There are well-established links between major depression and general medical conditions such as diabetes and cardiovascular disease. For example, a meta-analysis of 11 epidemiological studies indicated that the relative risk of future coronary heart disease in people with depressive symptomatology was 1.81 (95% CI 1.53–2.15). In a Finnish study of 2500 young men, those with depressive symptomatology had significantly elevated risk of manifesting insulin resistance (odds ratio (OR) = 3.15, 95% CI 1.48–6.68), which is itself a risk factor for the development of type 2 diabetes and cardiovascular disease. To some extent this association might reflect the consequences of depression and its treatment. For example, depression can be associated with diminished self-care and activity and many psychotropic medications cause excessive weight gain. However, it is also possible that depression and some medical conditions could share common aetiological factors.

If the latter is the case it might be expected that markers of potential general medical comorbidity would be present at the onset of depression or even before its development in high-risk individuals. For instance, a recent study reported that decreased cardiovascular fitness in male conscripts predicted future serious depressive disorder. In a previous investigation we found elevated waking salivary cortisol levels in young people at increased familial risk of depression through virtue of having a parent with depression, and increased cortisol secretion has been linked to the development of hypertension, diabetes and obesity. In the present study therefore, we examined a similar group of at-risk young people to assess whether they exhibited differences from controls in a variety of measures linked to metabolic and cardiovascular disease.
(HADS), and the Perceived Stress Scale (PSS) was used to give a measure of subjective stress over the past month. Adverse life events and the impact of these events on emotional well-being were assessed with the Life Events Rating Scale (LERS), which assesses adverse events at two time points; first, at a distal time point that includes childhood adversity and second, events experienced in the past year. We assessed the quality of perceived parenting style for the first 16 years of life with the Parental Bonding Instrument (PBI), obtaining both maternal and paternal PBI scores. Physical activity was assessed with the self-rated International Physical Activity Questionnaire (IPAQ), which measures the number of minutes per week spent in physical activities. Parental history of diabetes and cardiovascular disease was sought from each participant. All participants gave full informed consent to the study, which was approved by the local ethics committee.

Metabolic and cardiovascular measures

Participants were asked to fast from midnight and present to the unit the next day at approximately 08.30 h for fasting blood sampling of glucose and insulin. We also sampled for lipid profile as well as high-sensitivity C-reactive protein (CRP), a general measure of inflammation. We measured body weight and height to calculate body mass index (BMI) and also waist and hip circumference for waist/hip ratio.

Blood samples were drawn, centrifuged and separated within 30 min, then stored at −20°C for later analysis. Fasting blood glucose, insulin, lipids and CRP were measured at the Oxford Radcliffe Hospital Biochemistry Laboratory using routine validated clinical biochemistry assays masked to diagnostic status. Homeostatic model assessment to determine insulin sensitivity was calculated with the HOMA2 computer model (HOMA calculator, version 2.2; Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Medicine, Oxford, UK, www.dtu.ox.ac.uk/homacalculator/).

Peripheral and central blood pressure and aortic stiffness

Peripheral blood pressure readings were obtained following 15 min supine rest using a calibrated oscillometric device. Radial artery waveform was recorded by application tonometry of the radial pulse to generate an ascending aortic waveform and central blood pressure derived based on a mathematical transfer function. Aortic stiffness was assessed non-invasively by measuring carotid–femoral pulse wave velocity as previously described.

Salivary cortisol sampling

Participants were asked to provide waking saliva samples with a salivette device (Sarstedt, Leicester, UK, www.sarstedt.com) for cortisol measurement. They performed sampling at home on a work day. Participants began sampling as soon as they woke up and remained resting in bed and fasting for a further 30 min during which they took two further saliva samples at 15-minute intervals, as previously described. Plasma cortisol was measured by direct double-antibody radioimmunoassay utilising labelled cortisol. The inter- and intra-assay coefficients of variation were 6% and 4.9% respectively and the limit of detection was 0.3 μg/ml.

Statistical analysis

All data were analysed with SPSS v20 for Windows. Analyses were conducted using unpaired t-tests (two-tailed) or analysis of variance (ANOVA) with ‘group’ (FH+ participants v. controls) and ‘gender’ as between-participant factors. The glucose, insulin and homeostasis model of assessment – insulin resistance index (HOMA-IR) – data were skewed, and to normalise the distribution in preparation for analysis, logarithmic transformation of the data was performed as previously recommended. There was no significant difference in BMI, waist/hip ratio, smoking, alcohol consumption and physical activities of all intensities (Table 2). However, of the 85 individuals in the FH+ group, 6 reported a parent with diabetes compared with none from the 69 controls (χ² = 5.07, P = 0.02). Only one of the FH+ group and two of the control group reported a parental history of cardiovascular disease (χ² = 0.59, P = 0.44).

Psychosocial measures and health-related behaviours

The groups were well-matched for age and gender and had similar scores for current mood and anxiety and perceived stress. There were no significant differences in reported adverse life events, either recent or lifetime. The FH+ group and controls also scored similarly in measures of parental attachment in the first 16 years of life (Table 1). There were no group differences in BMI, waist/hip ratio, smoking, alcohol consumption and physical activities of all intensities (Table 2). However, of the 85 individuals in the FH+ group, 6 reported a parent with diabetes compared with none from the 69 controls (χ² = 5.07, P = 0.02). Only one of the FH+ group and two of the control group reported a parental history of cardiovascular disease (χ² = 0.59, P = 0.44).

Glucose regulation, lipids, CRP and cortisol

Fasting glucose levels were similar between the two groups (F = 0.23, d.f. = 1,142, P = 0.63); however, the FH+ group showed increased insulin levels (F = 9.9, d.f. = 1,139, P = 0.002) and also increased insulin resistance on the HOMA-IR (F = 7.6, d.f. = 1,130, P = 0.007) (Table 3). The ANOVA for both glucose and the HOMA-IR showed significant main effects of gender (glucose: F = 4.17, d.f. = 1,42, P = 0.043; HOMA-IR: F = 4.50, d.f. = 1,130, P = 0.036) where men had mildly greater glucose levels and lower HOMA-IR scores than women (data not shown); however, there were no significant group × gender interactions (all P-values > 0.1). The effect of FH+ status on insulin levels and HOMA-IR remained significant when controlling for parental history of diabetes (F = 10.66, d.f. = 1,138, P = 0.001, and F = 8.37, d.f. = 1,129, P = 0.004).

None of the lipid measures distinguished the FH+ group from the controls and there were no significant interactions between group and gender for any of the lipid measures (all P-values > 0.1). Similarly there was no difference in CRP values between participants in the FH+ group and controls, and no significant gender × group interactions (all P-values > 0.1) (Table 3).

Assayable salivary cortisol was obtained from 147 participants (81 in the FH+ group and 66 in the control group). Participants with initial waking salivary cortisol values more than 3 standard deviations from the mean (one from each group) were excluded. Area under the curve (AUC, without subtraction for baseline secretion) was computed and no significant difference was found between the FH+ and control group in salivary cortisol secretion (F = 1.88, d.f. = 1,141, P = 0.172) (Table 3). There was no significant main effect of gender or gender × group interaction (all P-values > 0.1).

Cardiovascular measures

The ANOVA of peripheral systolic blood pressure showed a main effect of gender (F = 6.01, d.f. = 1,142, P = 0.015); there was also a main effect of gender (F = 10.2, d.f. = 1,42, P = 0.002) but no group gender interaction (F = 0.16, d.f. = 1,142, P = 0.69). Mean peripheral
systolic blood pressure was higher in the FH+ group than controls (Table 4) and higher in men than in women (116.5 (s.d. = 1.4) v. 111.3 (s.d. = 1.0), P = 0.002). Central systolic blood pressure was similarly higher in the FH+ group (F = 7.99, d.f. = 1,142, P = 0.005) with no main or interactive effects of gender (all P-values > 0.1). There was a trend for peripheral diastolic blood pressure to be higher in the FH+ group (F = 3.34, d.f. = 1,142, P = 0.07). There was also a main effect of gender (F = 24.53, d.f. = 1,142, P = 0.001) with peripheral diastolic blood pressure being higher in women (mean 62.3 (s.d. = 1.1) v. 68.7 (s.d. = 0.8), P = 0.001). There was no interaction between group and gender (F = 0.055, d.f. = 1,142, P = 0.81). Central diastolic blood pressure did not differ between the FH+ group and controls (F = 2.32, d.f. = 1,142, P = 0.13). However, central diastolic blood pressure was higher in women than men (F = 25.81, d.f. = 1,142, P = 0.001; men 62.8 (s.d. = 1.1) v. 69.8 (s.d. = 0.9), P = 0.001).
Finally, pulse wave velocity was significantly higher in the FH+ group than controls ($F = 4.62$, d.f. = 1.135, $P = 0.033$) with no main or interactive effects of gender (all values $> 0.1$) (Table 4). In all participants considered together, waist/hip ratio correlated positively and significantly with fasting insulin ($r = 0.24$, $P = 0.007$) and peripheral systolic blood pressure ($r = 0.18$, $P = 0.041$). The BMI correlated positively and significantly with fasting insulin ($r = 0.28$, $P = 0.001$), HOMA-IR ($r = 0.29$, $P = 0.001$), peripheral systolic blood pressure ($r = 0.218$, $P = 0.009$), central systolic blood pressure ($r = 0.25$, $P = 0.002$) and pulse wave velocity ($r = 0.21$, $P = 0.015$). Including BMI as a covariate did not produce any meaningful changes in the statistical differences found between the FH+ group and controls in glucose regulation and cardiovascular measures. In the FH+ group considered alone there was no correlation between either CRP or cortisol AUC and fasting insulin levels or peripheral and central systolic blood pressure or pulse wave velocity. Finally, there was no correlation in this group between fasting insulin levels and any of the above cardiovascular measures.

**Table 4  Cardiovascular measures**

<table>
<thead>
<tr>
<th></th>
<th>FH+ group a</th>
<th>Control group</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>115.1 (1.2)</td>
<td>111.3 (1.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Central</td>
<td>96.8 (0.9)</td>
<td>93.1 (1.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>67.3 (0.9)</td>
<td>64.9 (1.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Central</td>
<td>68.1 (0.9)</td>
<td>65.9 (1.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>5.3 (0.07)</td>
<td>5.1 (0.08)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

a. Participants with a parent with depression but no personal history of depressive illness.

Depressive symptoms are associated with insulin resistance, which is itself a risk factor for diabetes. Our data suggest that a degree of insulin resistance is also present in young people without depression at familial risk of illness. The mechanisms that link depression with insulin resistance are not clear. It is possible, for example, that depression increases the prevalence of adverse health behaviours such as physical inactivity and obesity but this does not seem to be a factor in the present findings. In addition, biochemical changes associated with depression, for example elevated levels of cortisol and inflammatory cytokines, may be implicated in the development of insulin resistance. Our study, however, does not suggest that our FH+ group have increased cortisol secretion as measured by the waking cortisol response. In addition, there was no difference between the FH+ group and controls in levels of high-sensitivity CRP, a general measure of inflammation.

**Link between depression and hypertension**

As with diabetes, it appears that depression predisposes to hypertension. For example, in a meta-analysis of nine studies (22,367 participants), Meng et al found that after adjustment for confounders, significant depressive symptomatology increased the relative risk of developing hypertension (1.81, 95% CI 1.09–1.86) and a further meta-analysis found an association between depression and subsequent stroke. Conversely, as noted above, diminished cardiovascular fitness in young people increased the risk of developing severe depression subsequently. In our study we found that young people with a family history of depression but who themselves were not depressed had a 3–4 mmHg higher peripheral systolic blood pressure, consistent with a change in cardiovascular risk profile, that pre-dates clinical symptoms of depression. This increase in blood pressure is also accompanied by a small 0.2 m/sec higher pulse wave velocity and increases in central systolic blood pressure. Both of these measures provide information about central haemodynamics relevant to organ perfusion and in older individuals predict cardiovascular events independently of brachial measures.

**Impact of childhood adversity**

Young people who have experienced a variety of social disadvantages as children (social isolation, low socioeconomic status, parental maltreatment) show elevated risk markers for cardiovascular disease, including increased blood pressure, abnormal lipid profile, high glycated haemoglobin (a measure of insulin resistance) and increased CRP, when examined in their 20s and 30s. These findings have some similarities to our own in terms of hypertension and insulin resistance but the mechanisms involved may be different because levels of childhood adversity did not apparently distinguish our two participant groups, at least as measured by life events and parental relationships. Indeed, Danese et al suggest that the raised CRP levels seen in their socially disadvantaged participants may be a consequence of childhood hardship and could be an important pathophysiological mechanism leading to the development of cardiovascular risk markers and cardiovascular disease. However, our findings suggest that increased familial risk of depression does not itself lead to increased levels of CRP despite also being associated with insulin resistance and increased blood pressure. However, it would have been better had we measured childhood maltreatment more directly.

**Use of elevated waking cortisol secretion as a marker**

As noted above, raised cortisol levels have also been implicated in the association between depression and diabetes, and depression
and hypertension. Nevertheless, it is possible that common genetic mechanisms might underlie both the risk of depression and cardiovascular disease, and a recent study in schizophrenia (which is also associated with an increased risk of cardiovascular disease) used a ‘pleiotropy-informed’ approach to identify a number of single nucleotide polymorphisms common to both disorders.30 It is also worth notating that, mechanistically, insulin resistance has been linked to depression in a functional imaging study of healthy adults in which higher levels of insulin resistance covaried with increased functional connectivity between ventral striatum and cingulate cortex, which in turned correlated with depressive symptoms.31 Finally, in a subset of the sample we found increased saliva levels of the mineralocorticoïd, aldosterone (details available from the author on request), which is of interest in view of the role of this adrenal hormone in stress and blood pressure regulation.32 However, this finding was unexpected and requires replication.

In conclusion, our data suggest that young people with a parent with depression show changes in markers of insulin sensitivity and blood pressure regulation. This implies that the association between depression, diabetes and cardiovascular disease may pre-date the onset of clinical depression and supports the notion that depression and certain general medical conditions could share common pathophysiological mechanisms. Our data do not provide information on what these mechanisms might be; however, the current findings argue against an important role for either inflammation or cortisol hypersecretion in this particular group of at-risk individuals. Further work is needed to confirm these findings and to explore other potential neurobiological and social mechanisms.

Possible explanations for our findings
At present the mechanism by which increased familial risk of depression is associated with altered insulin secretion and systolic blood pressure is unclear. Genetic factors are likely to explain part of the increased risk of familial depression but reliable identification of susceptibility genes has proved elusive. Nevertheless, it is possible that common genetic mechanisms might underlie both the risk of depression and cardiovascular disease, and a recent study in schizophrenia (which is also associated with an increased risk of cardiovascular disease) used a ‘pleiotropy-informed’ approach to identify a number of single nucleotide polymorphisms common to both disorders.30

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References

Serotonin

Philip J. Cowen

Serotonin is a neurotransmitter conserved through at least 500 million years of nervous system evolution. Serotonin orchestrates adaptive responses to aversive stimuli in invertebrates and an analogous role can be discerned in the more complex behavioural repertoire displayed by mammals to adversity. However, this formulation fails to capture the range of human social behaviours influenced by serotonin, for example, affiliation, empathy and cooperation. In a psychopharmacology experiment I received paroxetine for three weeks. This boost in brain serotonin levels failed to alter my subjective ratings of mood and anxiety. My wife felt differently; ‘Can’t you stay on it?’ she said.
Cardiovascular and metabolic risk profile in young people at familial risk of depression
Zola N. Mannie, Clare Williams, Jonathan Diesch, Andrew Steptoe, Paul Leeson and Philip J. Cowen
BJP 2013, 203:18-23.
Access the most recent version at DOI: 10.1192/bjp.bp.113.126987

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