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# The Vitamin D in Pregnancy Study: a prospective prebirth cohort in southern Australia

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## ABSTRACT

**Purpose** The Vitamin D in Pregnancy Study is a long-term ongoing cohort study. It was conceived to explore relationships between maternal vitamin D status in pregnancy and offspring growth and development, and has since diversified to include a wide range of physical and mental health exposures and outcomes.

**Participants** Recruitment was from the University Hospital Geelong (Barwon Health) antenatal clinic, Geelong, Victoria, Australia, between 2002 and 2004. 475 women were initially recruited, which resulted in 400 eligible mother–child pairs at birth.

**Findings to date** The cohort has been followed up twice in pregnancy, at birth, and 1 year, 6 years and 11 years post birth. The study has reported an association between vitamin D in pregnancy and musculoskeletal health and body composition in the children.

**Future plans** Subject to funding, there will be a prospective young adult follow-up. This profile aims to foster both cross-national and international collaborations with both existing and future data collection.

## Strengths and limitations of this study

- Pregnant women had measures taken at two time points in pregnancy, which allows for the examination of temporal factors with relevant exposures during pregnancy.
- There has been many follow-ups of both mother and children across time and a wide range of exposure and outcome variables collected.
- The study is observational in nature; thus, residual confounding cannot be discounted.

## INTRODUCTION

There is substantial evidence supporting the Developmental Origins of Health and Disease hypothesis which ties early-life exposures to an increased risk of non-communicable disease in adult life by means of 'fetal programming'.[1] Fetal programming represents the phenomenon by which nutritional, environmental and genetic influences (such as epigenetic adaptation to maternal environment and paternal and intergenerational epigenetic transmission) influence fetal growth and development in utero, which, in turn, may permanently alter disease risk trajectories.[2]

Vitamin D status represents a modifiable and affordable target for nutritional intervention during pregnancy. At the time of inception of the Vitamin D in Pregnancy (VIP) Study, and in more recent times, a significant number of women residing in Australia, including those of childbearing age, recorded low serum vitamin D levels by currently accepted standards (<50 nmol/L).[3 4] Suboptimal levels of vitamin D during pregnancy is of concern not only for the mothers, but also because it exposes the developing fetus to insufficiency during critical phases of development, and thus may predispose the offspring to an increased risk of disease, such as rickets in infancy and childhood, and osteoporosis in adulthood.

The VIP Study was originally designed to investigate the potential role of vitamin D during pregnancy on infant bone development and growth measures; however, based on a growing body of literature,[5 6] the study has since expanded to encompass longitudinal investigations of several aspects of offspring growth and development. Importantly, the VIP cohort was recruited at a time when vitamin D measurement and supplementation were relatively uncommon in Australia, resulting in relatively high rates of maternal vitamin D deficiency.[7 8] The study thus provides an important opportunity to investigate the relationship between low maternal vitamin D status and offspring outcomes.

The aims of the study are to identify whether maternal vitamin D insufficiency during pregnancy is associated with the following outcomes in the offspring:

1. Bone growth, density and mineral content.
2. Muscle mass and strength.

3. Adiposity.
4. Atopic and respiratory symptoms.
5. Behaviour and psychological symptomatology.

The study design of the VIP cohort will contribute information to the growing policy debate surrounding vitamin D supplementation and sun exposure during pregnancy to alleviate chronic disease burden in the offspring.

This cohort profile aims to describe the methods, recruitment phases, breadth and scope of the data collected to date and future plans of the cohort to external researchers to facilitate collaboration. The children will begin turning 18 years of age from September 2020, at which point we will plan to embark on a young adult follow-up.

## COHORT DESCRIPTION

### Patient and public involvement

No patient involved.

### Participants

In total, 475 pregnant women were recruited prior to 16 weeks gestation from the antenatal clinic at the University Hospital Geelong (formerly known as the Geelong Hospital), in south-eastern Australia (latitude: −38.15). This recruitment target was based on the assumption, using a conservative estimate of 4.2% of women having vitamin D levels below 28 nmol/L, that with 360 women there would be 80% power to detect a 0.75 SD in knee–heel length in babies above and below 28 nmol/L vitamin D. Assuming 20% attrition, 450 women would have to be targeted. A further 25 women were recruited to allow for failure to provide a blood sample at the off-site testing facilities. At the time of recruitment, the University Hospital Geelong served as the sole public teaching hospital in the region. Recruitment took place over an 18-month period and was completed in 2004. During the recruitment period, the population in the Barwon Statistical Division was approximately 260 000. There were an estimated 2470 women who registered for antenatal care at the University Hospital Geelong during the study period. Inclusion and exclusion criteria are presented in table 1. At birth, 400 mother–child pairs had data recorded, with a maternal serum 25-hydroxyvitamin D (25(OH)D) concentration measured in early and/or late pregnancy. At recruitment 169/415 (40.7%) women, and at 28–32 weeks gestation 148/380 (38.9%) women had 25(OH)D serum level below 50 nmol/L, respectively.

### Data collection and methodology

Following baseline recruitment, which occurred before 16 weeks gestation, mothers were reassessed at 28–32 weeks gestation, and mother–child pairs underwent follow-up appointments once the offspring were born, with subsequent clinical assessments at 12 months and 11 years post birth (figure 1). There were 209 of the 475 (44%) women recruited who returned at the 11-year follow-up. There were no differences between vitamin D levels at either time point, smoking status during pregnancy, height, weight, parity or education detected for non-responders versus responders. Mothers who participated in the 11-year follow-up were slightly older at recruitment than non-responders (29.65±4.34 (responders) vs 28.71±4.10 (non-responders) years, p=0.049).

When offspring were approximately 5 years of age (n=342, 92% of those eligible), telephone interviews were conducted with women who had a vitamin D sample taken during late pregnancy. Additionally, in a substudy conducted after the telephone interviews, lung function was tested in a selection of children 5 years post birth whose mothers were in the highest or lowest quartile of vitamin D at 28–32 weeks gestation (n=58). Participant characteristics at each follow-up are listed in table 2.

Throughout the study, a series of clinical and questionnaire data has been collected from both parents, and offspring; these data are briefly described below. Table 3 presents the schedule of data collection at each time point. Where possible, self-reported health outcomes which would require hospital admission were verified with (1) medical records from the University Hospital Geelong and (2) the comprehensive fracture register for the Barwon Statistical Division, known as the Geelong Osteoporosis Study Fracture Grid.[9]

#### Maternal data

##### *Blood collection*

Maternal venous blood samples were taken at recruitment and 28 weeks gestation. Serum samples were centrifuged within 2 hours and stored at −70°C. Samples were analysed for 25(OH)D by radioimmunoassay (Immunodiagnostic Systems, Tyne and Wear, UK); coefficient of variation at 30 nmol/L was 10.2%, and 10.1%

**Table 1** Inclusion and exclusion criteria for recruitment of pregnant mothers into the study

| Inclusion criteria | Exclusion criteria |
|---|---|
| 1. Singleton pregnancy<br>2. Over the age of 18 years<br>3. Gestational age of less than 16 weeks<br>4. Unlikely to leave the area within the foreseeable future | 1. Evidence of insulin-dependent diabetes, anticonvulsant therapy, renal disease<br>2. Sarcoidosis or familial hypocalciuric hypercalcaemia<br>3. Substance use/abuse<br>4. Maintenance systematic or high-dose glucocorticoid therapy<br>5. Significant maternal illness and/or disability<br>6. Dark skinned and/or veiled (as of known high risk for deficiency and usually screened and treated) |

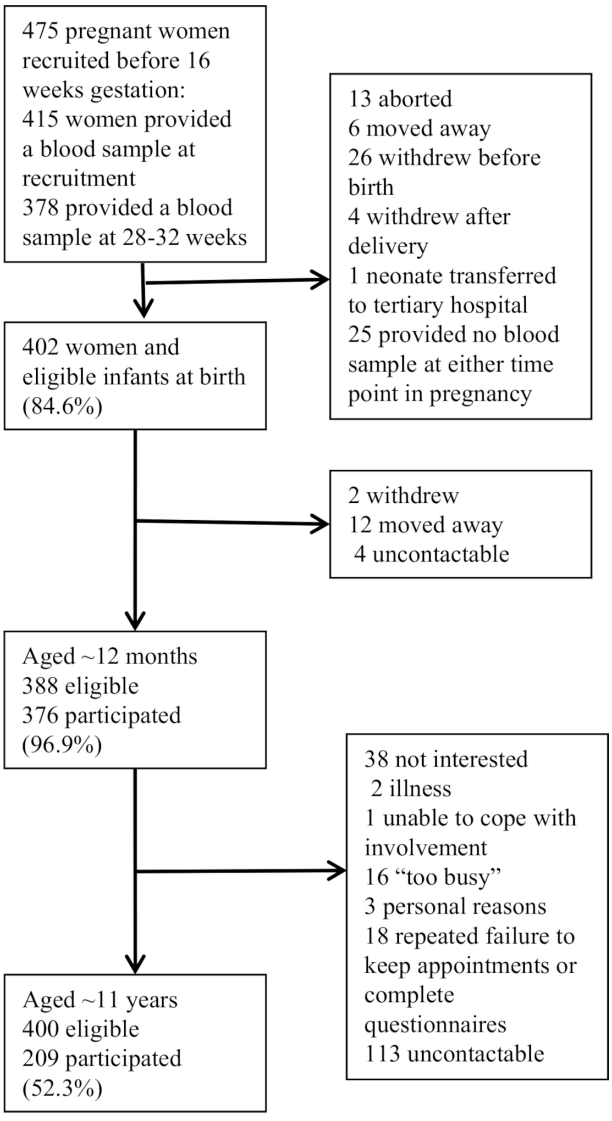



**Figure 1** Participation rates at clinical follow-up assessments.

at 100 nmol/L, parathyroid hormone by chemiluminescent enzyme-labelled immunometric assay (Diagnostic Products Corporation, Los Angeles, California, USA) and total calcium and albumin using Vitros 250 autoanalyzer (Ortho-Clinical Diagnostics, Rochester, New York, USA).

### *Anthropometry, other clinical measures and demographics*

Maternal body weight (±0.1 kg) was measured with electronic scales and height (±0.1 cm) ascertained by use of a wall-mounted stadiometer at recruitment, 28 weeks gestation and at the follow-up performed 11 years post birth of their offspring. Clinical measures included head circumference at recruitment, and hip and waist circumferences at 11 years post birth of their offspring. Blood pressure during pregnancy was extracted from patient obstetric records. Area-based socioeconomic status was calculated by matching the residential address of each participant at baseline recruitment, and of the mother at 11 years post birth, to the corresponding Australian Bureau of Statistics (ABS) Census Collection District (each area that encompasses approximately 250 households). Using ABS software, Socio-Economic Indexes for Areas values were determined from the 2001 census for residential addresses at baseline, and from the 2016 census for addresses at 11 years post birth.[10 11] Information on educational attainment, employment status, occupation type, living arrangements (home ownership and how many occupants in the home), marital status and country of birth was collected by self-report (table 3).

### *Bone measures*

Quantitative heel ultrasound was performed at the 11 years follow-up using a Lunar Achilles ultrasonometer (GE, Madison, USA) on the left foot, to obtain measures of broadband attenuation, speed of sound and stiffness index as measures of bone quality.

**Table 2** Participant characteristics at each clinical follow-up of the Vitamin D in Pregnancy Study

| Characteristic | At birth n=402 | 12 months post birth n=376 | 11 years post birth n=209 |
|---|---|---|---|
| Maternal | | | |
| Age (year) | 29.7 (±0.4.72) | 30.9 (±4.73) | 41.4 (±4.40) |
| Height (cm)* | 165.0 (161.0–172.0) | – | 165.2 (±5.96) |
| Weight (kg)* | 76.65 (68.60–88.15) | – | 74.5 (64.03–89.78) |
| Offspring | | | |
| Sex n (%) males | 196 (48.9) | 188 (50.0) | 106 (50.7) |
| Age (year) | – | 1.00 (0.98–1.04) | 10.92 (10.71–11.39) |
| Length/height (cm) | 50.50 (48.80–52.00) | 76.96 (±3.12) | 147.45 (143.43–154.25) |
| Weight (kg) | 3.54 (±0.53) | 9.97 (±1.27) | 40.05 (35.00–48.25) |

Data are presented as median (IQR) or mean (±SD).
*Measures under at birth were collected at 28–32 weeks gestation visit.

**Table 3** Schedule of measurements collected at each follow-up appointment of the Vitamin D in Pregnancy Study

| | Recruitment | 28–32 weeks gestation | At birth | 12 months post birth | 5 years post birth | 11 years post birth |
|---|---|---|---|---|---|---|
| Maternal measures | | | | | | |
| Blood sample | X | X | | | | |
| Anthropometric | X | X | | | | X |
| Sociodemographic | X | X | | | | X |
| Medication/supplement use | X | X | | | | |
| Diet | X | X | | | | X |
| Smoking status | X | X | | | | X |
| Skin type | X | X | | | | |
| Sun exposure | X | X | | | | |
| Obstetric data | X | X | X | | | |
| Mental health | | | | | | X |
| Bone measures | | | | | | X |
| Health literacy | | | | | | X |
| Paternal measures | | | | | | |
| Anthropometric | X | | | | | |
| Sociodemographic | X | | | | | X |
| Smoking Status | X | | | | | X |
| Child measures | | | | | | |
| Anthropometric | | | X | X | X | X |
| Fetal ultrasound measures | | X | | | | |
| Sociodemographic | | | X | X | X | X |
| Medication/supplement use | | | | X | X | X |
| Breast feeding | | | | X | | |
| Diet | | | | X | X | X |
| Blood testing | | | X | | | |
| Body composition | | | X | X | | X |
| Bone measures | | | | | | X |
| Self-reported fracture | | | | | | X |
| Muscle strength | | | | | | X |
| Allergy/eczema symptoms | | | | X | X | X |
| Asthma/wheezing symptoms | | | | X | X | X |
| Spirometry | | | | X | X | |
| General health | | | | X | X | X |
| Immunisations | | | | | X | X |
| Physical activity | | | | | X | X |
| Sun exposure | | | | | X | X |
| Dental history | | | | | | |
| Sleeping habits | | | | | | X |
| Screen time | | | | | X | X |
| Skin type | | | | | X | X |
| Living arrangements | | | | | X | X |
| Mental health | | | | | | X |
| Hygiene | | | | | X | |

X denotes that the relevant measurement was collected at the noted follow-up phase.

### Health behaviours

Maternal skin pigmentation on the back of hands, inner underarm and shoulder, was determined using a flash spectrophotometer at recruitment and at 28–32 weeks gestation. Maternal sun exposure was self-reported as time spent outdoors in the sun and sunbathing behaviours were concurrently recorded.

Maternal smoking status was self-reported at baseline recruitment and at the 5-year and 11-year follow-up assessments. In addition, the number of occupants smoking in the main residence and the number of cigarettes smoked by each individual were reported by the mother.

Maternal dietary macro and micronutrient and alcohol intakes were recorded at recruitment, 28–32 weeks gestation and at 11 years using the Victorian Cancer Council Food Frequency Questionnaire.[12]

Maternal health literacy was measured at 11 years using the Health Literacy Questionnaire (HLQ).[13] The HLQ is a multidimensional tool that measures nine specific domains: healthcare provider support, access to sufficient health information, ability to actively manage health, social support, level of critical appraisal, level of active engagement with healthcare providers, ability to navigate the healthcare system, ability to find quality health information and comprehension of health information.

### Mental health

Maternal mental health status was assessed using semi-structured clinical interviews at 11 years. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) Axis I Disorders, non-patient edition (SCID-I/NP) was used to obtain diagnoses for current and past mood, anxiety, alcohol and non-alcohol substance misuse, and eating disorders.[14] Personality disorders were identified using the Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II).[15] The Perinatal Grief Scale was also completed by the mothers at 11 years to determine factors that may be important with the relationship between mother and her living children after the loss of a child.[16]

## Paternal data

Fathers self-reported their height (±cm), weight (±kg) and head circumference (±cm) at baseline recruitment. Sociodemographic information, including living arrangements, employment status, occupation type and educational attainment, was collected at recruitment and 11 years. Smoking status was recorded at recruitment and 11 years.

## Offspring data

### Blood sample

DNA was extracted from the offspring's blood spot on their Guthrie card sample to determine vitamin D receptor genotype using Chelex reagent (BioRad, Hercules, California, USA).

### Anthropometry and other clinical measures

At birth, weight was measured by obstetric staff on regularly calibrated scales (±1 g). Crown-heel length was measured using a length board (Ellard Instrumentation, Seattle, Washington, USA) and knee–heel length to the nearest millimetre using a hand-held BK5 knemometer (Force Technology, Brondby, Denmark) within 12–72 hours post birth. At 12 months and 11 years post birth, offspring body weight (±0.1 kg) was measured with electronic scales and height (±0.1 cm) collected by use of a wall-mounted stadiometer. Skinfold measurements were collected at various sites at birth, 12 months and 11 years in the offspring, according to International Society for the Advancement of Kinanthropometry protocol using Holtain calipers (±0.1 mm; Holtain, Crymych, UK).[17] Mid-arm, calf and head circumferences were collected at birth, 12 months and 11 years, with the addition of hip and waist circumferences at 11 years. Triplicate blood pressure was measured at 12 months (Critikon Dinamap Pro 100 oscillometric device, GE Healthcare, UK), and at 11 years using a digital metre (A&D Company). Muscle strength was measured at 11 years by use of a manual muscle tester (Nicholas, Model 01163), and grip strength using a hand-held dynamometer (JAMAR Plus Digit). Balance and explosive force were measured in a subset of participants (n=13) by use of a Ground Reaction Force Platform (Leonardo). Self-reported pubertal staging was completed using Tanner staging at 11 years[18 19].

### Bone and body composition measures

Bone densitometry was performed for each child at age 11 years by dual energy x-ray absorptiometry (DXA) using a Lunar Prodigy densitometer (GE Lunar, Madison, Wisconsin, USA) at the lumbar spine (L1–4), forearm and total body). From the total body scans, total and regional fat and non-bone lean tissue mass was obtained. Trabecular bone score was calculated from spine scans (iNsight, V.2.1, Med-Imaps). Quantitative heel ultrasound was also performed (Achilles Insight, GE Lunar). In a subset of participants (n=13), bone density and geometry were measured by peripheral quantitative CT (XT3000, Stratec, Pforzheim, Germany) at 11 years at the forearm and proximal femur. At the time of writing, the identification of incident fractures up to the age of 16 years was being completed via a previously validated method using radiological reports.[9]

### Allergy, wheezing and asthma

Wheezing and doctor-diagnosed asthma and eczema in the offspring were self-reported by the mothers when the children were aged 12 months. The International Study of Asthma and Allergies in Children questionnaire was completed by the mothers at 5 and 11 years.[20] Spirometry was conducted in a subsample of offspring at age 5 years, and for all the offspring at 11 years, using processes in accordance with the American Thoracic Society guidelines.[21 22]

### Health behaviours

Information about sun exposure, skin type and sunburn history of the offspring was collected at 5 and 11 years. Additionally, a naevi count was performed at 11 years of age, whereby higher naevi counts were indicative of higher past sun exposure.[23]

Physical activity was documented at 5 years by recording how much time was spent on sporting activities. At 11 years, activity was recorded using an after-school diary.[24] This diary recorded activity for a 2 hours period, 3 days after school on a scale of resting/sleeping to intense activity. Breastfeeding status and age of introduction to solids were recorded at 12 months. At 5 years of age, intake of vitamin D-rich food sources, such as oily fish, was recorded by questionnaire, and at 11 years dietary patterns were assessed using the Children's Dietary Questionnaire.[25]

All health behaviour measures were maternally reported on behalf of the child.

### Mental health

Behaviour and mental health symptomatology of the offspring were assessed at 11 years. Self-reported psychological symptoms were identified using the Spence Children's Anxiety Scale,[26] psychotic life exposures and the Short Mood and Feelings Questionnaire.[27] Mothers provided informant responses on the Strengths and Difficulties Questionnaire, which assessed emotional, internalising and externalising symptoms and behaviours[28] and the Australian Scale for Asperger's syndrome to identify behaviours and abilities that typify Asperger's Syndrome during childhood.

### Future plans

Subject to obtaining funding, we will be seeking to embark on a follow-up of the offspring in young adulthood. The primary focus of this follow-up will align with the original focus of maternal vitamin D status in pregnancy offspring growth and development.

## FINDINGS TO DATE

Data generated from the VIP cohort have been published in peer-reviewed journals, and presentations made at national and international scientific meetings. We have reported several findings with relation to our primary exposures and outcomes. Specifically, that maternal vitamin D levels were:

- Positively associated with knee–heel length at birth (a proxy measure of long bone growth in utero), mid-upper arm and calf circumference and gestation length.[29]
- Positively associated with bone mineral density of the spine and total body at 11 years in boys but not in girls.[30]
- Negatively associated with total fat mass pecentage and positively associated with total lean mass percentage at 11 years in offspring whose mothers also smoked.[31]
- Positively associated with trabecular bone scores at 11 years in boys, but not girls.[32]

Moreover, we have reported that infant vitamin D receptor genotype potentially plays a role in the association between low maternal vitamin D status and offspring birth measures.[33] Pregnant women were shown to be more likely to consume more calcium and phosphorus through diet than non-pregnant peers in late pregnancy; this was not detected for other important nutrients with an increased demand.[34] Maternal diet was shown to be associated with offspring linear growth, but not with bone measures at 11 years.[35] Analyses with other health outcomes such as respiratory, atopic and behavioural measures are ongoing, and investigators encourage collaboration from researchers with these particular interests.

## Strengths and limitations

The major strengths of this project are that data were collected during two stages of pregnancy (prior to 16 weeks, and at 28–32 weeks gestation), and that at the time of recruitment, maternal vitamin D insufficiency was relatively common. Furthermore, the prospective study design enables us to discern temporal associations between exposures during both early and late stages of pregnancy and offspring outcomes ranging from birth to 11 years of age. The Barwon Statistical Division, from which the study population was drawn, is comparable to the wider Australian population, thus enhancing the generalisability of findings at a national level.[36] At the 2001 ABS census, the Barwon Statistical Division was similar to the wider Australian population in terms of age (0.7% difference), marital status (2.2%), weekly income (1.4%) and school leavers' age (7.5%). As we recruited from a publicly funded hospital, our sample may be relatively more disadvantaged than mothers in the region who accessed prenatal care via private options. A further consideration is that the majority of our sample is Caucasian given the relative lack of ethnic diversity within the region and the exclusion of dark skinned or veiled women, thus impacting the generalisability of the findings from this cohort. This may decrease the ability to extrapolate findings to the broader international community but assist with internal validity. The ethnic homogeneity, however, has advantages, in that it reduces potential for confounding by biological and genetic differences in both the exposure (eg, vitamin D metabolism) and outcomes (eg, bone mineral density). In comparison to some of the larger birth cohorts such as the Hertfordshire Cohort Study,[37] 400 mother–child pairs could be considered a relatively small number that may limit statistical power to test for associations in less prevalent outcomes. However, unlike larger studies, the VIP encompasses significantly detailed prospective information and blood samples, and thus does not rely on proxy measures or recalled information for exposures during pregnancy. There are other cohorts such as the Southampton Women's Study,[38] Avon Longitudinal Study of Parents and Children,[39] Raine Study[40] and Generation

R Study[41] that have collected both gestational vitamin D levels and child DXA measures. However, this study differentiates itself from with the others by objectively measuring gestational vitamin D, as serum 25(OH) D, at two defined time points in pregnancy. There has also been considerable attrition from recruitment to the recent 11 year follow-up. However, the remaining participants appeared to be largely representative in terms of maternal measures as those who did not attend the 11-year follow-up, although they were slightly older; these findings suggest a non-differential loss to follow-up in terms of maternal characteristics. Lastly, given the observational design, there is the possibility for residual confounding that is unaccounted for.

## COLLABORATION

Data are archived by the Epi-Centre for Healthy Ageing, Deakin University and Barwon Health, located at University Hospital Geelong (Barwon Health). Collaborations are encouraged and data requests can be sent to the principle investigator Professor Julie Pasco (juliep@barwonhealth.org.au). Establishment of collaborative projects will be overseen by the VIP research group and the Barwon Health Human Research Ethics Committee. All participants in the study have provided written informed consent on behalf of themselves and their children: additionally at the 11-year follow-up, children provided optional assent.

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**Contributors** NKH wrote the initial draft of the manuscript and performed all descriptive statistics. SLB-O provided initial edits to first and subsequent drafts and provided critical feedback on the structure and content. JDW was involved with the inception of the cohort and initiation of the 11-year follow-up, and provided critical feedback on intellectual content of the manuscript. SMH provided information about health literacy and provided critical feedback on intellectual content of the manuscript. PJV led and provided information about the 5-year follow-up and provided critical feedback on the content and structure. LJW provided information about psychiatric measures and provided critical feedback on the content and structure. JAP was involved in the inception of the initial cohort and initiation of 11-year follow-up, provided initial edits to first and subsequent drafts and provided critical feedback on the structure and content.

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**Competing interests** JDW declares that he received in-kind support from Swisse Wellness for an unrelated study of vitamin D in young women.

**Patient consent for publication** Not required.

**Ethics approval** Informed consent was obtained at all follow-up phases of the study by the mother on behalf of herself and her child. In addition, optional assent was provided by the child at 11 years. Copies of relevant approved documentation are available to potential collaborators on reasonable request. All follow-up phases have been approved by the Barwon Health Research Ethics Committee (01/43).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data are archived by the Epi-Centre for Healthy Ageing, Deakin University and Barwon Health, located at University Hospital Geelong (Barwon Health). Collaborations are encouraged and deidentified data requests can be sent to the principle investigator Julie Pasco (juliep@barwonhealth.org.au). Access to data will be overseen by the Vitamin D in Pregnancy Study team and subject to approval from the relevant ethics committees.

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