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**Title:**

Association of Birth Weight and the Development of Antipsychotic Induced Adiposity in Individuals with Treatment Resistant Schizophrenia

**Short title:** birth weight and obesity in chronic schizophrenia

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**Abstract:**

Though weight gain is a common side effect of antipsychotic treatment, there are no useful predictors of which patients are likely to be affected and to what degree. It has been shown that exposure to adverse conditions during intra-uterine life confers a vulnerability to the development of later life metabolic complications and low birth weight for gestational age has been shown to be a robust marker of such prenatal adversity. We hypothesized that patients with schizophrenia with a lower birth weight will have increased vulnerability to the weight inducing effects of antipsychotic treatment. The relationship between birth weight and total and central adiposity, measured as body mass index (BMI) and waist-to-hip ratio (WHR) respectively, was examined in three groups: drug naïve first episode of psychosis (FEP) patients (n=41), treatment resistant schizophrenia (TRS) patients (n=42) and matched healthy volunteers (n=72). All analyses were controlled for age, gender and duration of treatment exposure. We found that a lower birth weight was associated with higher BMI and WHR only in TRS patients but not in FEP or controls, suggesting that prenatal adversity, as indicated by the surrogate marker of a lower birth weight, confers an increased vulnerability to clozapine induced weight gain.

**Key words:** Birth weight, developmental programming, clozapine, schizophrenia, weight gain, first episode psychosis.

## **Introduction**

Up to 75% of patients taking antipsychotic for schizophrenia gain excessive weight (NICE, 2014). This has important implications for treatment compliance and health of a patient group that already has an average life expectancy 16-25 years less than the general population (Saha et al., 2007). A major limitation is the paucity of effective treatments for this weight gain or reliable predictors of who is more likely to gain weight on these treatments and to what degree (Fernandez-Egea et al., 2011).

Low birth weight for gestational age, a surrogate marker of intra-utero growth stress, is a risk factor common to both schizophrenia (Cannon et al., 2002) and metabolic disease (Cottrell and Ozanne, 2008). Studies of the Dutch Hunger Winter and the Chinese famine showed that individuals who experienced caloric deprivation during intra-uterine life, and consequently were born with low birth weight, were at greater risk for developing both metabolic disorders and schizophrenia (Susser and St Clair, 2013). The role of suboptimal prenatal environment in the development of metabolic and cardiovascular disease has been extensively studied and it is now widely recognised that adversity during fetal life, caused by for example placental insufficiency or maternal malnutrition, triggers various fetal adaptations as a predictive adaptive response in anticipation of similar conditions in postnatal life (Hales and Barker, 2001). These include the sparing of vital organs such as the brain at the expense of other organs such as the pancreas, and are protective for immediate postnatal survival and remain so if the postnatal environment is similar (Barnes and Ozanne, 2011). While the individual may have small abnormalities in the cardiovascular and metabolic systems such as mildly elevated blood pressure or impaired glucose tolerance, it is

when the postnatal environment does not match the predicted one, for example with widespread availability of calorie rich food, that these adaptations increase the risk for the development of obesity, type 2 diabetes and hypertension.

While this model has been extensively studied in animal models and human population studies (Bann et al., 2014; Eriksson et al., 2001), there has been little exploration of the possible association of schizophrenia and obesity as part of a shared developmental programming effect (Garcia-Rizo et al., 2014). Subtle metabolic abnormalities such as glucose dysregulation (Fernandez-Egea et al., 2009) and increased intra-abdominal fat (Thakore et al., 2002) have been described in drug naive psychotic patients, and these would be consistent with such a programming effect.

We hypothesized that in schizophrenia, birth weight is a marker of a vulnerability to weight gain and metabolic complications (See Figure 1). This vulnerability interacts with an environmental factor, namely antipsychotic treatment, resulting in the development of excessive adiposity in those individuals with a lower birth weight. To test this hypothesis, we examined two patient groups with schizophrenia and a matched healthy control group. The two patient groups were treatment naive first episode non-affective psychosis patients (with diagnosis, no treatment) and treatment resistant patients (with diagnosis, on treatment) on clozapine, which has one of the highest propensities to induce weight gain, second only to olanzapine (Leucht et al., 2013). Our aim was to examine if birth weight modulated the degree of development of weight gain in response to antipsychotic treatment.

## **Experimental Procedures**

The study was conducted using data from two clinical databases described elsewhere, the 'Diabetes in neuropsychiatric disorders' database for drug naive first episode psychosis (FEP) patients at Hospital Clinic in Barcelona, Spain (Fernandez-Egea et al., 2009), and the 'Clinical and Research Database in Persistent Schizophrenia' in the Cambridgeshire and Peterborough Foundation NHS Trust Mental Health in the UK ([www.psychiatry.cam.ac.uk/f20](http://www.psychiatry.cam.ac.uk/f20)). Informed consent was taken from participants prior to inclusion in the databases. Ethical approval to collect the patient data was granted by the Hospital Clinic Ethics Committee (Barcelona) and the NRES Cambridge Central Research Ethics Committee (13/EE/0121).

Birth weight was collected as part of the study protocol for the FEP patients and clinical routine practice for TRS patients. Birth weight data were self-reported and only included if verified by a parent or if the patient reported the same birth weight at a minimum of two separate consultations. All participants from the two databases for whom a reliable birth weight was available were included and this was the only inclusion criterion. Clinical and anthropometric data were collected from the research project for the FEP and healthy control groups and the clinical notes and routine physical monitoring that all TRS patients undergo. Data on sex, age, height, current weight and waist and hip circumference, were collected on all individuals by observers blind to the status of the birth weight information. Body Mass Index (BMI) and waist-to-hip ratio (WHR) were derived from the anthropometric data. All subjects had data on either BMI or WHR. The included participants did not differ from those on whom no birth weight data were available in terms of their BMI or WHR. For the TRS patients data on the duration and

dose of antipsychotic treatment, use of other drugs affecting weight (e.g. mirtazapine), known metabolic complications and smoking status, were obtained from the clinical notes. All TRS patients were on clozapine with the exception of one on high-dose olanzapine.

**Statistical Analyses:** All analyses were carried out using linear regression (lm package in R). The primary analyses tested the hypothesis that the relationship between birth weight and adult adiposity would only be seen in patients exposed to antipsychotic treatment. The model included birth weight, group and a birth weight x group interaction. The group variable contains the treatment effect: controls (no diagnosis, no treatment), FEP (diagnosis present, no treatment) and TRS (diagnosis present, treatment present). However FEP and TRS groups may vary in other respects so the group variable was coded as a factor with 3 levels and not as a continuous variable as this approach makes fewer assumptions about the relationship between the groups. Treatment duration, age and gender were included as covariates as the groups differed significantly in terms of age and the sample had more males than females. Treatment duration was chosen as the measure of total antipsychotic exposure and calculated as the total duration of treatment from the first initiation of antipsychotic treatment. The primary analyses were carried out separately for the dependent variables of BMI and WHR and a Bonferroni correction was applied.

Two secondary analyses were carried out in the TRS group alone. In the primary analyses the TRS factor includes both diagnosis and treatment variables and it is not possible to separate these. To explore this further the secondary analyses examined the relationship between birth weight and the adiposity measures after controlling for treatment exposure (treatment duration). Age, gender and

smoking status (associated with lower clozapine plasma levels) were included as covariates and BMI and WHR were examined as separate dependent variables and a Bonferroni correction was applied.

## Results

The final sample included only subjects on whom reliable data on birth weight was available. This included 41 drug naive FEP patients from Barcelona (out of 92 included in the database), 42 individuals with TRS from the UK (out of 152 patients) and 72 healthy controls from both UK and Spain (out of 135 recruited). The overall sample characteristics are shown in Table 1. There was a strong correlation between BMI and WHR across the whole sample ( $r = 0.59$ ,  $p < 0.0001$ ). The correlation between age and birth weight was examined to check for potential collinearity and was found to be nonsignificant ( $r = 0.11$ ,  $p = 0.17$ ). After controlling for age, sex and treatment duration, there was a significant effect of TRS group status on BMI ( $T = 6.06$ ,  $p < 0.0001$ ), with TRS status being associated with higher BMI. There was a significant negative TRS group  $\times$  birth weight interaction ( $T = -3.78$ ,  $p = 0.0002$ ) i.e. a unit increase in birth weight produces a corresponding decrease in adult BMI. For the WHR analysis, there was a significant effect of TRS group ( $T = 2.88$ ,  $p = 0.0046$ ) but the birth weight  $\times$  treatment interaction term did not reach significance ( $T = -1.72$ ,  $p = 0.087$ ). The significant effect of TRS group status was investigated further in the secondary analyses. Lower birth weight in TRS patients was significantly associated with greater BMI ( $T = -2.38$ ,  $p = 0.023$ ) and WHR ( $T = -2.51$ ,  $p = 0.017$ ). These associations remained even if the one TRS patient on high dose olanzapine was removed from the sample. There was no effect of smoking status on these associations.

## **Discussion**

We found that a lower birth weight was significantly associated with adiposity in TRS patients. This association was not found in drug naive patients and healthy volunteers, suggesting that the metabolic consequences of developmental programming only become grossly apparent after exposure to an additional insult, in this case antipsychotic treatment, and it modulates the degree of weight gain and fat distribution in response to the treatment.

We hypothesized that in schizophrenia, antipsychotic treatment represented the key environmental factor that interacts with this vulnerability, especially as it is likely that all individuals in the current study will already have had a significant exposure to a similar environment (occidental caloric rich food environment).. In our study there was no difference in birth weight between the three groups. There was no effect of lower birth weight on adiposity in un-medicated individuals (controls and FEP patients). In these groups BMI and WHR were associated with age and gender but it is only in the TRS group that we saw an effect of a lower birth weight, suggesting that antipsychotic medication may be the environmental factor that un-masks this vulnerability.

Our findings are novel in the field of schizophrenia, but are in line with a large body of evidence in metabolic science that shows that low birth weight (as a marker of prenatal adversity) is associated with later life obesity and metabolic disease, especially when associated with a second “hit” such as postnatal over-nutrition (Ozanne et al., 2004). Patients with schizophrenia treated with antipsychotics represent a particular case in this model of obesity with intra-



uterine stressors conferring vulnerability to developing both schizophrenia and metabolic complications, with both conditions probably developing in response to additional factors. Recent evidence shows that severe prenatal stress in mice confers vulnerability for developing both metabolic and neural disturbances, the latter manifest as abnormalities in prepulse inhibition (PPI) abnormalities, a pre-attentive process known to be impaired in schizophrenia (Pacheco-Lopez et al., 2011). Subtle metabolic abnormalities have been described in schizophrenia in drug naive patients, such as increased visceral fat (Thakore et al., 2002) or prediabetes (Fernandez-Egea et al., 2009). Interestingly, these are subclinical abnormalities that were only observed when using more precise tools (such as CT scan or glucose tolerance tests). This is in keeping with the idea that they represent vulnerability traits rather than overt disorders.

Our findings add to the accumulating evidence suggesting that a lower birth weight is not only a risk factor for developing schizophrenia (Cannon et al., 2002) but is also associated with a poorer prognosis. Low birth weight is a predictor of poorer cognitive functioning (Torniainen et al., 2013); it has been associated with smaller cortical area (Haukvik et al., 2014), more severe clinical symptomatology and attentional impairment (Wegelius et al., 2013). This cross-sectional study cannot adequately address this. While the distribution of birth weight in the three groups is very similar, there is the possibility that patients with first episode psychosis with a lower birth weight may go on to develop a more severe form of the illness. However what we do find is that even if we consider only patients who have reached the stage of treatment resistance, there is a clear relationship between a lower birth weight and adiposity.

Our results also suggest that birth weight might be a useful predictor of antipsychotic induced weight gain. A more comprehensive model should include genetic (Shungin et al., 2015) as well as neurodevelopmental information (birth weight), environmental factors (i.e. antipsychotic medication), and behavioural factors (i.e. sedentarism). Birth weight could be a rapidly accessible measure that could help clinicians to predict who will be at greater risk for weight gain and/or will need more regular physical health checks. However a larger longitudinal study will be required to provide a more robust quantification of the effect of birth weight on future weight gain that could be used reliably in the clinic. It would also be important to examine if this effect is seen with other antipsychotics apart from clozapine.

We acknowledge some limitations to our study. Lower birth weight was considered exclusively as a surrogate marker of intra-utero stress, but this is not the only possible cause of low birth weight. We did not examine the potential role of adverse childhood experiences and this might require further study in the future. The sample size is relatively small and the main dependent variable was obtained by self-report. However, where possible the birth weight data were corroborated by collateral history from a parent and in all other instances data were only included if the self-report was consistent across a minimum of two consultations. Importantly, birth weight data were collected in the same way for all 3 groups. There was a significant age difference between the TRS and the other groups and while we controlled for age in all analyses, given the difference in age distribution across the groups, its contribution cannot be reliably determined by co-varying for it in our statistical models. However, the effect of birth weight on adi-

positivity in the TRS group was seen in total fat (BMI) and also in the central fat distribution (WHR), being the latter being less associated with age. Duration of treatment exposure is an important factor in these analyses. Ideally one should examine total cumulative antipsychotic exposure but we did not have sufficient data from clinical records or clozapine plasma levels to estimate this. We therefore calculated treatment exposure as the time from first initiation of antipsychotic to the present. This variable does not account for dosage, periods of non-compliance or treatment cessation and does not capture the number of different drugs prescribed. However for the purposes of this analysis it is likely to exaggerate the effect of antipsychotic treatment (i.e. as per the variable all individuals have been on clozapine for their entire treatment history) in the models and reduces the chances of detecting a birth weight effect. This variable also captures duration of illness and assumes that individuals have been continuously ill since first initiation of treatment. Given that we are studying a trait and not state vulnerability, we believe that this is a reasonable assumption. Finally, the study is cross-sectional as a prospective longitudinal study to test these hypotheses would be extremely challenging to carry out, as it should ideally include drug naive patients followed up for a number of years. Nevertheless the limitations of cross-sectional designs remain but replication of this association in larger samples such as well-described cohorts would help corroborate our findings.

In conclusion, our study suggests that birth weight, as a measure of intra-uterine adversity, modulates the susceptibility to antipsychotic induced weight gain. Though one must be cautious given the small sample size and cross-sectional design of this study, it does accord with the paradigm that considers schizophre-

nia not just as a brain disorder but also as a whole body-disease (Khandaker et al., 2014; Kirkpatrick et al., 2014). Indeed early life stress been theoretically described as a risk factor for both, mental and metabolic disorders over time, in this model metabolic disturbances are a constitutive part of the disorder (Garcia-Rizo et al., 2014), expressed at a later stage but earlier than the general population (Kirkpatrick et al., 2008). This might also help revise our interpretation of the early morbidity and mortality associated with schizophrenia (Laursen et al., 2014) and promote the use of secondary and tertiary strategies for preventing metabolic disturbances in cases at higher risk.

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Association of Birth Weight and the Development of Antipsychotic Induced Adiposity in Individuals with Treatment Resistant Schizophrenia

**Short title:** birth weight and obesity in chronic schizophrenia

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**Abstract:**

Though weight gain is a common side effect of antipsychotic treatment, there are no useful predictors of which patients are likely to be affected and to what degree. It has been shown that exposure to adverse conditions during intra-uterine life confers a vulnerability to the development of later life metabolic complications and low birth weight for gestational age has been shown to be a robust marker of such prenatal adversity. We hypothesized that patients with schizophrenia with a lower birth weight will have increased vulnerability to the weight inducing effects of antipsychotic treatment. The relationship between birth weight and total and central adiposity, measured as body mass index (BMI) and waist-to-hip ratio (WHR) respectively, was examined in three groups: drug naïve first episode of psychosis (FEP) patients (n=41), treatment resistant schizophrenia (TRS) patients (n=42) and matched healthy volunteers (n=72). All analyses were controlled for age, gender and duration of treatment exposure. We found that a lower birth weight was associated with higher BMI and WHR only in TRS patients but not in FEP or controls, suggesting that prenatal adversity, as indicated by the surrogate marker of a lower birth weight, confers an increased vulnerability to clozapine induced weight gain.

**Key words:** Birth weight, developmental programming, clozapine, schizophrenia, weight gain, first episode psychosis.

## **Introduction**

Up to 75% of patients taking antipsychotic for schizophrenia gain excessive weight (NICE, 2014). This has important implications for treatment compliance and health of a patient group that already has an average life expectancy 16-25 years less than the general population (Saha et al., 2007). A major limitation is the paucity of effective treatments for this weight gain or reliable predictors of who is more likely to gain weight on these treatments and to what degree (Fernandez-Egea et al., 2011).

Low birth weight for gestational age, a surrogate marker of intra-utero growth stress, is a risk factor common to both schizophrenia (Cannon et al., 2002) and metabolic disease (Cottrell and Ozanne, 2008). Studies of the Dutch Hunger Winter and the Chinese famine showed that individuals who experienced caloric deprivation during intra-uterine life, and consequently were born with low birth weight, were at greater risk for developing both metabolic disorders and schizophrenia (Susser and St Clair, 2013). The role of suboptimal prenatal environment in the development of metabolic and cardiovascular disease has been extensively studied and it is now widely recognised that adversity during fetal life, caused by for example placental insufficiency or maternal malnutrition, triggers various fetal adaptations as a predictive adaptive response in anticipation of similar conditions in postnatal life (Hales and Barker, 2001). These include the sparing of vital organs such as the brain at the expense of other organs such as the pancreas, and are protective for immediate postnatal survival and remain so if the postnatal environment is similar (Barnes and Ozanne, 2011). While the individual may have small abnormalities in the cardiovascular and metabolic systems such as mildly elevated blood pressure or impaired glucose tolerance, it is

when the postnatal environment does not match the predicted one, for example with widespread availability of calorie rich food, that these adaptations increase the risk for the development of obesity, type 2 diabetes and hypertension.

While this model has been extensively studied in animal models and human population studies (Bann et al., 2014; Eriksson et al., 2001), there has been little exploration of the possible association of schizophrenia and obesity as part of a shared developmental programming effect (Garcia-Rizo et al., 2014). Subtle metabolic abnormalities such as glucose dysregulation (Fernandez-Egea et al., 2009) and increased intra-abdominal fat (Thakore et al., 2002) have been described in drug naive psychotic patients, and these would be consistent with such a programming effect.

We hypothesized that in schizophrenia, birth weight is a marker of a vulnerability to weight gain and metabolic complications (See Figure 1). This vulnerability interacts with an environmental factor, namely antipsychotic treatment, resulting in the development of excessive adiposity in those individuals with a lower birth weight. To test this hypothesis, we examined two patient groups with schizophrenia and a matched healthy control group. The two patient groups were treatment naive first episode non-affective psychosis patients (with diagnosis, no treatment) and treatment resistant patients (with diagnosis, on treatment) on clozapine, which has one of the highest propensities to induce weight gain, second only to olanzapine (Leucht et al., 2013). Our aim was to examine if birth weight modulated the degree of development of weight gain in response to antipsychotic treatment.

## Experimental Procedures

The study was conducted using data from two clinical databases described elsewhere, the 'Diabetes in neuropsychiatric disorders' database for drug naive first episode psychosis (FEP) patients at Hospital Clinic in Barcelona, Spain (Fernandez-Egea et al., 2009), and the 'Clinical and Research Database in Persistent Schizophrenia' in the Cambridgeshire and Peterborough Foundation NHS Trust Mental Health in the UK ([www.psychiatry.cam.ac.uk/f20](http://www.psychiatry.cam.ac.uk/f20)). Informed consent was taken from participants prior to inclusion in the databases. Ethical approval to collect the patient data was granted by the Hospital Clinic Ethics Committee (Barcelona) and the NRES Cambridge Central Research Ethics Committee (13/EE/0121).

Birth weight was collected as part of the study protocol for the FEP patients and clinical routine practice for TRS patients. Birth weight data were self-reported and only included if verified by a parent or if the patient reported the same birth weight at a minimum of two separate consultations. [All participants from the two databases for whom a reliable birth weight was available were included and this was the only inclusion criterion.](#) Clinical and anthropometric data were collected from the research project for the FEP and healthy control groups and the clinical notes and routine physical monitoring that all TRS patients undergo. Data on sex, age, height, current weight and waist and hip circumference, were collected on all individuals [by observers blind to the status of the birth weigh information.](#) Body Mass Index (BMI) and waist-to-hip ratio (WHR) were derived from the anthropometric data. All subjects had data on either BMI or WHR. [The included participants did not differ from those on whom no birth weight data were available in terms of their BMI or WHR.](#) For the TRS patients [data on](#) the duration [and](#)

[dose](#) of antipsychotic treatment, use of other drugs affecting weight (e.g. mirtazapine), known metabolic complications and smoking status, [were obtained from the clinical notes](#). All TRS patients were on clozapine with the exception of one on high-dose olanzapine.

**Statistical Analyses:** All analyses were carried out using linear regression (lm package in R). The primary analyses tested the hypothesis that the relationship between birth weight and adult adiposity would only be seen in patients exposed to antipsychotic treatment. The model included birth weight, group and a birth weight x group interaction. The group variable contains the treatment effect: controls (no diagnosis, no treatment), FEP (diagnosis present, no treatment) and TRS (diagnosis present, treatment present). However FEP and TRS groups may vary in other respects so the group variable was coded as a factor with 3 levels and not as a continuous variable as this approach makes fewer assumptions about the relationship between the groups. Treatment duration, age and gender were included as covariates as the groups differed significantly in terms of age and the sample had more males than females. Treatment duration was chosen as the measure of total antipsychotic exposure and calculated as the total duration of treatment from the first initiation of antipsychotic treatment. The primary analyses were carried out separately for the dependent variables of BMI and WHR and a Bonferroni correction was applied.

Two secondary analyses were carried out in the TRS group alone. In the primary analyses the TRS factor includes both diagnosis and treatment variables and it is not possible to separate these. To explore this further the secondary analyses examined the relationship between birth weight and the adiposity measures after controlling for treatment exposure (treatment duration). Age, gender and

smoking status (associated with lower clozapine plasma levels) were included as covariates and BMI and WHR were examined as separate dependent variables and a Bonferroni correction was applied.

## Results

The final sample included only subjects on whom reliable data on birth weight was available. This included 41 drug naive FEP patients from Barcelona (out of 92 included in the database), 42 individuals with TRS from the UK (out of 152 patients) and 72 healthy controls from both UK and Spain (out of 135 recruited). The overall sample characteristics are shown in Table 1. There was a strong correlation between BMI and WHR across the whole sample ( $r = 0.59$ ,  $p < 0.0001$ ). The correlation between age and birth weight [was examined to check for potential collinearity and was found to be nonsignificant](#) ( $r = 0.11$ ,  $p = 0.17$ ). After controlling for age, sex and treatment duration, there was a significant effect of TRS group status on BMI ( $T = 6.06$ ,  $p < 0.0001$ ), with TRS status being associated with higher BMI. There was a significant negative TRS group x birth weight interaction ( $T = -3.78$ ,  $p = 0.0002$ ) i.e. a unit increase in birth weight produces a corresponding decrease in adult BMI. For the WHR analysis, there was a significant effect of TRS group ( $T = 2.88$ ,  $p = 0.0046$ ) but the birth weight x treatment interaction term did not reach significance ( $T = -1.72$ ,  $p = 0.087$ ). The significant effect of TRS group status was investigated further in the secondary analyses. Lower birth weight in TRS patients was significantly associated with greater BMI ( $T = -2.38$ ,  $p = 0.023$ ) and WHR ( $T = -2.51$ ,  $p = 0.017$ ). [These associations remained even if the one TRS patient on high dose olanzapine was removed from the sample.](#) There was no effect of smoking status on these associations.

## Discussion

We found that a lower birth weight was significantly associated with adiposity in TRS patients. This association was not found in drug naive patients and healthy volunteers, suggesting that the metabolic consequences of developmental programming only become grossly apparent after exposure to an additional insult, in this case antipsychotic treatment, and it modulates the degree of weight gain and fat distribution in response to the treatment.

We hypothesized that in schizophrenia, antipsychotic treatment represented the key environmental factor that interacts with this vulnerability, especially as it is likely that all individuals in the current study will already have had a significant exposure to a similar environment (occidental caloric rich food environment).. In our study there was no difference in birth weight between the three groups. There was no effect of lower birth weight on adiposity in un-medicated individuals (controls and FEP patients). In these groups BMI and WHR were associated with age and gender but it is only in the TRS group that we saw an effect of a lower birth weight, suggesting that antipsychotic medication may be the environmental factor that un-masks this vulnerability.

Our findings are novel in the field of schizophrenia, but are in line with a large body of evidence in metabolic science that shows that low birth weight (as a marker of prenatal adversity) is associated with later life obesity and metabolic disease, especially when associated with a second “hit” such as postnatal over-nutrition (Ozanne et al., 2004). Patients with schizophrenia treated with antipsychotics represent a particular case in this model of obesity with intra-



uterine stressors conferring vulnerability to developing both schizophrenia and metabolic complications, with both conditions probably developing in response to additional factors. Recent evidence shows that severe prenatal stress in mice confers vulnerability for developing both metabolic and neural disturbances, the latter manifest as abnormalities in prepulse inhibition (PPI) abnormalities, a pre-attentive process known to be impaired in schizophrenia (Pacheco-Lopez et al., 2011). Subtle metabolic abnormalities have been described in schizophrenia in drug naive patients, such as increased visceral fat (Thakore et al., 2002) or prediabetes (Fernandez-Egea et al., 2009). Interestingly, these are subclinical abnormalities that were only observed when using more precise tools (such as CT scan or glucose tolerance tests). This is in keeping with the idea that they represent vulnerability traits rather than overt disorders.

Our findings add to the accumulating evidence suggesting that a lower birth weight is not only a risk factor for developing schizophrenia (Cannon et al., 2002) but is also associated with a poorer prognosis. Low birth weight is a predictor of poorer cognitive functioning (Torniainen et al., 2013); it has been associated with smaller cortical area (Haukvik et al., 2014), more severe clinical symptomatology and attentional impairment (Wegelius et al., 2013). This cross-sectional study cannot adequately address this. While the distribution of birth weight in the three groups is very similar, there is the possibility that patients with first episode psychosis with a lower birth weight may go on to develop a more severe form of the illness. However what we do find is that even if we consider only patients who have reached the stage of treatment resistance, there is a clear relationship between a lower birth weight and adiposity.

Our results also suggest that birth weight might be a useful predictor of antipsychotic induced weight gain. A more comprehensive model should include genetic (Shungin et al., 2015) as well as neurodevelopmental information (birth weight), environmental factors (i.e. antipsychotic medication), and behavioural factors (i.e. sedentarism). Birth weight could be a rapidly accessible measure that could help clinicians to predict who will be at greater risk for weight gain and/or will need more regular physical health checks. However a larger longitudinal study will be required to provide a more robust quantification of the effect of birth weight on future weight gain that could be used reliably in the clinic. It would also be important to examine if this effect is seen with other antipsychotics apart from clozapine.

We acknowledge some limitations to our study. Lower birth weight was considered exclusively as a surrogate marker of intra-utero stress, but this is not the only possible cause of low birth weight. We did not examine the potential role of adverse childhood experiences and this might require further study in the future.

The sample size is relatively small and the main dependent variable was obtained by self-report. However, where possible the birth weight data were corroborated by collateral history from a parent and in all other instances data were only included if the self-report was consistent across a minimum of two consultations. Importantly, birth weight data were collected in the same way for all 3 groups. There was a significant age difference between the TRS and the other groups and while we controlled for age in all analyses, given the difference in age distribution across the groups, its contribution cannot be reliably determined by co-varying for it in our statistical models. However, the effect of birth weight on adi-

[positivity in](#) the TRS group was seen in total fat (BMI) and also in the central fat distribution (WHR), being the latter [being](#) less associated with age. Duration of treatment exposure is an important factor in these analyses. Ideally one should examine total cumulative antipsychotic exposure but we did not have sufficient data from clinical records or clozapine plasma levels to estimate this. We therefore calculated treatment exposure as the time from first initiation of antipsychotic to the present. This variable does not account for dosage, periods of non-compliance or treatment cessation and does not capture the number of different drugs prescribed. However for the purposes of this analysis it is likely to exaggerate the effect of antipsychotic treatment (i.e. as per the variable all individuals have been on clozapine for their entire treatment history) in the models and reduces the chances of detecting a birth weight effect. This variable also captures duration of illness and assumes that individuals have been continuously ill since first initiation of treatment. Given that we are studying a trait and not state vulnerability, we believe that this is a reasonable assumption. Finally, the study is cross-sectional as a prospective longitudinal study to test these hypotheses would be extremely challenging to carry out, as it should ideally include drug naive patients followed up for a number of years. Nevertheless the limitations of cross-sectional designs remain but replication of this association in larger samples such as well-described cohorts would help corroborate our findings.

In conclusion, our study suggests that birth weight, as a measure of intra-uterine adversity, modulates the susceptibility to antipsychotic induced weight gain. Though one must be cautious given the small sample size and cross-sectional design of this study, it does accord with the paradigm that considers schizophre-

nia not just as a brain disorder but also as a whole body-disease (Khandaker et al., 2014; Kirkpatrick et al., 2014). Indeed early life stress been theoretically described as a risk factor for both, mental and metabolic disorders over time, in this model metabolic disturbances are a constitutive part of the disorder (Garcia-Rizo et al., 2014), expressed at a later stage but earlier than the general population (Kirkpatrick et al., 2008). This might also help revise our interpretation of the early morbidity and mortality associated with schizophrenia (Laursen et al., 2014) and promote the use of secondary and tertiary strategies for preventing metabolic disturbances in cases at higher risk.

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## Highlights

Birth weight modulates clozapine associated weight gain.

Total fat and central fat distribution was higher in those with lower birth weight.

This association is not seen in drug naïve psychosis or matched controls.

**Table 1: Sample characteristics**

All data are presented as mean ± standard deviation (range). All significant differences are between the TRS group and the others. The only difference between FEP and controls is in the BMI where there is a small negative effect (parameter estimate -1.58, p = 0.042).

	TRS	FEP	Controls	Difference
N	42	41	72	
Age	40.45 ± 8.84 (23-59)	27.6 ± 6.1 (19-45)	28.96 ± 7 (19-50)	<0.0001*
Sex	31M: 11F	25M: 16F	42M: 30F	
Birth weight	3.45 ± 0.65 (2.26-5.1)	3.31 ± 0.51 (2.25-4.6)	3.49 ± 0.52 (2.1-4.62)	n.s.
WHR	0.967 ± 0.078 (0.81-1.122)	0.839 ± 0.067 (0.66-0.979)	0.858 ± 0.078 (0.68-1.045)	<0.0001*
BMI	30.66 ± 4.63 (21.9-41.3)	22.3 ± 3.9 (15.9-38.5)	23.96 ± 3.55 (18.89-33.14)	<0.0001*
Years on antipsychotic treatment	18.7 ± 8.32 (5-41)			
Years on clozapine	10.65 ± 6.38 (1-24)			
Clozapine dose (mg/day)	312.2 ± 118.47 (125-600)			

Figure 1

Figure 1: Hypothesised simplified relationship between intra-uterine adversity and antipsychotic induced weight gain and metabolic complications

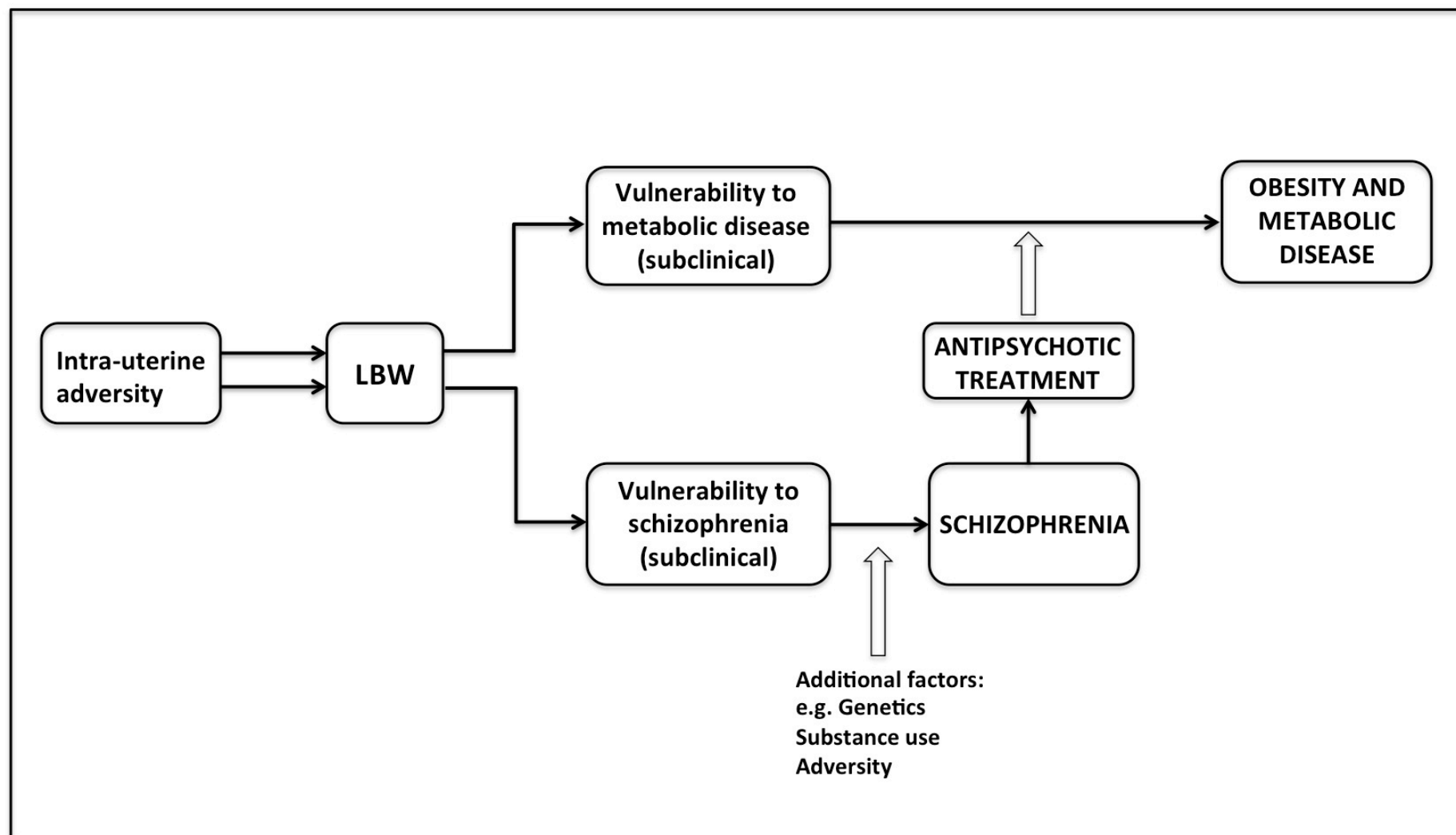


Figure 2

Figure 2: Relationship between birth weight and Body Mass Index (BMI) across the groups (shaded intervals represent 95% confidence intervals)

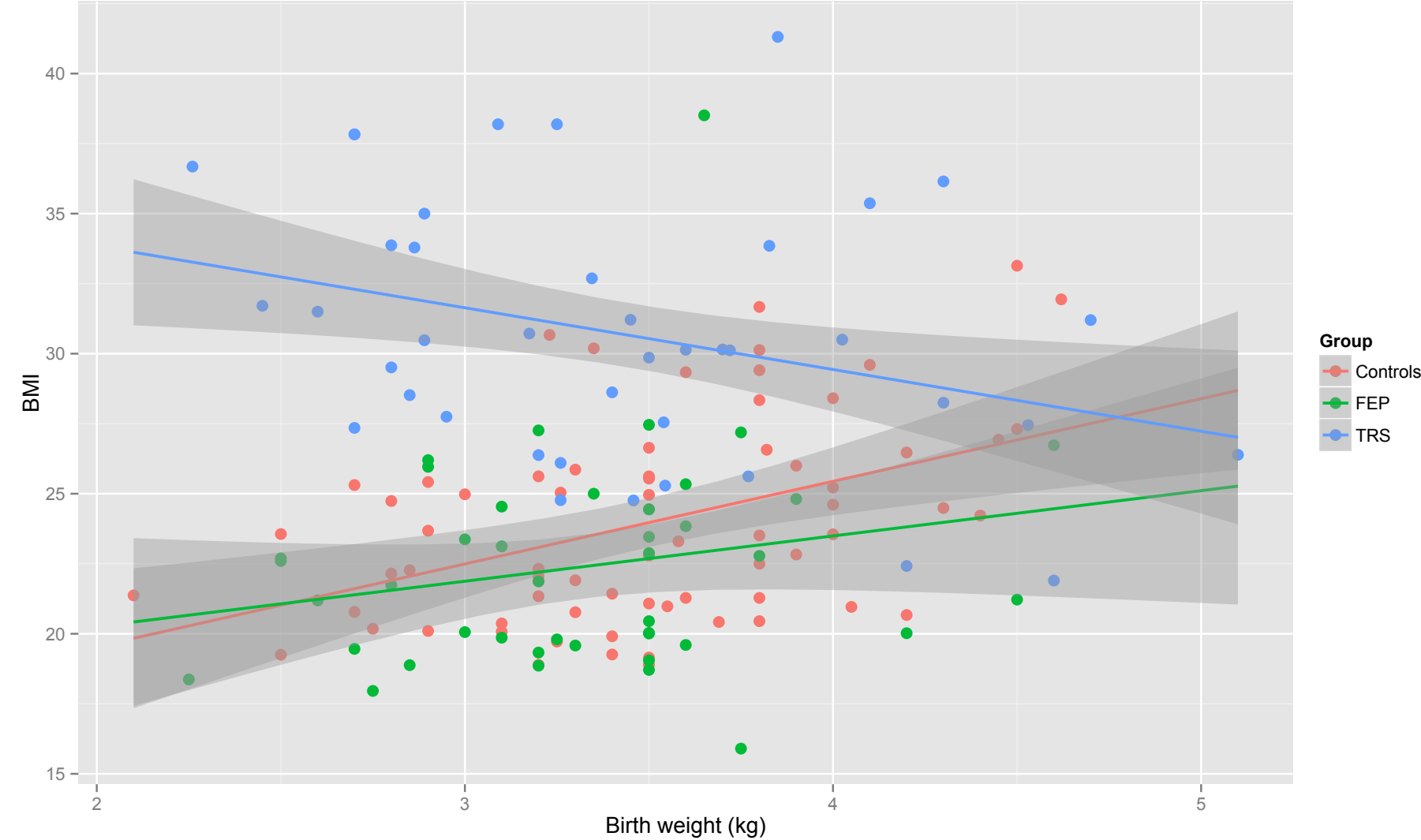
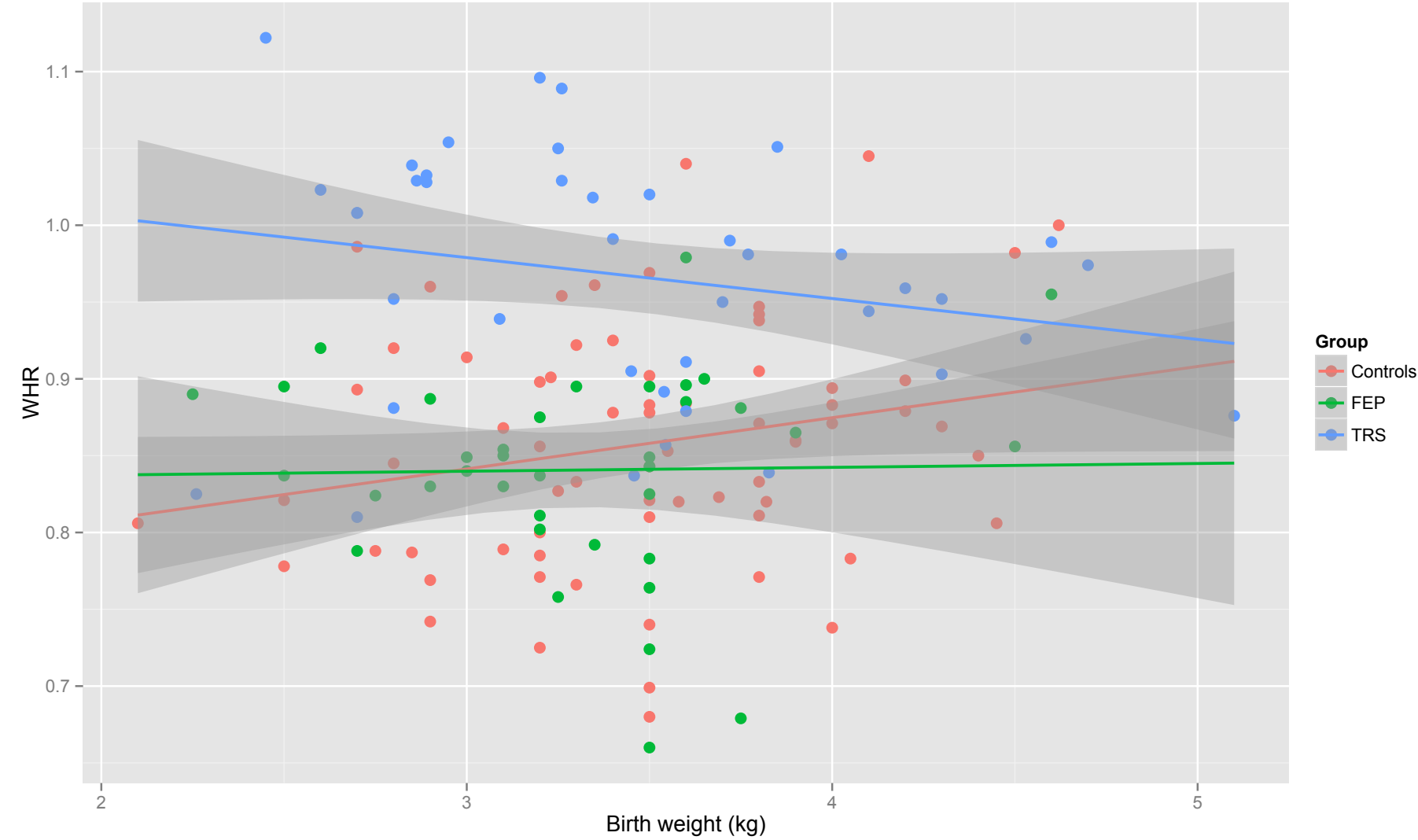


Figure 3

**Figure 3: Relationship between birth weight and Waist to Hip ratio (WHR) across the groups** (shaded intervals represent 95% confidence intervals)



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## **Authors Disclosures**

Contributors. Authors HZ, CGR, EFE designed the study, EFE and CGR collected the data, HZ did the analyses, MB, BK, SEO and PBJ collaborated in the first draft of the study. All authors contributed to the final version and approved the study.

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