaller 'Before Breakfast Study' sub-study (Ong *et al.*, 2004). At both ages 9 and 18 years, fasting samples were taken at 0900 after a 10-h fast (water only). The 2hrGT test was obtained following the above fasting procedure, with the addition of a 75 g oral bolus of sugary syrup at 0900, with blood being sampled 2 h later. Blood samples were immediately spun and frozen at -80 °C.

IR was calculated as a continuous measure from FPG and FI by using the computerised, updated version of the homoeostatic measurement for insulin resistance (HOMA<sub>2</sub>) (Levy *et al.*, 1998). The algorithm generates a relatively precise measurement of IR taking into account variations in hepatic and peripheral glucose resistance, increases in the insulin secretion curve for plasma glucose concentrations above 10 mmol/L (180 mg/dL) and the contribution of circulating proinsulin (Levy *et al.*, 1998). We did not include a binary measure for clinical IR due to the known variation in HOMA<sub>2</sub> score between populations (Wallace *et al.*, 2004) thus ascertaining a clinical 'cut-off' may be problematic.

#### BMI

BMI was calculated from clinic data in the ALSPAC cohort, from measurements of height (m) and weight (kg). We used data collected at ages 9 and 18 years.

#### Demographic confounders

We adjusted for paternal social class at birth (questionnaire data, categorical) and maternal education (questionnaire data, categorical) as proxies of participant social class and potential adversity, sex (clinic data, categorical), ethnicity (questionnaire data, categorical) and maternal Edinburgh Post-Natal Depression Score (EPDS) at 8-week post-partum (questionnaire data, continuous).

#### Lifestyle confounders

For analyses on DGIH we adjusted for BMI (clinic data, continuous, ages 9 and 18 years as per the exposure), smoking (questionnaire data, categorical), cortisol levels [age 9 only, continuous, clinic data from BBS sub-study (Ong *et al.*, 2004)], physical activity (questionnaire data on average frequency of physical activity/exercise per week in the last year, categorical) and alcohol use (questionnaire data on average frequency of use, categorical). For BMI analyses, we used the same adjustments, however with HOMA<sub>2</sub> (as previously described, continuous) in place of BMI.

#### Inflammatory confounders

We adjusted for IL-6 (age 9 years) and CRP (age 18 years). IL-6 was not available at age 18 years. Blood samples were collected from non-fasting participants (age 9 years), and fasting participants (age 18 years) and were immediately spun and frozen at -80 °C. IL-6 was measured by enzyme-linked immunosorbent assay (R&D Systems), and high-sensitivity CRP (hs-CRP) was measured by automated particle-enhanced immunoturbidimetric assay (Roche). All inter-assay coefficients of variation were less than 5%.

#### **Statistical analysis**

Biomarker values that were non-normally distributed (all except for FPG) were natural log-transformed. Resultant variables, alongside the continuous outcome 'total depression score' were standardised (*Z*-transformed) so the statistical estimations represent the increase in risk of depressive symptoms per S.D. increase in exposure. We completed tests for multi-collinearity of exposures/confounders in a linear regression model. The variance inflation factor for all covariates was between 1.01 and 1.11, suggesting minimal multi-collinearity. Adjustments were added using the enter method of multiple regression. All statistical analysis was performed using IBM SPSS 24.0.

#### Aims 1 and 2: cross-sectional and longitudinal relationships between DGIH/BMI (ages 9 and 18 years) and depression (age 18 years)

We completed cross-sectional linear and logistic regression analyses which examined the relationship between markers of DGIH/BMI and depressive symptoms/depressive episode (age 18 years). We completed longitudinal linear and logistic regression analyses which examined the relationship between markers of DGIH/BMI (age 9 years) and depressive symptoms/episode (age 18 years). Regression coefficients and 95% confidence intervals (95% CIs) were calculated per s.D. increase in the continuous 'total depression score' outcome, per s.d. increase in exposure, using linear regression. Odds ratios (ORs) and 95% CIs for the categorical depressive episode outcome, per s.D. increase in exposure, were estimated using logistic regression. Quadratic terms were created separately for all exposures and entered into a logistic regression model to simulate curvilinear regression, to test the linearity of relationships between exposures and depression; these data are only shown where there was evidence of a non-linear relationship.

## *Aim 3: adjusting for demographic factors, lifestyle factors and inflammation*

We performed adjustments using linear and logistic regression as described above. First, we adjusted for the demographic, lifestyle and inflammation factors listed above, separately. Second, we completed a total adjustment model including all potential confounders together.

#### Missing data

Missing data for exposures and confounders were present in 30% of cases for cross-sectional analyses, and 90% of cases for longitudinal analyses. Due to the substantial amount of missing data in longitudinal analyses [which may be related to the age 9 glycaemic data being derived from a smaller ALSPAC sub-study (Ong *et al.*, 2004)], we longitudinally analysed only complete cases (Lee and Huber, 2011). For our cross-sectional analyses, Little's Missing Completely at Random (MCAR) test (p = 0.008) indicated that the data were not MCAR. We then used the missing value analysis function of SPSS to perform separate variance independent *t* tests (continuous variables) and  $\chi^2$  tests (categorical variables) to check the missing at random (MAR) assumption. Each variable returned significance (p < 0.05) with at least one other included variable, indicating that missingness was correlated with another variable in the model, suggesting the missing data met the MAR assumption.

We completed multiple imputation (MI) using the fully conditional Markov chain Monte Carlo method, for all exposure and confounder variables, plus axillary continuous variables that were indicators of missingness in the population. The selected axillary variables included age 9 biochemical data (high-density lipoprotein, low-density lipoprotein, triglycerides), as well as birthweight and gestational age. As missing data were present in 30% of cases, we used 30 imputations as recommended (White *et al.*, 2011). Complete case analysis for the cross-sectional analyses is presented in online Supplementary Tables 1 and 2.

#### Results

Following imputation for exposure and confounder variables, our total sample was 3208 participants. The mean depression score in the imputed sample was 3.09; range 0–21 (complete cases 3.10; range 0–21). The number of participants meeting criteria for a depressive episode at age 18 was n = 227 (7%) (complete cases n = 179; 8%). Table 1 shows the sample clinical and biomarker characteristics at age 18.

## Aim 1: cross-sectional association between DGIH/BMI and depression (age 18 years)

In the unadjusted analyses; HOMA<sub>2</sub>, FI and BMI were positively associated with depressive symptoms at age 18 years [ $\beta$  = 0.04 (95% CI 0.03–0.30) p = 0.02;  $\beta$  = 0.05 (95% CI 0.03–0.33) p = 0.01;  $\beta$  = 0.03 (95% CI 0.01–0.08) p = 0.04 respectively]; FPG was negatively associated with depressive symptoms [ $\beta$  = –0.05 (95% CI –0.36 to –0.02) p = 0.01]. See Table 2. The results from our complete case analysis were broadly similar. See online Supplementary Table 1.

#### Table 1. Baseline characteristics of sample

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Characteristic	All sample	Depressive episode	No depressive episode	Test statistic <sup>a</sup> <i>p</i> -value
Participants, n (% total)	3208 (100)	227 (7)	2981 (93)	-
Male sex, <i>n</i> (column %)	1553 (48)	62 (27)	1491 (50)	9.167; <i>p</i> = 0.002
Smoking at 18 years, $n$ (column %) (current)	231 (10)	27 (11)	220 (7)	7.535; <i>p</i> = 0.006
Maternal EPDS score <sup>b</sup> , mean (s.d.)	5.89 (4.65)	5.78 (4.65)	5.98 (4.69)	0.476 <i>p</i> = 0.322
Maternal education (A-levels or above), $n$ (column %)	1116 (35)	74 (33)	1049 (35)	0.267 <i>p</i> = 0.096
Alcohol use <sup>c</sup> (greater than once per week), $n$ (column %)	1320 (41)	132 (58)	1070 (36)	8.756 <i>p</i> = 0.024
Physical activity d (greater than once per week), $n$ (column %)	2213 (69)	78 (35)	2337 (78)	9.967 <i>p</i> < 0.001
Father's social class, <i>n</i> (column %)				4.235; <i>p</i> = 0.055
I	186 (6)	15 (7)	184 (6)	
II	1119 (35)	73 (32)	1077 (36)	
III – non-manual	1257 (39)	87 (38)	1145 (38)	
III – manual	96 (3)	7 (3)	85 (3)	
IV	465 (14)	36 (16)	394 (13)	
V	95 (3)	9 (4)	96 (3)	
White British ethnicity, <i>n</i> (column %)	3143 (98)	221 (97)	3175 (99)	0.243; <i>p</i> = 0.588
BMI at 18 years, mean (s.p.), kg/m <sup>2</sup>	22.68 (3.81)	23.06 (5.38)	22.65 (3.79)	8.141; <i>p</i> = 0.330
BMI at 9 years, mean (s.p.), kg/m <sup>2</sup>	17.54 (2.53)	17.88 (2.23)	17.51 (2.46)	1.967; <i>p</i> = 0.223
FPG at 18 years, mean (s.d.), mmol/L	5.04 (0.59)	4.95 (0.76)	5.09 (0.48)	0.044; <i>p</i> = 0.389
HOMA <sub>2</sub> at 18 years, mean (s.p.)	0.92 (0.73)	1.32 (0.55)	0.87 (0.44)	3.860; <i>p</i> = 0.035
CRP at 18 years, mean (s.p.), mg/L	1.11 (1.41)	1.20 (1.05)	1.08 (1.43)	0.423; <i>p</i> = 0.701
IL-6 at 9 years, mean (s.p.), pg/mL	1.21 (0.78)	1.27 (1.58)	1.18 (1.52)	7.687; <i>p</i> = 0.004
CRP at 9 years, mean (s.p.), pg/mL	0.68 (2.52)	0.76 (1.92)	0.65 (3.54)	4.723; <i>p</i> = 0.226

<sup>a</sup>Categorical variables (sex, social class, ethnicity, smoking) were compared using the χ<sup>2</sup> test, normally distributed continuous variables (FPG, birthweight, gestational age) were compared using the two tailed *t* test; non-normally distributed continuous variables (HOMA<sub>2</sub>, CRP, IL-6, BMI) were compared using the Mann–Whitney *U* test.

<sup>c</sup>Frequency participant has had drinks containing alcohol

<sup>d</sup>Physical activity corresponded to frequency respondent engaged in going to gym, brisk walking or any sports activity during the past year

In the unadjusted analyses, both HOMA<sub>2</sub> and FI were associated with the categorical depressive episode [OR 1.14 (95% CI 1.01–1.31) p = 0.04 and OR 1.16 (95% CI 1.01–1.33) p = 0.03respectively]. See Table 3. The results are similar to those for our complete case analysis. See online Supplementary Table 2.

## Aim 2: longitudinal association between DGIH/BMI (age 9 years) and depressive symptoms/episode (age 18 years)

Our longitudinal analysis of DGIH included 399 participants, and for BMI 2571 participants. There were no evident longitudinal associations between DGIH/BMI at age 9 years and depressive symptoms/episode at age 18. See Tables 4 and 5.

#### Aim 3: adjusting for confounders

As shown in Tables 2–5, after adjustments for demographic and lifestyle factors the point estimates did not change considerably but the 95% CIs widened to include the null. Adjustment for immune markers did not significantly alter the unadjusted associations. Following adjustment for all confounder variables in one model, there were no significant associations. Results from

the complete case analysis are broadly similar. See online Supplementary Tables 1 and 2.

#### Discussion

In this study, we first tested the cross-sectional associations between DGIH/BMI and depression in a sample of young people who may have been less affected by years of illness, before and after adjustments for potential demographic, lifestyle and immune confounders. We then used longitudinal analysis to test the direction of association between these factors. To our knowledge, this is one of the first analyses of detailed longitudinal associations among DGIH, BMI, inflammation and depression, in a relatively young sample, albeit the sample size for some of the analyses was relatively small. We present several findings of note.

We found that the broadest marker of glycaemic function, FPG, was negatively associated with depressive symptoms at age 18 years. In addition, more sensitive markers of pre-clinical glucose dysregulation (FI, HOMA<sub>2</sub>) were positively associated with depression at age 18 years. IR in combination with low FPG shows biological plausibility; FPG can present low-normal in early IR, in response to the IR phenotype of increased insulin secretion thus increased intracellular glucose uptake (Ensling

#### Table 2. Cross-sectional association between DGIH/BMI and depressive symptoms (age 18)

Predictor		Regression coefficient (95% CI) for depressive symptoms													
		Adjustments													
		Unadjusted model		Demographic adjus (sex, birth social o ethnicity, mater education, materna score)	tments class, nal l EPDS	Lifestyle adjustme (BMI <sup>a</sup> , HOMA2 <sup>b</sup> , smo alcohol use physical a	nts king, ctivity)	Immune adjustme [IL-6 (9 years), CRP (18	Complete model (all adjustments)						
Depressive symptoms	n	β (95% CI)	p	β (95% CI)	р	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p				
HOMA <sub>2</sub>	3208	0.04 (0.02–0.30)	0.023*	0.05 (-0.07-0.21)	0.336	0.04 (-0.09 to 0.18)	0.100	0.04 (0.01-0.31)	0.031*	0.03 (-0.01 to 0.18)	0.638				
FPG	3208	-0.05 (-0.36 to -0.02)	0.014*	-0.02 (-0.17-0.13)	0.816	-0.04 (-0.30 to 0.07)	0.067	-0.04 (-0.32 to -0.02)	0.021*	-0.04 (-0.18 to 0.11)	0.636				
Fasting insulin	3208	0.05 (0.03–0.33)	0.013*	0.06 (-0.06-0.13)	0.282	0.05 (-0.02 to 0.12)	0.059	0.04 (0.01-0.17)	0.023*	0.05 (-0.11 to 0.20)	0.553				
BMI	3208	0.03 (0.01–0.08)	0.046*	0.03 (-0.01-0.07)	0.144	0.03 (-0.01 to 0.07)	0.062	0.03 (0.01-0.09)	0.031*	0.02 (-0.02 to 0.06)	0.240				

<sup>a</sup>Not adjusted for in BMI analysis.

<sup>b</sup>Not adjusted for in HOMA/FPG/FI analysis.

\*Indicates p < 0.05.

#### Table 3. Cross-sectional associations between DGIH/BMI and depressive episode (age 18 years)

Predictor						Odds ratio	0 (95% CI) for depress	ive episode						
							Adjustments							
			Unadjusted model	Demographic adjustments (sex, birth social class, ethnicity, maternal education, maternal EPDS score)		Lifestyle adjustments (BMI <sup>a</sup> , HOMA <sub>2</sub> <sup>b</sup> , smoking, alcohol use, physical activity)		Immune adjustments [IL-6 (9 years), CRP (18 years)]		Complete model (all adjustments)				
Depressive episode	N outcome	п	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p		
HOMA <sub>2</sub>	227	3208	1.14 (1.01–1.31)	0.047*	1.07 (0.97–1.24)	0.296	1.12 (0.97–1.30)	0.132	1.15 (1.01–1.32)	0.042*	1.05 (0.91–1.23)	0.498		
FPG	227	3208	0.90 (0.77-1.05)	0.174	1.02 (0.88-1.18)	0.787	0.89 (0.76-1.03)	0.115	0.89 (0.77-1.05)	0.165	1.00 (0.87-1.17)	0.959		
FI	227	3208	1.16 (1.01–1.33)	0.034*	1.09 (0.94–1.25)	0.269	1.13 (0.98–1.32)	0.098	1.16 (1.02–1.34)	0.029*	1.06 (0.91–1.24)	0.794		
BMI	227	3208	1.02 (0.99–1.06)	0.138	1.02 (0.98–1.05)	0.305	1.01 (0.98–1.05)	0.486	1.03 (0.99–1.07)	0.107	1.02 (0.98–1.06)	0.368		

<sup>a</sup>Not adjusted for in BMI analysis.

<sup>b</sup>Not adjusted for in HOMA/FPG/FI analysis.

\*Indicates *p* < 0.05.

Predictor	Regression co-efficient (95% CI) for depressive symptoms (age 18 years)														
		Adjustments													
		Unadjusted model		Demographic adjust (sex, birth social c ethnicity, maternal ed maternal EPDS sc	ments lass, ucation, ore)	Lifestyle adjustme (BMI <sup>a</sup> , HOMA <sub>2</sub> <sup>b</sup> , phy activity)	ents /sical	Immune adjustme [IL-6 (9 years)]	ents	Complete model (all adjustments)					
Depressive symptoms (18 years)	n	eta (95% CI)	p	eta (95% CI)	p	eta (95% CI)	p	eta (95% CI)	p	eta (95% CI)	p				
2hrGT (age 9 years)	399	0.07 (-0.33 to 0.34)	0.172	0.01 (-0.36 to 0.37)	0.980	0.06 (-0.26 to 0.46)	0.563	0.04 (-0.26 to 0.23)	0.595	0.01 (-0.36 to 0.37)	0.980				
HOMA <sub>2</sub> (age 9 years)	399	0.02 (-0.28 to 0.39)	0.739	0.01 (-0.24 to 0.27)	0.917	0.01 (-0.25 to 0.27)	0.954	0.01 (-0.25 to 0.27)	0.942	0.01 (-0.25 to 0.26)	0.972				
FPG (age 9 years)	399	0.02 (-0.28 to 0.39)	0.750	0.03 (-0.31 to 0.44)	0.878	0.02 (-0.14 to 0.44)	0.270	0.02 (-0.15 to 0.44)	0.276	0.02 (-0.28 to 0.40)	0.801				
FI (age 9 years)	399	0.07 (-0.10 to 0.57)	0.172	0.05 (-0.21 to 0.19)	0.768	0.01 (-0.25 to 0.26)	0.992	0.01 (-0.24 to 0.27)	0.928	-0.01 (-0.25 to 0.24)	0.949				
BMI (age 9 years)	2571	0.04 (-0.04 to 0.10)	0.054	0.03 (-0.02 to 0.09)	0.247	0.05 (-0.02 to 0.11)	0.065	0.04 (-0.02 to 0.10)	0.154	0.02 (-0.03 to 0.08)	0.416				

<sup>a</sup>Not adjusted for in BMI analysis.

<sup>b</sup>Not adjusted for in HOMA/FPG/FI analysis.

\*Indicates p < 0.05.

Table 5. Longitudinal association between DGIH/BMI (age 9) and depressive episode (age 18 years)

Predictor Odds ratio (95% CI) for depressive episode (age 18 years)													
			Adjustments										
			Unadjusted model	Demographic adjustments (sex, birth social class, ethnicity, maternal education, maternal EPDS score)		Lifestyle adjustments (BMI <sup>a</sup> , HOMA2 <sup>b</sup> , physical activity)		lmmune adjusti [IL-6 (9 year	nents s)]	Complete model (all adjustments)			
Depressive episode (18 years)	n outcome	п	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
2hrGT (age 9 years)	23	313	1.21 (0.95–1.54)	0.235	0.98 (0.73–1.31)	0.891	0.91 (0.60-1.38)	0.641	0.91 (0.60–1.39)	0.651	0.85 (0.55-1.30)	0.427	
HOMA <sub>2</sub> (age 9 years)	23	313	1.16 (0.86–1.20)	0.387	1.14 (0.75–1.72)	0.538	0.98 (0.74–1.31)	0.896	0.98 (0.74–1.30)	0.893	0.98 (0.83–1.31)	0.977	
FPG (age 9 years)	23	313	1.03 (0.90–1.07)	0.446	0.85 (0.55–1.30)	0.442	1.08 (0.73-1.61)	0.693	1.05 (0.69–1.58)	0.830	1.19 (0.78–1.84)	0.678	
FI (age 9 years)	23	313	1.10 (0.90–1.21)	0.250	1.01 (0.75–1.34)	0.971	1.01 (0.75–1.33)	0.995	1.02 (0.77-1.34)	0.916	0.97 (0.74–1.33)	0.916	
BMI (age 9 years)	170	2571	1.23 (0.76-1.32)	0.687	1.04 (0.98-1.10)	0.127	1.05 (0.98-1.11)	0.058	1.06 (0.97-1.12)	0.060	1.05 (0.98-1.12)	0.070	

<sup>a</sup>Not adjusted for in BMI analysis.

<sup>b</sup>Not adjusted for in HOMA/FPG/FI analysis.

\*Indicates p < 0.05.

*et al.*, 2011). These associations were not significant following demographic and lifestyle adjustments suggesting that the metabolic dysfunction present in depression may be attributable to sociodemographic and lifestyle factors. Interestingly however, whilst the CIs became larger (and included the null) after confounding adjustments, the point estimates did not change substantially. Research conducted on larger samples of depressed patients would therefore be appropriate to increase statistical power, to further test these findings.

Our findings differ from previous longitudinal research from the Northern Finland Birth Cohort (NFBC) (Timonen et al., 2006), which found IR to be cross-sectionally associated with depressive symptoms even after adjustments for similar confounders. However, in that study, a different mathematical method, the Qualitative Insulin Sensitivity Check Index (QUICKI) (Katz et al., 2000) was used to measure IR. The QUICKI is limited in being blind to several important physiological aspects of glucose homoeostasis; and being calibrated to an aged insulin assay (Wallace et al., 2004). We used the computerised, updated HOMA<sub>2</sub> model that addresses the shortcomings of QUICKI and other early models. Additionally, the participants in the Finnish study were older (age 31 years) thus the potential for confounding by the potential chronic lifestyle factors of depression was increased. Another previous study using NFBC data found no association between depression and the wider metabolic syndrome as a whole, after controlling for similar adjustments at age 31 years (Herva et al., 2006). The metabolic syndrome classification may be less sensitive to early metabolic dysfunction than measures of IR. For example, a smaller cross-sectional study from Taiwan of 323 participants (mean age of 19.5 years) found no association between depression and the metabolic syndrome as a whole, but did find associations with specific elements of metabolic dysfunction such as BMI and hypertension, though the associations attenuated following adjustments (Lin et al., 2014). Whilst this latter study was relatively small, the results are in line with ours. Another study of young adults from the USA found depression to be associated with the metabolic syndrome at age 30 years (Kinder et al., 2004).

We found no associations longitudinally between age 9 markers of DGIH/BMI and later development of depressive symptoms/episode by age 18 years. However, our longitudinal analyses of glycaemic function were susceptible to reduced statistical power due to the smaller sample that underwent glycaemic testing at age 9 years in the cohort. Therefore, since the number of depression events in the longitudinal analyses of glycaemic function was relatively small, the corresponding demographic and lifestyle adjustment models may have been susceptible to model overfit (Peduzzi *et al.*, 1996), limiting the generalisability of these results. Results for the longitudinal analyses should therefore be interpreted with caution.

Taken together, our results suggest that the sociodemographic and lifestyle features of the depressive syndrome such as gender, ethnicity, paternal social class, smoking, alcohol use and physical activity levels may be driving the known associations between T2DM, obesity and depression. Nonetheless, sensitive metabolic changes are apparent from a relatively early age. This is an important finding. Whilst the demographic confounders we adjusted for are fixed, the lifestyle confounders we adjusted for may be malleable. For that reason, our results demonstrate the crucial importance for even relatively young patients diagnosed with depression to receive a full and comprehensive assessment of metabolic function. Encouragement and importance should be placed on encouraging and incentivising positive lifestyle changes, such as smoking cessation and reducing alcohol intake. Interestingly, other relevant lifestyle changes such as encouraging a healthy diet and regular exercise show some evidence for having intrinsic mood-boosting properties (Jacka *et al.*, 2010; Cooney *et al.*, 2014).

#### Strengths and limitations

The ALSPAC cohort provided a relatively large sample size in which to conduct analyses and we were able to consider detailed potential confounders including current/recent inflammation, alcohol use, BMI (in IR analyses), IR (in BMI analyses), smoking, physical activity, maternal post-natal EPDS score, paternal social class, ethnicity and sex. We attempted to reduce bias and increase statistical power (Dong and Peng, 2013) by using the MI method to account for missing data where possible.

However, there are several limitations that should be considered. Firstly, we have put emphasis on the effects of lifestyle on glycaemic and anthropometric parameters, however the lifestyle data we collected in our analyses was mostly collected via selfreport questionnaires. Self-report questionnaire data on lifestyle factors can be limited in its validity and reliability, for reasons such as social desirability or recall bias (Sallis and Saelens, 2000; Del Boca and Darkes, 2003; Shipton et al., 2009). ALSPAC does have a quantitative measure for physical activity at age 18 years. Participants were invited to take part in a week-long wrist accelerometer study, however, the sample size that were able to provide full data on this study was much smaller than data available for the self-report measure; participants were asked to remove the accelerometer for certain types of exercise; and, we felt that data collected in this manner may be susceptible to the Hawthorne effect. Nonetheless, the limitations of using self-report data for lifestyle parameters should be taken into account when interpreting our findings.

Due to the significant amount of missing data in our longitudinal analyses, imputing such missing data may have led to both to selection bias and to type-II statistical error (Lee and Huber, 2011). It is therefore likely our longitudinal analyses, particularly of glycaemic function, are underpowered. In such analyses, models including demographic or lifestyle adjustments are likely to be overfit, limiting their generalisability. Our longitudinal findings should therefore be interpreted with caution. Selection bias is also a possibility since not all ALSPAC participants attended voluntary CIS-R assessment at age 18. In addition, we have used paternal social class at birth as a proxy of social class and potential adversity of the participant and these suppositions may be open to challenge. Furthermore, whilst most biochemical tests were sampled in the fasting state, age 9 inflammatory markers were sampled in the non-fasting state, which may increase measurement error. Measurement error can introduce a bias towards the null, so the results for IL-6 may be underestimated. Also, we have examined an a priori hypothesis based upon potential biological plausibility involving immune dysfunction upstream of both DGIH and BMI. However, obesity is known to be a pro-inflammatory state itself (Jung and Choi, 2014), thus reverse causality may be a possibility. Future research may seek to take this into account. Additionally, whilst we restricted our analyses to participants with CRP < 10 mg/L to account for chronic/acute infection/inflammatory illness, we were unable to ascertain whether included participants were in receipt of immunemodulating medications. Finally, whilst we included data for

IL-6 and CRP, future analyses may seek to examine additional circulating markers of innate and adaptive immune response.

#### Implications and future directions

Our findings have implications both in the assessment and management of patients who present with symptoms of depression. We found that even at the relatively young age of 18 years, depression is associated with DGIH and raised BMI. That the metabolic associations with depression can occur at such an early phase of a potentially chronic course of depression is significant and underlines the need for swift and comprehensive assessment and management of metabolic risk factors in people that present with depression. Our findings may provide impetus for the monitoring of more sensitive measures of metabolic function in people first presenting with depression, since the elements that make up the 'metabolic syndrome', of which IR and BMI are a part, are by definition reversible (Alberti et al., 2005), and therefore early intervention may help to attenuate the significant morbidity (Goldney et al., 2004) and socioeconomic cost (Molosankwe et al., 2012) associated with comorbid depression and metabolic dysfunction. Taken together with previous research (Khandaker et al., 2014; Miller and Raison, 2016; Khandaker et al., 2018a) which suggests that immune dysfunction could be a target for prevention and treatment of depression, our findings may suggest that other factors also play an important role in increasing the physical health burden associated with depression. Impetus should be placed on encouraging healthy lifestyles such as with a healthy diet and exercise, which have both shown to be beneficial in improving depression (Schuch et al., 2016a, 2016b; Teasdale et al., 2017).

Future research should seek to examine associations between young adults with depression and measures of dyslipidaemia, which may also be relevant (Parekh *et al.*, 2017), and should seek to address whether improved recognition and interventions for modifiable lifestyle factors in the early treatment of depression may result in more favourable long-term physical health outcomes.

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#### References

- Alberti KG, Zimmet P, Shaw J and Group IDFETFC (2005) The metabolic syndrome a new worldwide definition. *Lancet* **366**, 1059–1062.
- Ali S, Stone MA, Peters JL, Davies MJ and Khunti K (2006) The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine* 23, 1165–1173.
- Anderson RJ, Freedland KE, Clouse RE and Lustman PJ (2001) The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 24, 1069–1078.
- Belgardt BF, Mauer J, Wunderlich FT, Ernst MB, Pal M, Spohn G, Bronneke HS, Brodesser S, Hampel B, Schauss AC and Bruning JC (2010) Hypothalamic and pituitary c-Jun N-terminal kinase 1 signaling coordinately regulates glucose metabolism. Proceedings of the National Academy of Sciences of the United States of America 107, 6028–6033.
- Blazer DG, Moody-Ayers S, Craft-Morgan J and Burchett B (2002) Depression in diabetes and obesity: racial/ethnic/gender issues in older adults. *Journal of Psychosomatic Research* 53, 913–916.
- Bowes L, Carnegie R, Pearson R, Mars B, Biddle L, Maughan B, Lewis G, Fernyhough C and Heron J (2015) Risk of depression and self-harm in teenagers identifying with goth subculture: a longitudinal cohort study. *The Lancet. Psychiatry* **2**, 793–800.
- Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S and Davey Smith G (2013) Cohort profile: the 'children of the 90s' – the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology* **42**, 111–127.
- Cooney G, Dwan K and Mead G (2014) Exercise for depression. JAMA 311, 2432–2433.
- Dagenais GR, Gerstein HC, Zhang X, McQueen M, Lear S, Lopez-Jaramillo P, Mohan V, Mony P, Gupta R, Kutty VR, Kumar R, Rahman O, Yusoff K, Zatonska K, Oguz A, Rosengren A, Kelishadi R, Yusufali A, Diaz R, Avezum A, Lanas F, Kruger A, Peer N, Chifamba J, Iqbal R, Ismail N, Xiulin B, Jiankang L, Wenqing D, Gejie Y, Rangarajan S, Teo K and Yusuf S (2016) Variations in diabetes prevalence in low-, middle-, and high-income countries: results from the prospective urban and rural epidemiological study. *Diabetes Care* 39, 780–787.
- Dandona P, Aljada A and Bandyopadhyay A (2004) Inflammation: the link between insulin resistance, obesity and diabetes. *Trends in Immunology* 25, 4–7.
- Davies SJ, Pearson RM, Stapinski L, Bould H, Christmas DM, Button KS, Skapinakis P, Lewis G and Evans J (2016) Symptoms of generalized anxiety disorder but not panic disorder at age 15 years increase the risk of depression at 18 years in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study. *Psychological Medicine* **46**, 73–85.
- DeFronzo RA and Ferrannini E (1991) Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14, 173–194.
- Del Boca FK and Darkes J (2003) The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction* **98** (suppl. 2), 1–12.
- Ding EL, Song Y, Malik VS and Liu S (2006) Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and metaanalysis. *JAMA* 295, 1288–1299.
- **Dong Y and Peng CY** (2013) Principled missing data methods for researchers. *Springerplus* **2**, 222.
- Ensling M, Steinmann W and Whaley-Connell A (2011) Hypoglycemia: a possible link between insulin resistance, metabolic dyslipidemia, and heart and kidney disease (the Cardiorenal Syndrome). *Cardiorenal Medicine* 1, 67–74.
- Everson SA, Maty SC, Lynch JW and Kaplan GA (2002) Epidemiologic evidence for the relation between socioeconomic status and depression, obesity, and diabetes. *Journal of Psychosomatic Research* 53, 891–895.

- Firth J, Stubbs B, Teasdale SB, Ward PB, Veronese N, Shivappa N, Hebert JR, Berk M, Yung AR and Sarris J (2018) Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. *World Psychiatry* **17**, 365–367.
- Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM and Lawlor DA (2013) Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International Journal of Epidemiology 42, 97–110.
- Goldney RD, Phillips PJ, Fisher LJ and Wilson DH (2004) Diabetes, depression, and quality of life: a population study. *Diabetes Care* 27, 1066–1070.
- Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM and Mathers CD (2011) Global burden of disease in young people aged 10– 24 years: a systematic analysis. *Lancet* **377**, 2093–2102.
- Herva A, Räsänen P, Miettunen J, Timonen M, Läksy K, Veijola J, Laitinen J, Ruokonen A and Joukamaa M (2006) Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosomatic Medicine* 68, 213–216.
- Insel TR and Charney DS (2003) Research on major depression: strategies and priorities. *JAMA* 289, 3167–3168.
- Jacka FN, Kremer PJ, Leslie ER, Berk M, Patton GC, Toumbourou JW and Williams JW (2010) Associations between diet quality and depressed mood in adolescents: results from the Australian Healthy Neighbourhoods Study. *Australia and New Zealand Journal of Psychiatry* 44, 435–442.
- Jung UJ and Choi MS (2014) Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *International Journal of Molecular Science* **15**, 6184–6223.
- Katon W, von Korff M, Ciechanowski P, Russo J, Lin E, Simon G, Ludman E, Walker E, Bush T and Young B (2004) Behavioral and clinical factors associated with depression among individuals with diabetes. *Diabetes Care* 27, 914–920.
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G and Quon MJ (2000) Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *Journal of Clinical Endocrinology & Metabolism* 85, 2402–2410.
- Khandaker GM, Pearson RM, Zammit S, Lewis G and Jones PB (2014) Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA Psychiatry* **71**, 1121–1128.
- Khandaker GM, Zammit S, Burgess S, Lewis G and Jones PB (2018*a*) Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort. *Brain Behavior Immunology* **69**, 264–272.
- Khandaker GM, Stochl J, Zammit S, Goodyer I, Lewis G and Jones PB (2018b) Childhood inflammatory markers and intelligence as predictors of subsequent persistent depressive symptoms: a longitudinal cohort study. *Psychological Medicine* **48**, 1514–1522.
- Kinder LS, Carnethon MR, Palaniappan LP, King AC and Fortmann SP (2004) Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosomatic Medicine* **66**, 316–322.
- Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctôt KL and Carvalho AF (2017) Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatrica Scandinavica 135, 373–387.
- Lee HJ and Huber J (2011) Multiple imputation with large proportions of missing data: How much is too much? In United Kingdom Stata Users' Group Meetings 2011. Stata Users Group.
- Levy JC, Matthews DR and Hermans MP (1998) Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 21, 2191–2192.
- Lewis G, Pelosi AJ, Araya R and Dunn G (1992) Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological Medicine* 22, 465–486.

- Li C, Ford ES, Strine TW and Mokdad AH (2008) Prevalence of depression among U.S. adults with diabetes: findings from the 2006 behavioral risk factor surveillance system. *Diabetes Care* **31**, 105–107.
- Lin KP, Liang TL, Liao IC and Tsay SL (2014) Associations among depression, obesity, and metabolic syndrome in young adult females. *Biological Research for Nursing* 16, 327–334.
- Lloyd CE, Nouwen A, Sartorius N, Ahmed HU, Alvarez A, Bahendeka S, Basangwa D, Bobrov AE, Boden S, Bulgari V, Burti L, Chaturvedi SK, Cimino LC, Gaebel W, de Girolamo G, Gondek TM, de Braude MG, Guntupalli A, Heinze MG, Ji L, Hong X, Khan A, Kiejna A, Kokoszka A, Kamala T, Lalic NM, Lecic Tosevski D, Mankovsky B, Li M, Musau A, Mussig K, Ndetei D, Rabbani G, Srikanta SS, Starostina EG, Shevchuk M, Taj R, Vukovic O, Wolwer W and Xin Y (2018) Prevalence and correlates of depressive disorders in people with Type 2 diabetes: results from the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study, a collaborative study carried out in 14 countries. *Diabetic Medicine* **35**, 760–769.
- Lysy Z, Da Costa D and Dasgupta K (2008) The association of physical activity and depression in Type 2 diabetes. *Diabetic Medicine* **25**, 1133–1141.
- Mangurian CV, Schillinger D, Newcomer JW, Vittinghoff E, Essock SM, Zhu Z, Dyer WT and Schmittdiel JA (2018) Diabetes and prediabetes prevalence by race and ethnicity among people with severe mental illness. *Diabetes Care* **41**, e119–e120.
- Menke A, Rust KF, Fradkin J, Cheng YJ and Cowie CC (2014) Associations between trends in race/ethnicity, aging, and body mass index with diabetes prevalence in the United States: a series of cross-sectional studies. *Annals of Internal Medicine* 161, 328–335.
- Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, Forstner AJ, Grabe HJ, Homuth G, Kan C, Lewis C, Mullins N, Nauck M, Pistis G, Preisig M, Rivera M, Rietschel M, Streit F, Strohmaier J, Teumer A, Van der Auwera S, Wray NR, Boomsma DI, Penninx B, Group CIW and the Major Depressive Disorder Working Group of the Psychiatric Genomics C (2017) Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry 74, 1214–1225.
- Miller AH and Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology* 16, 22–34.
- Molosankwe I, Patel A, Jose Gagliardino J, Knapp M and McDaid D (2012) Economic aspects of the association between diabetes and depression: a systematic review. *Journal of Affective Disorders* **142**(suppl), S42–S55.
- Nichols GA and Brown JB (2003) Unadjusted and adjusted prevalence of diagnosed depression in type 2 diabetes. *Diabetes Care* 26, 744–749.
- Ong KK, Petry CJ, Emmett PM, Sandhu MS, Kiess W, Hales CN, Ness AR, Dunger DB and team As (2004) Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. *Diabetologia* **47**, 1064–1070.
- Parekh A, Smeeth D, Milner Y and Thure S (2017) The role of lipid biomarkers in major depression. *Healthcare (Basel)* 5(1), 5.
- Peduzzi P, Concato J, Kemper E, Holford TR and Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology* 49, 1373–1379.
- Perreault L, Ma Y, Dagogo-Jack S, Horton E, Marrero D, Crandall J, Barrett-Connor E and Diabetes Prevention P (2008) Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. *Diabetes Care* 31, 1416–1421.
- Pickup JC (2004) Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 27, 813–823.
- Pisto L, Vaden A, Sillanmaki L and Mattila K (2014) Childhood adversities are associated with diabetes management in working age in Finland. *International Journal of Family Medicine* 2014, 864572.
- Quarini C, Pearson RM, Stein A, Ramchandani PG, Lewis G and Evans J (2016) Are female children more vulnerable to the long-term effects of maternal depression during pregnancy? *Journal of Affective Disorders* 189, 329–335.
- Rader DJ (2007) Effect of insulin resistance, dyslipidemia, and intraabdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *American Journal of Medicine* **120**, S12–S18.

- Roy T and Lloyd CE (2012) Epidemiology of depression and diabetes: a systematic review. *Journal of Affective Disorders* 142(suppl), S8–21.
- Sallis JF and Saelens BE (2000). Assessment of physical activity by self-report: status, limitations, and future directions. *Research Quarterly for Exercise & Sport* 71(suppl. 2), 1–14.
- Schuch FB, Deslandes AC, Stubbs B, Gosmann NP, Silva CT and Fleck MP (2016a) Neurobiological effects of exercise on major depressive disorder: a systematic review. *Neuroscience and Biobehavioral Reviews* 61, 1–11.
- Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB and Stubbs B (2016b) Exercise as a treatment for depression: a metaanalysis adjusting for publication bias. *Journal of Psychiatric Research* 77, 42–51.
- Shipton D, Tappin DM, Vadiveloo T, Crossley JA, Aitken DA and Chalmers J (2009) Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. *BMJ* 339, b4347.
- Slopen N, Kubzansky LD, McLaughlin KA and Koenen KC (2013) Childhood adversity and inflammatory processes in youth: a prospective study. *Psychoneuroendocrinology* 38, 188–200.
- Tamayo T, Christian H and Rathmann W (2010) Impact of early psychosocial factors (childhood socioeconomic factors and adversities) on future risk of type 2 diabetes, metabolic disturbances and obesity: a systematic review. *BMC Public Health* **10**, 525.
- Tann SS, Yabiku ST, Okamoto SK and Yanow J (2007) triADD: the risk for alcohol abuse, depression, and diabetes multimorbidity in the American

Indian and Alaska Native populations. *American Indian Alaskan Native Mental Health Research* 14, 1–23.

- Teasdale SB, Ward PB, Rosenbaum S, Samaras K and Stubbs B (2017) Solving a weighty problem: systematic review and meta-analysis of nutrition interventions in severe mental illness. *British Journal of Psychiatry* **210**, 110–118.
- Timonen M, Rajala U, Jokelainen J, Keinanen-Kiukaanniemi S, Meyer-Rochow VB and Rasanen P (2006) Depressive symptoms and insulin resistance in young adult males: results from the Northern Finland 1966 birth cohort. *Molecular Psychiatry* 11, 929–933.
- Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, Rosenbaum S, Gaughran F, Lally J and Stubbs B (2016) Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* 15, 166–174.
- Vancampfort D, Firth J, Schuch FB, Rosenbaum S, Mugisha J, Hallgren M, Probst M, Ward PB, Gaughran F, De Hert M, Carvalho AF and Stubbs B (2017) Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. World Psychiatry 16, 308–315.
- Wallace TM, Levy JC and Matthews DR (2004) Use and abuse of HOMA modeling. *Diabetes Care* 27, 1487–1495.
- White IR, Royston P and Wood AM (2011) Multiple imputation using chained equations: issues and guidance for practice. *Statistical Medicine* **30**, 377–399.