

Sex-specific effects of nutritional supplements in infants born early or small: protocol for an individual participant data meta-analysis (ESSENCE-IPD)

Supplement document

Appendix 1. Definitions for Primary Outcome of Metabolic Risk

| Measurement | Guideline/ Equipment | Age | Abnormal | Notes |
|-----------------------------|--|----------------------------|---|--|
| Size for gestation at birth | INTERGROWTH 21 Charts ¹ | ≤ 6 months | ≤ 10th centile vs > 10th centile | INTERGROWTH 21 charts for babies younger than 6 months ¹ |
| Overweight/obese | WHO Growth Charts ^{2,3} | <5 years ² | Overweight: weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; Obesity: weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median. | Charts and tables: WHO child growth standards for children aged under 5 years ² |
| | | 5-19 years ³ | Overweight: BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; Obesity: greater than 2 standard deviations above the WHO Growth Reference median. | Charts and tables: WHO growth reference for children aged between 5–19 years ² |
| Waist Circumference | NHANES 2011-2014 ⁴ | 2- 60 years | ≥90 th percentile ⁵ | |
| Fat mass (FM) | DEXA-NHANES ⁶ | ≥8 years | Fat Mass Index (kg/m ²) classification ranges for sex | |
| | BIA ⁷ | 5-18 years | ≥85 th percentile (%FM) | |
| | ADP- BodPod ⁷ | 5-18 years | ≥85 th percentile (%FM) | |
| | ADP- PedPod ⁸ | 0.5-24 months | %FM greater than 1 standard deviation above the reference mean | |
| | skinfolds-NHES II, NHES III, NHANES I, NHANES II and NHANES III ⁹ | 1.5-19 years | ≥85 th percentile ⁹ | |
| | Multicomponent model | 0.5- 24 month ⁸ | %FM greater than 1 standard deviation above the reference mean | |

| Measurement | Guideline/ Equipment | Age | Abnormal | Notes |
|--|--|--------------------------|--|--|
| | | 5-20 years ¹⁰ | FM greater than 1 standard deviation above the reference mean | Fat mass reference data for males and females by Z-score or percentile ¹⁰ |
| Blood pressure | NHBPEP ¹¹ | 1 to 17 years | ≥90 th centile ⁵ (age, sex and height specific) Charts and tables: WHO Child growth standards for length/height | Compared with Jackson LV 2007 ¹² , although the NHBPEP is older, it contains the appropriate age range and reported the actual numbers at each cut point. |
| Triglycerides | NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton ¹³ | 4-18 years | ≥90 th centile ¹⁴ | Compared to NHANES III, NCEP, and NGHS, this includes a wider age range. |
| | NHANES | >18 years | ≥150mg/dL (8.3 mmol/L) ¹³ | |
| HDL-C | NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton ¹³ | 4-18 years | ≤10 th centile ¹⁴ | Compared to NHANES III, NCEP, and NGHS, this includes a wider age range. |
| | NHANES ¹³ | >18 years | <40 mg/dL (2.2 mmol/L) ¹³ for male <50 mg/dL (2.8 mmol/L) ¹³ for female | |
| LDL-C | NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton ¹³ | 4-18 years | ≥90 th centile ¹³ | Compared to NHANES III, this includes a wider age range. |
| | NCEP ATP III | >18 years | >130 mg/dL (7.2 mmol/L) ¹³ | |
| Fasting plasma glucose concentration | ADA criterion ¹⁵ (increased risk for diabetes or prediabetes) | | FPG ≥100 mg/dL (5.6 mmol/L) | |
| Impaired glucose tolerance | ADA criterion ¹⁵ (increased risk for diabetes or prediabetes) | | 2-h PG ≥140mg/dL (7.8 mmol/L) during a 75g OGTT | |
| Abbreviation WHO: World Health Organisation NHANES: National Health and Nutrition Examination Survey BIA: Bioelectrical impedance analysis DEXA: Dual-energy X-ray absorptiometry FM: Fat mass | | | | |

| Measurement | Guideline/ Equipment | Age | Abnormal | Notes |
|--|----------------------|-----|----------|-------|
| ADP: Air displacement plethysmography NHBPEP: National High Blood Pressure Education Program NCEP: National Cholesterol Education Program NGHS: National Lung, Heart and Blood Institute's Growth and Health Study HDL-C: High triglyceride concentration LDL-C: Low triglyceride concentration ATP III: Adult Treatment Panel III ADA: American Diabetes Association | | | | |

Appendix 2. Definitions for Secondary outcomes

| Term | Classification | Definition | Note |
|----------------------------|-----------------|--|---|
| Cerebral palsy | | <p>1. Cerebral palsy is a physical disability that affects movement and posture.</p> <p>Any definition that includes the following five key elements:</p> <p>(1) is an umbrella term for a group of disorders</p> <p>(2) is a condition that is permanent but not unchanging</p> <p>(3) involves a disorder of movement and/or posture and of motor function</p> <p>(4) is due to a non-progressive interference, lesion or abnormality, and</p> <p>(5) the interference, lesion or abnormality originates in the immature brain</p> <p>2. As defined by investigators</p> | Australian cerebral palsy register report - CP Register ¹⁶ |
| Severity of cerebral palsy | GMFCS Level I | Children walk at home, school, outdoors and in the community. They can climb stairs without the use of a railing. Children perform gross motor skills such as running and jumping, but speed, balance and coordination are limited. | Gross Motor Function Classification System (GMFCS) ¹⁷ |
| | GMFCS Level II | Children walk in most settings and climb stairs holding onto a railing. They may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas or confined spaces. Children may walk with physical assistance, a handheld mobility device or used wheeled mobility over long distances. Children have only minimal ability to perform gross motor skills such as running and jumping. | |
| | GMFCS Level III | Children walk using a hand-held mobility device in most indoor settings. They may climb stairs holding onto a railing with supervision or assistance. Children use wheeled mobility when traveling long distances and may self-propel for shorter distances. | |
| | GMFCS Level IV | Children use methods of mobility that require physical assistance or powered mobility in most settings. They may walk for short distances at home with physical assistance or use powered mobility or a body support walker when positioned. At school, outdoors and in the community children are transported in a manual wheelchair or use powered mobility. | |
| | GMFCS Level V | Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control leg and arm movements. | |
| | Mild | A score on scale from 2 SD to <1 SD below test mean | Scores were obtained relative to the mean and standard deviation (SD) |
| | Moderate | A score on scale from 3 SD to <2 SD below test mean | |

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| Developmental delay or intellectual impairment | Severe | A score on scale 3 SD below test mean | for the normal birth weight population. ¹⁸ |
| Visual impairment | None | Presenting visual acuity 6/18 or better in the better eye. | WHO Definition of visual impairment ¹⁹ |
| | Moderate/ low vision | Can see a toy and able to follow a toy. Presenting visual acuity worse than 6/18, equal to or better than 6/60 in the better eye in the better eye. | |
| | Severe/ no useful vision | Able to see light or gross movement up close (within 40cm). Presenting visual acuity worse than 6/60, equal to or better than 1/60 in the better eye. | Visual Standards- Aspects and Ranges of Vision Loss ²⁰ |
| | Blindness/ no light perception | No useful vision. Presenting visual acuity worse than 1/60 in the better eye or no light perception. | |
| | Legal blindness | Medically diagnosed central visual acuity of 20/200 (6/60) or less in the better eye with the best possible correction, and/or a visual field of 20 degrees or less | |
| Hearing impairment (Classification 1) | None | None diagnosed | WHO Grades of hearing impairment- Prevention of blindness and deafness ²² |
| | Mild | Hearing level in decibels: 26-40dB A child with this level of hearing loss will have trouble hearing and understanding soft speech, speech from a distance or speech against a background of noise | |
| | Moderate | Hearing level in decibels: 41-60db A child with this level of hearing loss will have difficulty hearing regular speech, even at close distance | |
| | Severe | Hearing level in decibels: 61-80dB A child with this level of hearing loss may only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversational speech is not heard. | |
| | Profound | Hearing level in decibels: over 81dB A child with this level of hearing loss may perceive loud sounds as vibrations. | |
| Motor dysfunction | mild impairment | Test score between 5th and 15th centile on the Movement ABC / A score from 2 SD to <1 SD below the population mean on the BOTMP | Movement Assessment Battery for Children (Movement ABC) Bruininks–Oseretsky Test of Motor Proficiency (BOTMP) ²³ |
| | moderate to severe impairment | Test score less than 5th centile on the Movement ABC / more than 2 SD below the population mean on the BOTMP | |
| School performance | Defined by teachers based on their observation and academic scores; | | Poor school performance ²⁴ |

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| | at or above vs below expected performance/level for age | |
| Growth Z-scores | WHO Growth Charts | Charts and tables: WHO child growth standards for children ² |
| Abbreviation: CP: Cerebral palsy GMFCS: Gross Motor Function Classification System SD: Standard deviation Movement ABC: Movement Assessment Battery for Children BOTMP: Bruininks–Oseretsky Test of Motor Proficiency | | |

Appendix 3. Data items to be collected

Trial level information

- Protocols of each individual trial
- Data forms or case report forms (CRFs) of each individual trial
- Country
- Setting (neonatal intensive care unit (NICU), hospital, or home)
- Dates of start and end of trial
- Number of infants randomised
- Informed consent procedures
- Methods of random allocation
- Methods of allocation concealment
- Blinding of outcome assessment
- Blinding of researchers/ caregivers
- Stratification factors used
- Purpose of intervention
- Planned intervention
- Specific details of the planned nutrition in the experimental and control arms of the trial (including composition, whether given as sole feed or in addition to breast milk and duration)
- Outcomes collected (primary and secondary)

Participant level information: Infant characteristics at trial entry

- Unique identification code
- Gestational age at birth
- Age at trial entry
- Birthweight
- Weight, length and head circumference at trial entry
- Sex
- Single/multiple (if multiple order of birth)

Participant level information: After trial entry

- Actual intervention or comparison received
- Age at commencement of nutritional supplement
- Age at ceasing the nutritional supplement
- Receipt of breast milk and whether mother's own or donor/banked
- Size at discharge or term-equivalent age (36-42 weeks' post-menstrual age)- including weight, length, head circumference, and measures of body composition e.g. skinfolds, bioimpedance, plethysmography

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