Supplementary Materials

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# Tables

## Table S1. Results of studies synthesised narratively

| Study | Variable synthesised narratively  | Reason for non-inclusion in meta-analyses | Comparison for this review | Results |
| --- | --- | --- | --- | --- |
| Brownell 2018 [1] | Wt, length and HC gain, change in z-score | Multivariable linear regression models used for associations between feeding and growth. Feeding groups were not mutually exclusive | C3 | Associations between diet composition and growth velocity, using MOM as reference and 10% increases in PTF intake

|  |  |  |  |
| --- | --- | --- | --- |
|  | Weight gain, g/kg/dayn=313β (95% CI) | HC growth, cm/wkn=307β (95% CI) | Length gain, cm/wkn=311β (95% CI) |
| Adjusted mean for MOM | 17.08 (12.7, 21.45) | 1.17 (0.75, 1.58) | 3.18 (2.25, 4.11) |
| Proportion of diet as DHM | -0.17 (-0.28, -0.05)P=0.01 | -0.01 (-0.02, -0.001)P=0.03 | -0.001 (-0.3, 0.03)P=0.95 |
| Proportion of diet as PTF | 0.09 (-0.04, 0.21) P=0.18 | 0.01 (-0.01, 0.020) P=0.23 | -0.01 (-0.05, 0.02) P=0.44 |

Associations between diet composition and growth z-scores, using MOM as reference and 10% increases in PTF intake

|  |  |  |  |
| --- | --- | --- | --- |
|  | Weight z-score changen=314β (95% CI) p | HC z-score changen=312β (95% CI) p | Length z-score changen=298β (95% CI) p |
| Adjusted mean change in z-score for MOM | -0.93 (-1.15, -0.72) | -0.31 (-0.51, -0.10) | -0.12 (-0.62, 0.40) |
| Proportion of diet as DHM | -0.04 (-0.06, -0.02) P <0.001 | -0.06 (-0.10, \_0.02)P= 0.002 | -0.05 (-0.13, 0.03)P= 0.22 |
| Proportion of diet as PTF | 0.03 (0.01, 0.05)P= 0.01 | 0.002 (-0.04, 0.04)P= 0.92 | -0.09 (-0.17, -0.01)P=0.04 |

 |
| Castellano Yanez 2019 [2] | Wt, length, HC, change in z-score | Data reported as mean z-score difference over hospital stay between groups | C3 | Mean difference in z-score between higher dose HM (n=78) and lower dose HM (n=52) over hospital stay

|  |  |  |
| --- | --- | --- |
|  | MD (95% CI) | P |
| Weight z-score | -0.104 (-0.175 to -0.032) | 0.004 |
| Length z-score | -0.312 (-0.469 to -0.154) | <0.001 |
| HC z-score | -0.166 (-0.301 to -0.30) | <0.017 |

 |
| Carlson 1998 [3] | Wt gain  | Growth reported in time periods 0 -14 d, 15 – 35 d, 36 – 56 d, 57 d to TCA and not comparable with other data | C1, C2 & C3 | Wt gain (mean ± SD) according to feeding type

|  |  |  |
| --- | --- | --- |
| Feeding type | N | Weight gain, g/kg/day |
| Age 0 – 14 days |  |  |
|  EHM | 23 | 1.7 ± 4.9 |
|  Mixed feeds | 14 | -0.1 ± 4.8 |
|  EPTF | 14 | 2.4 ± 7.1 |
| Age 15 – 35 days1,2  |  |  |
|  EHM | 23 | 11.5 ± 4.0 |
|  Mixed feeds | 14 | 13.2 ± 4.4 |
|  EPTF | 14 | 15.9 ± 3.3 |
| Age 36-56 days |  |  |
|  EHM | 21 | 12.2 ± 3.6 |
|  Mixed feeds | 13 | 16.0 ± 4.1 |
|  EPTF | 11 | 14.0 ± 3.2 |
| Age 57 days to term1,3 |  |  |
|  EHM | 15 | 9.9 ± 3.9 |
|  Mixed feeds | 9 | 11.9 ± 2.8 |
|  EPTF | 10 | 13.7 ± 4.3 |
| 1 EPTF vs EHM P<0.052 EPTF vs any HM MD 3.76 g/kg/d, 95% CI 1.57 to 5.95 (not reported in paper – calculated using Revman 4.1)3 EPTF vs any HM MD 3.05, 95% CI 0.02 to 6.08 (not reported in paper – calculated using Revman 4.1) |

 |
| Hoban 2019 [4] | Wt length and HC z-scores | Data reported as deviation from the reference growth trend for each week (NICU LOS, GA), female sex, and for each 10% increase in proportion offormula.  | C3 |

|  |  |  |  |
| --- | --- | --- | --- |
|  | Weight(change in z-score)n=321 | Length(change in z-score)n=321 | HC(change in z-score)n=321 |
|  | Parameter estimate (SE) | Parameter estimate (SE) | Parameter estimate (SE) |
| Growth for reference infant1 | -0.216 (0.029)P <0.0012 | -0.333 (0.027)P <0.0012 | 0.013 (0.030)P = 0.6542 |
| Proportion formula3 | 0.018 (0.007) P = 0.0092 | 0.016 (0.006)P = 0.012 | 0.013 (0.007)P = 0.0572 |

1 Average monthly change in z-score for reference subjects who received 100% MOM (n=255) at mean NICU LOS, GA and sex.2 P value testing hypothesis that the change in z-score is zero3 Deviation from the reference growth trend for each week (NICU LOS GA) female sex and for each 10% increase in proportion of PTF |
| Jacobi-Polishook, 2016 [5] | Body mass index gain | Only study reporting body mass index | C3 | Body mass index gain

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Full cohortn=611 | No HMn=46 | Quartile 1 HMn=141 | Quartile 2 HMn=141 | Quartile 3 HMn=142 | Quartile 4 HMn=141 |
| BMI gain, birth to discharge (kg/m2/wk) | 0.47 ± 0.20 | 0.52 ± 0.16 | 0.49 ± 0.21 | 0.44 ± 0.24 | 0.44 ± 0.16 | 0.50 ± 0.20 |

 |
| Kaempf 1998 [6] | Length gain | Measured lower leg length | C3 | Lower leg length growth

|  |  |  |
| --- | --- | --- |
|  | Fortified HMn=8 | PTFn=11 |
| Lower leg length growth velocity (mean ± SD mm/d) | 0.51 ± 0.04 | 0.54 ± 0.09 |

 |
| Li 2019 [7] | Change in wt, length and HC z-scoresFat mass (g) Fat-free mass (g) | Multivariable regression used for association between feed exposure and outcomes. | C3 | Regression analysis of HM intake and growth outcomes

|  |  |  |  |
| --- | --- | --- | --- |
|  | EHMn=56 | High dose HM(predominantly HM)n=39 | Low dose HM(predominantly formula)n= 38 |
| Wt z-score change | Reference | 0.2 (−0.2 to 0.6), P=0.32 | 0.6 (0.2 to 0.1), P<0.01 |
| Length z-score change | Reference | 0.5 (−0.1 to 1.2), P=0.13 | 0.3 (−0.5 to 1.0), P=0.48 |
| HC z-score change | Reference | −0.1 (−0.9 to 0.6), P=0.73 | 0 (−0.9 to 0.8), P=0.94 |
| FM, g | Reference | 11.2 (−61.9 to 84.4), P=0.76 | 26.1 (−49.2 to 101.5), P=0.50 |
| FFM, g | Reference | 86.1 (−28.8 to 201.1), P=0.14 | 257.4 (139.1 to 375.7), P<0.01 |

Data are adjusted mean difference with 95% CIs compared to reference infant fed EHM (n=56) adjusted for covariates including baseline characteristics, age at imaging, total nutrient intake before 34 weeks PMA, and level of care |
| Manea 2016 [8] | Wt gain | SD not reported | C1 | Weight gain of infants with BW <1kg, within the first 5 weeks of life, according to type of early enteral nutrition given (g/d)

|  |  |
| --- | --- |
|  | Average wt gain |
| EHM (n= 18) | 17.26 |
| EPTF (n=16) | 13.89 |

No SD or p values reported |
| Nicholl 1999 [9] | Length gain | Measured lower leg length | C1 | Lower leg length velocity – between group change, mean ± SD

|  |  |  |  |
| --- | --- | --- | --- |
|  | EHM (Gp2) | EPTF (Gp3) |  |
| Lower leg length gain (mm/d) | 0.17 ± 0.38 | 0.28 ± 0.50 | P=0.9 |

 |
| Soldateli 2020 [10] | Wt gain (g/kg/day), change in weight and length z-scores  | SD not reported | C3 | Human milk feeding and growth to discharge or transfer

|  |  |  |
| --- | --- | --- |
|  | Days fed any HM | P values |
|  | 0-25% n=40 | 26-50% n=151 | 51-75% n=268 | 76-99% n=375 | All HM n=594 | Across all Groups | Between 0-25% and All HM |
| Wt gain, g/kg/d | 13.8 | 13.5 | 13.5 | 13.7 | 13.6 | 0.6 | 0.3 |
| Change in wt z-score | -0.6 | -0.7 | -0.7 | -0.6 | -0.7 | 0.7 | 0.2 |
| HC gain, cm/wk | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.4 | 0.1 |
| Change in HC z-score | -0.1 | -0.3 | -0.4 | -0.3 | -0.3 | 0.8 | 0.2 |
| Change in length z-score | -0.9 | -1.3 | -1.3 | -1.2 | -1.1 | 0.09 | 0.2 |

Diet recorded on days of life 7, 14, 21, 28, 42, 56, 70, 84, and at NICU discharge or transfer |
| *Abbreviations:* DHM, donor human milk; EHM, exclusive human milk; EPTF, exclusive preterm formula; GA, gestational age; HC, head circumference; HM, human milk; LOS, length of stay; MD, mean difference; MOM, mother’s own milk; NICU, neonatal intensive care unit; PTF, preterm formula; SD, standard deviation; SE, standard error; Wt, weight |

## Table S2. Summary of findings: Preterm formula vs Human milk – Weight gain (g/d)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** RCT | - | MD 2 higher (1.54 lower to 5.54 higher) | - | 53 (1 RCT) | Not graded as only one study. ROB moderate |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design: Observational** | - | MD 0.83 lower (1.65 lower to 0 ) | - | 1606 (2 observational studies) | ⊕⊕⊝⊝LOW1 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S3. Summary of findings: Preterm formula vs Human milk – Weight gain (g/kg/d)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 2.03 higher(0.31 lower to 4.38 higher) | - | 364 (4 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| **Intervention:** Exclusive preterm formula**Comparison:** Any human milk**Study design:** Observational | - | MD 1.97 higher(0.21 higher to 3.72 higher) | - | 795 (5 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** RCT | - | MD 2.41 higher(1.09 higher to 3.72 higher) | - | 373 (2 RCTs) | ⊕⊕⊝⊝LOW 3 4 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.56 higher(0.09 higher to 1.03 higher) | - | 3162(13 observational studies) | ⊕⊝⊝⊝VERY LOW 1 5 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%)3Downgraded for imprecision4Downgraded for ROB – one RCT with high ROB, one RCT with low ROB5Downgraded for inconsistency – substantial heterogeneity (I2 50-74%) |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S4. Summary of findings: Preterm formula vs Human milk – change in weight z-score

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 0.26 higher(0.03 higher to 0.48 higher) | - | 494(2 observational studies) | ⊕⊕⊝⊝LOW 1 |
| **Intervention:** Exclusive preterm formula**Comparison:** Any human milk**Study design:** Observational | - | MD 0.21 higher (0.15 lower to 0.56 higher) | - | 1532(3 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2  |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** RCT | - | MD 0 (0.29 lower to 0.29 higher) | - | 326 (1 RCT) | Not graded as only one study. ROB low |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.19 higher(0.06 higher to 0.33 higher) | - | 4059(12 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%) |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S5. Summary of findings: Preterm formula vs Human milk - head circumference gain (cm/wk)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** RCT | - | MD 0.1 higher(0.02 lower to 0.22 higher) | - | 53(1 RCT) | Not graded as only one study. ROB moderate |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 0.09 higher(0.1 lower to 0.29 higher) | - | 78(2 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| **Intervention:** Exclusive preterm formula**Comparison:** Any human milk**Study design:** Observational | - | MD 0.06 higher(0.01 higher to 0.11 higher) | - | 495(4 observational studies) | ⊕⊕⊝⊝LOW 1 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** RCT | - | MD 0(0.06 lower to 0.06 higher) | - | 373(2 RCTs) | ⊕⊕⊕⊝MODERATE 4 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.04 higher (0.02 higher to 0.07 higher) | - | 4080(10 observational studies) | ⊕⊝⊝⊝VERY LOW 5 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%)3Downgraded for imprecision4Downgraded for ROB – one RCT with high ROB, one RCT with low ROB5Downgraded for inconsistency – substantial heterogeneity (I2 50-74%) |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S6. Summary of findings: Preterm formula vs Human milk – change in head circumference z-score

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 0.1 higher(0.42 lower to 0.62 higher) | - | 32(1 observational study) | Not graded as only one study. ROB low |
| **Intervention:** Exclusive preterm formula**Comparison:** Any human milk**Study design:** Observational | - | MD 0.43 higher(0.18 higher to 0.69 higher) | - | 322(2 observational studies) | ⊕⊕⊝⊝LOW 1 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** RCT | - | MD 0.2 higher(0.08 lower to 0.48 higher) | - | 326(1 RCT) | Not graded as only one study. ROB low |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.09 higher(0.19 lower to 0.38 higher) | - | 2627(8 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%)3Downgraded for imprecision |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S7. Summary of findings: Preterm formula vs Human milk – length gain (cm/week)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** RCT | - | MD 0.28 higher(0.14 higher to 0.42 higher) | - | 53(1 RCT) | Not graded as only one study. ROB moderate |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 0.06 higher(0.07 lower to 0.19 higher) | - | 78 (2 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 |
| **Intervention:** Exclusive preterm formula**Comparison:** Any human milk**Study design:** Observational | - | MD 0.09 higher(0.05 lower to 0.22 higher) | - | 778(3 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** RCT | - | MD -0.04(0.28 lower to 0.21 higher) | - | 373(2 RCTs) | ⊕⊕⊝⊝LOW 1 4 5 |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.05 higher(0.02 higher to 0.08 higher) | - | 2423(8 observational studies) | ⊕⊕⊝⊝LOW 1 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for imprecision3Downgraded for inconsistency – considerable heterogeneity (I2 75-100%)4Downgraded for ROB – one RCT with high ROB, one RCT with low ROB5Downgraded for inconsistency – substantial heterogeneity (I2 50-74%) |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S8. Summary of findings: Preterm formula vs Human milk - change in length z-score

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 0(0.63 lower to 0.63 higher) | - | 32(1 observational study) | Not graded as only one study. ROB low |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** RCT | - | MD 0.1 higher(0.26 lower to 0.46 higher) | - | 326(1 RCT) | Not graded as only one study. ROB low |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.09 higher(0.07 lower to 0.25 higher) | - | 1131(3 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%)3Downgraded for imprecision |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S9. Summary of findings: Preterm formula vs Human milk - % fat-free mass

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 1.46 lower(4.35 lower to 1.43 higher) | - | 87(3 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2  |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 5.1 lower(12.45 lower to 2.25 higher) | - | 73(1 observational study) | Not graded as only one study. ROB low |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; RCT, randomised controlled trial; ROB, risk of bias |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%) |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S10. Summary of findings: Preterm formula vs Human milk - fat-free mass (g)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 130.18 higher(53.86 higher to 206.5 higher) | - | 134(4 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2  |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference |
| 1Observational studies considered low quality evidence2Downgraded for imprecision |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S11. Summary of findings: Preterm formula vs Human milk - % fat mass

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 1.82 higher(0.59 lower to 4.23 higher) | - | 141(4 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2  |
| **Intervention:** Lower dose human milk**Comparison:** Higher dose human milk**Study design:** Observational | - | MD 0.48 lower(1.7 lower to 0.73 higher) | - | 133(1 observational study) | Not graded as only one study. ROB low |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference; ROB, risk of bias  |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%) |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

## Table S12. Summary of findings: Preterm formula vs Human milk - fat mass (g)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes** | **Anticipated absolute effects\* (95% CI)** | **Relative effect(95% CI)** | **№ of participants(studies)** | **Certainty of the evidence(GRADE)** |
| **Risk with human milk (exclusive, any or high dose)** | **Risk with preterm formula** |
| **Intervention:** Exclusive preterm formula**Comparison:** Exclusive human milk**Study design:** Observational | - | MD 60.94 higher(5.42 lower to 127.31 higher) | - | 134(4 observational studies) | ⊕⊝⊝⊝VERY LOW 1 2 3 |
| \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*Abbreviations*: CI, Confidence interval; MD, mean difference |
| 1Observational studies considered low quality evidence2Downgraded for inconsistency – considerable heterogeneity (I2 75-100%)3Downgraded for imprecision |
| GRADE Working Group grades of evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effectVery low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |

# Figures

## Figure S1. Prisma diagram – selection of studies



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