Vitamin D and cardiometabolic outcomes: a prospective cohort study

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Dear Editor,

Schizophrenia and other psychotic disorders are associated with increased premature mortality, with cardiovascular disease a major contributor to this(Correll et al., 2017, Lin et al., 2018).

Cardiometabolic dysfunction is evident at the time of first presentation with psychosis with increases in cardiometabolic disturbance seen over the following year (Bioque et al., 2018, Gaughran et al., 2019).

Identification of modifiable risk factors may allow this risk to be addressed(Lally et al., 2018). Observational studies in the general population have demonstrated inverse associations between vitamin D status and the risk of death due to cardiovascular disease(Chowdhury et al., 2014). There is limited and inconclusive data regarding the associations between vitamin D and cardiometabolic risk factors in people with severe mental illness (SMI)(Adamson et al., 2017). In a large cohort of people with established psychosis we identified that those patients with the highest levels of vitamin D have a lower prevalence of metabolic syndrome compared to those with the lowest vitamin D levels(Lally et al., 2016). Further, we identified inverse cross-sectional correlations with a variety of cardiometabolic measures including obesity, dyslipidaemia, hypertension, and C-reactive protein levels.

While cross sectional studies have indicated a relationship between vitamin D deficiency and cardiovascular measures in established psychosis, no longitudinal studies in FEP have investigated associations between baseline 25 (OH) D concentrations and cardiometabolic parameters at follow up.

Given this lack, we set out to examine a) the cross-sectional relationship between vitamin D and cardiometabolic measures at first contact for psychosis; b) the

relationship between baseline vitamin D status and cardiometabolic measures at 12 months.

We hypothesised that 25(OH) D serum levels were cross sectionally associated with cardiometabolic measures at illness onset. We hypothesised that over the 12 months follow up period that lower vitamin D levels at baseline would be associated with Incident cardiometabolic risk, and that changes in vitamin D levels would be inversely associated with changes in cardiometabolic measures after controlling for confounders.

A prospective observational study of 168 adults (108 males) with a first episode psychosis (FEP) were recruited as part of a prospective observational cohort study, Physical health and substance Use Measures in first onset Psychosis (PUMP), part of the National Institute of Health Research funded IMPACT programme (grant RP-PG-0606-1049). The methodology, eligibility criteria, recruitment methods and are described previously (Lally et al., 2019) and the cardiovascular risk factor outcome measures are described in Lally et al., 2016 (Lally et al., 2016).

Between groups comparisons were made using x^2 test for categorical variables; independent student's *t*-test for continuous variables, or the Mann-Whitney *U* test for variables with non-normal distribution. Linear regression was used to test the association between baseline serum vitamin D levels and the 12-month mean cardiometabolic measure scores controlling for potential confounding factors, such as gender, age, season of sampling at baseline, and the corresponding baseline clinical variable.

Demographic and clinical characteristics of participants and their relationships with Vitamin D status are shown in supplementary table 1, with no significant association identified when allowance is made for multiple testing.

Similar to the cross-sectional analysis, suboptimal 25 (OH) D levels at baseline were not associated with increased weight, glycemic or lipid measures at 12 months compared to those with vitamin D levels in the highest quartile with the exception of LDL-cholesterol levels. In the adjusted analysis, those with the lowest quartile vitamin D levels had significantly increased LDL-cholesterol levels at 12 months compared to those with the higher quartile vitamin D levels (β=3.58, 95%CI 0.22-6.93, p=0.037) (Supplementary table 2).

In the unadjusted analysis, those with lowest quartile vitamin D levels at baseline had significantly elevated HbA1c levels at 12 months (B=0.37, 95% CI 0.11-0.64, p=0.007), however, this association was lost when adjusted for gender, age and season of baseline 25(OH) D sampling.

There were no significant associations between baseline vitamin D quartiles and the presence of defined cardiometabolic abnormality at 12 months (e.g. metabolic syndrome, obesity, glucose dysregulation, raised blood pressure, dyslipidaemia)) (supplementary table 3).

We assessed the longitudinal relationship between changes in 25(OH)D serum level over 12 months and incident cardiometabolic abnormality at 12 months follow-up (supplementary table 4). Reductions in serum 25(OH) D were associated with an increased odds ratio (OR) of incident dyslipidaemia (OR=1.13, 95% CI=1.02-1.20, p=0.012), hypercholesterolaemia (OR1.12, 95% CI 1.03-1.22, p=0.010) and reduced HDL-cholesterol (OR1.13, 95% CI 1.03-1.24, p=0.010) when adjusting for confounders (see table 3). No prospective associations with obesity, hypertension or glucose dysregulation were identified.

To our knowledge, this is the first cross-sectional and longitudinal assessment of associations between vitamin D and cardiovascular risk factors in FEP.

The first aim was to replicate the previously identified cross-sectional relationship in established psychosis between 25(OH)D levels and cardiometabolic risk factors. The second aim was to explore whether there is a longitudinal association between baseline serum 25(OH)D levels and cardiometabolic measures and outcomes at 12 months.

The study findings were largely negative, with no consistent findings except those relating to dyslipidaemia. A longitudinal relationship between low vitamin D at baseline and increased LDL-cholesterol and between prospective reductions in vitamin D and increased incidence of dyslipidaemia were identified.

Lower levels of cholesterol and LDL-cholesterol are found at first contact in FEP cases compared to controls (Pillinger et al., 2017) and further work is needed to explore the potential of vitamin D to act as a modifiable risk factor for the emergence of dyslipidaemia.

To date there have been no trials published examining vitamin D supplementation in FEP, although one is underway (Gaughran et al, 2020). A previous longitudinal study identified associations between low vitamin D and total psychotic and total negative symptoms at 12 months follow up(Lally 2019). This along with the current study are exploratory, but if later works shows vitamin D might improve symptom and cardiometabolic outcomes in psychosis, then first episode may be the ideal window of opportunity. No significant relationship between vitamin D and glucose dysregulation or weight change was identified in our cohort study. Observational data in general population studies link low vitamin D levels to poor cardiovascular outcomes and risk factors. However, interventional trials have been equivocal to date, which may reflect vitamin D not being a causative factor or may be as a result of poor study design or predominance of participants with optimal vitamin D status (Bouillon et al., 2019).

Maintaining adequate levels of vitamin D >50ng/ml are recommended, though whether this impacts on cardiovascular risk in early psychosis remains to be determined.

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