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MENTAL HEALTH DISORDERS AND NEUROSCIENCE

A comparison of epithelial cell content of oral samples estimated using cytology and DNA methylation

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Background

Saliva and buccal samples are popular for epigenome wide association studies (EWAS) due to their ease of collection compared and their ability to sample a different cell lineage compared to blood. As these samples contain a mix of white blood cells and buccal epithelial cells that can vary within a population, this cellular heterogeneity may confound EWAS. This has been addressed by including cellular heterogeneity obtained through cytology at the time of collection or by using cellular deconvolution algorithms built on epigenetic data from specific cell types. However, to our knowledge, the two methods have not yet been compared.

Results

Here we show that the two methods are highly correlated in saliva and buccal samples ($R = 0.84$, $P < 0.0001$) by comparing data generated from cytological staining and Infinium MethylationEPIC arrays and the EpiDISH deconvolution algorithm from buccal and saliva samples collected from twenty adults. In addition, by using an expanded dataset from both sample types, we confirmed our previous finding that age has strong, non-linear negative correlation with epithelial cell proportion in both sample types. However, children and adults showed a large within-population variation in cellular heterogeneity.

Conclusion

Our results validate the use of the EpiDISH algorithm in estimating the effect of cellular heterogeneity in EWAS and showed DNA methylation generally underestimates the epithelial cell content obtained from cytology.

Evaluation of the predictive performance of cardiovascular disease Risk Prediction Models in Community-dwelling australian and united states older adults

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Background

Owing to the rapid growth in the population of older adults, who are at an increased risk of developing cardiovascular disease (CVD), it is essential to have a CVD risk prediction model that is inclusive of the aged, in order to prevent and manage CVD burden in terms of mortality, morbidity, disability, functional decline, and healthcare cost, in this population. However, the old CVD risk prediction models were developed in middle-aged populations, and their usefulness in the aged population remains unclear. So, this study for the first time aimed to validate some established CVD risk prediction models including ACC/AHA, Framingham, Globorisk, SCORE2-OP, and Predict1 based on the Australian and the United States community-dwellers older adults.

Methods

Data from ASPREE (ASPirin in Reducing Events in the Elderly) cohort, which is a large-scale longitudinal, prospective study, are considered for CVD risk prediction. Models' performance of prediction function was assessed by discrimination (Harrell's C index and time-dependent ROC curves) and calibration (Calibration plots) assessments.

Results

All the original models showed poor discrimination (c-indexes range, 0.58-0.61 for males, and 0.61-0.66 for females, and AUC range, 0.60-0.64) as well as clearly miscalibration, with over-prediction. However, by updating, the models' discrimination (c-indexes range, 0.62-0.66 for males, and 0.67-0.70 for females, and AUC range, 0.66-0.69) and calibration power were notably improved.

Conclusion

These CVD risk prediction models indicated low performance in predicting CVD event in older adults and need to be updated to use in clinical practice for the aged population.

Reference

1. Australian Bureau of Statistics 2020, Causes of Death 2019, cat. no. 3303.0, October

2. SCORE2-OP working group and ESC Cardiovascular risk collaboration. European Heart Journal. 2021.

Identifying early-life epigenetic correlates of neurocognitive outcomes in twins at the age of 11 years

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Background

Poor neurocognitive outcomes significantly burden children, their families and healthcare systems. However, little is still known about the interactions among genetic and early ;life environmental processes that influence variation in cognition, behaviour and brain structure and function.

Methods

Our proposed study aimed to quantify the associations between DNA methylation state using Infinium Methylation EPIC array (850K) in buccal (cheek swab) samples at birth and the full-scale IQ, average cortical thickness and average cortical surface area at the age of 11 years from the Peri/postnatal Epigenetic Twins Study (PETS) cohort using twins as individuals and within pair differences models. We also aimed to identify whether the association of DNA methylation at birth with cognitive outcome and brain morphology at 11 years are stable in when DNA methylation is measured at 18 months, six years and 11 years.

Results

We expect that differentially methylated CpG sites will be significantly associated with full-scale IQ, cortical thickness and cortical surface area with false discovery (FDR) <0.05 and top CpGs ranked by p-value will be enriched in genes associated with neurocognitive development and the top ranked CpGs observed in associations between DNA methylation at birth and those outcomes at 11 years will be present at 18 months, 6 years and 11 years of age.

Conclusion

This proposed study will allow us to investigate the developmental stability of epigenetic effects over time and assess how early life events and epigenetic states associate with functional and structural differences in neurodevelopmental outcomes in mid-childhood.

Maternal adipose tissue DNA methylation and gene expression associated with excessive gestational weight gain

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Objective

Excessive gestational weight gain is associated with the risk of diabetes in later life for both mothers and offspring. To shed light on the mechanisms behind the association of gestational weight gain and maternal obesity, we aimed to study the association between gestational weight gain, DNA methylation and gene expression of genes associated with body weight regulation and inflammation in adipose tissue from women without pre-existing obesity, at birth.

Methods

Omental adipose tissue was obtained from 25 women aged 25-40 with a healthy singleton pregnancy and a pre-pregnancy BMI of 18.5-25 kg/m^2. DNA methylation and gene expression were analysed within the *LEP, TNF, NPY, POMC* and *SOCS3* genes using bisulfite amplicon sequencing and quantitative real-time RT-PCR, respectively.

Results

We found no evidence for an association at any CpGs from any amplicon at FDR <0.05. However, all 31 CpGs analysed within LEP exhibited a negative association with GWG, including six at P<0.05. Permutation testing showed that this relationship was unlikely to arise from random chance. Average DNA methylation across the whole LEP amplicon was negatively correlated with GWG, with a gradient of 0.79% DNA methylation decrease per kilo of GWG. The NPY amplicon had a gradient of 0.71% DNA methylation decrease per kilo of GWG, despite individual CpGs showing a mix of positive and negative correlations. Levels of messenger RNA showed a low negative correlation with DNA methylation at both *LEP* and *NPY*.

Conclusions

We present preliminary evidence that gestational weight gain is negatively correlated with DNA methylation in omental tissues in *LEP* and *NPY*. Such knowledge, if replicated, will shed light on the mechanisms that link gestational weight gain and maternal obesity.

Parental mental health during preconception years and its association with offspring ADHD: A systematic review protocol

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Background

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric condition prevalent in both the child and adult populations. With the growing awareness of the importance of the pre-conception period, and considering the diverse etiological background in ADHD including a combination of biomedical, psychological and social factors (1), it is essential to understand how parental mental health and related factors operating during preconception years affect offspring ADHD. Thus, we aim to systematically review the available evidence on associations between parental mental health conditions and/or use of psychotropic medications and the risk of offspring ADHD.

Methods

Studies will be eligible if they are: i) population- or clinically-based cohort studies; ii) examine preconception parental mental health conditions and/or use of psychotropic medications; and iii) offspring ADHD. Relevant peer-reviewed literature will be identified via electronic searching of research databases (Embase, PubMed, OVID, CINAHL, Medline). Reference lists of eligible articles will be hand searched and grey literature may be considered. The included studies will undergo critical appraisal using standardised critical appraisal checklist developed by JBI.

Results

A preliminary search strategy developed by listing and mapping keywords was implemented for Medline Complete via the EBSCOHost platform yielding 1,511 potentially relevant studies. Following the screening process, a descriptive synthesis will be conducted, and the key findings presented. This will include characteristics of the included studies, critical appraisal scores, and summary of findings (presented in text and visually). If appropriate, a meta-analysis will also be conducted.

Conclusion

To the best of our knowledge this will be the first systematic review to collate and critically appraise the existing evidence investigating parental mental health conditions during the preconception years and its association with offspring ADHD.

Reference

1. Nigg JT, Sibley MH, Thapar A, Karalunas SL. Development of ADHD: Etiology, heterogeneity, and early life course. Annual review of developmental psychology. 2020;2:559-83.

The development of a novel cell-based screening platform to improve bowel cancer screening in the community.

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Background

Bowel cancer is the abnormal growth of cells in the lining of the colon and rectum. It is a significant public health concern and the most common cancer in Australia, with 103 deaths per week. Early detection is therefore crucial and currently, a colonoscopy is the gold standard procedure for detecting possible underlying bowel cancer. However, the procedure can be very expensive, invasive, cumbersome and cause infection, bleeding, or bowel perforation. In response, new forms of non-invasive screening have been implemented like the immunochemical faecal occult blood test (iFOBT). However, they solely detect blood in faeces, to identify haemoglobin, resulting in high specificity but low sensitivity in detecting early-stage cancers which commonly exhibit no bleeding. Only 1 in 20 individuals with positive iFOBT result have bowel cancer after their required colonoscopy. The false positive rates (~ 96%), cause unnecessary invasive actions and stress. Cells from early-stage and asymptomatic advanced cancer, however, can shed and be released in stool. A more sensitive screening tool, especially for early-stage cancer would save more lives and unnecessary stress for many.

Our research project aims to develop a new cell-based bowel cancer screening tool to increase accuracy, reduce false positives by analysing the cells instead of just detecting blood. So far, our research team has successfully isolated human cells from healthy stool, and isolated HT-29 colon cancer cells spiked in healthy stool.

Methods

We will recruit iFOBT positive and negative participants' and collect stool samples (n=20) and perform a series of physical isolation methods to extract a pure population of human cells. We will then analyse the cells through cytological and immunocytochemical techniques.

Conclusion

Ultimately, we expect to better patient outcomes and early detection of bowel cancer through a novel cell-based method with higher sensitivity and more efficiency.

The impact of diet and stress on the sperm epigenome: A twin study

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Background

The global increase in obesity is largely attributed to the availability of processed foods and sedentary lifestyles. Concurrently, there is a growing prevalence of stress and mental health disorders. Both are linked with adverse health outcomes.

Animal studies have recently indicated that paternal diet, weight, and stress levels can impact offspring health, with epigenetic mechanisms being the proposed mediator. However, human research in this context is scant.

Methods

My research aims to bridge this gap by examining how modern dietary habits - a shift towards processed foods - might alter the sperm epigenome. I plan to recruit 25 twin pairs. Each twin will be randomly assigned to receive Diet A (unprocessed diet) or Diet B (processed diet) over a three-week period.

Furthermore, I aim to investigate the effect of stress across ones' life on the sperm epigenome, via responses to validated stress questionnaires.

Semen collected at baseline and post intervention will be processed and motile sperm isolated to assess epigenetic state. The level of DNA methylation will be measured using Reduced Representation Bisulfite Sequencing (RRBS). Small non-coding RNA sequencing will be performed and sorted based on RNA categories (miRNA, piRNA, and tRNA).

Conclusion

The findings from this research will contribute to our understanding of paternal epigenetic inheritance in humans and aid in formulating informed pre-conception dietary and lifestyle advice for prospective fathers, reducing the risk of adverse health outcomes in their offspring.

The role of inflammation in the relationship between obesity and perinatal depression in women.

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Background

Inflammation is one of the key mechanisms of major depressive disorder. However, the evidence regarding the role of inflammation in perinatal depression is inconsistent. We investigated the association between pre-pregnancy obesity, a chronic inflammatory state, and perinatal depressive symptoms in a pre-birth cohort, the Barwon Infant Study. We also assessed if circulating inflammatory markers during pregnancy mediated this relationship.

Methods

Body mass index (BMI) was calculated in 883 women and depressive/stress symptoms assessed using the Edinburgh Postnatal Depression and Perceived Stress scales (EPDS/PSS) at 28 weeks gestation and 4 weeks postpartum. Circulating glycoprotein acetyls (GlycA), high-sensitivity C-reactive protein (hsCRP), and cytokines were measured at 28 weeks gestation. We analysed data using regression modelling and assessed mediation using nested counterfactual models.

Results

Women with pre-pregnancy obesity (BMI≥30 kg/m^2) had greater antenatal EPDS and PSS scores, compared to healthy weight women (18.5-24.9 kg/m^2). Compared to healthy weight women, GlycA, hsCRP, interleukin (IL)-1ra and IL-6 were higher in women with obesity, while eotaxin and IL-4 were lower. While IL-6 and eotaxin were negatively associated with EPDS/PSS scores, with no evidence for mediation, higher GlycA, was associated with higher EPDS/PSS scores and partially mediated the association between pre-pregnancy obesity and antenatal depression.

Conclusions

Our findings highlight the role of inflammation in maternal mental health, showing that pre-pregnancy obesity increases the risk of antenatal depression and GlycA, a novel biomarker of systemic inflammation, partially mediates this relationship. These findings have wide significance to those investigating the biological underpinnings of mental health disorders.