INVESTIGATING THE RELATIONSHIP BETWEEN INFANT FEEDING PRACTICES AND INFLAMMATION-ASSOCIATED BIOMARKERS OF ONE-YEAR-OLD INFANTS IN THE CHILD COHORT STUDY

BY

SPENCER AMES

A Thesis Submitted to the Faculty of Graduate Studies of

The University of Manitoba

in Partial Fulfilment of the Requirements of the Degree of

MASTER OF SCIENCE

Department of Immunology

University of Manitoba

Winnipeg, Manitoba, Canada

ABSTRACT

Breastfeeding and human milk consumption are associated with immune system development; however, the impact of different infant feeding practices on this relationship is unclear. This research aimed to understand how current human milk feeding (HMF) status is related to immune activity, and how history of HMF (HMF duration, exclusivity, and method - directly from the breast, or pumped and bottled) is related to immune development, in one-year-old infants.

This study investigated a subset of 605 one-year-old infants from the CHILD Cohort Study, a cohort study that recruited pregnant women from four Canadian provinces. Infant feeding was captured from hospital birth records and parent questionnaires. Ninety-two biomarkers reflecting immune system activity and development were measured in infant serum using the Olink Target 96 Inflammation panel. Associations were determined using multivariable regression (adjusted for sex, time until blood sample centrifugation, and participant study site), with adjustment for multiple comparisons.

Nearly half (44%) of infants were still breastfeeding at the time of blood sampling (12.6 ± 1.4 months). Compared to infants who were never breastfed or had stopped breastfeeding, those who were still breastfeeding had higher levels of serum Fibroblast Growth Factor 21 (FGF-21, adjusted standardized β-coefficient=0.56, 95%CI=0.41-0.72), Cluster of Differentiation 244 (CD244, β=0.35, 0.19-0.50), Chemokine Ligand 6 (CXCL6, β=0.34, 0.18-0.50), and Chemokine Ligand 20 (CCL20, β=0.26 ,0.09-0.42), and lower levels of extracellular newly identified receptor for advanced glycation end-products binding protein (EN-RAGE, β=-0.16, -0.29- -0.03). Among infants not currently HMF, total HMF duration had a marginal positive association

with IL-7 serum levels (adjusted standardized β-coefficient =0.05, 0.02- 0.08). Exclusive HMF duration and HMF method (at three months of age) were not associated with any biomarkers in adjusted models.

Current HMF status, more so than prior infant feeding practices, is associated with changes in inflammation-associated biomarker profiles at one year of age. In addition to informing new hypotheses about the impact of breastfeeding on immune development and activity, these results highlight the importance of including current HMF status in immune-system-focused infant serum proteomic studies.

ACKNOWLEDGEMENTS

I want to acknowledge and thank **everyone** that contributed to the successful completion of this thesis and MSc program.

A huge thank you to my supervisor, Dr. Meghan Azad, for allowing me to join the THRiVE discovery lab, for providing incredible opportunities, training, and mentorship, for supporting me unconditionally, and for pushing me to be better. Dr. Larisa Lotoski, thank you for your invaluable feedback and for challenging me to become a more independent, critical, and thoughtful scientist.

Thank you to all past and present members of the THRiVE discovery lab – I feel extremely blessed to have been part of such a uniquely supportive group.

Thank you to Dr. Aaron Marshall and Dr. Christine Leong for serving on my advisory committee and for helping to guide my program, progress, and project.

This research would not have been possible without the dedication and effort of CHILD participants. Thank you for your contribution to this science. I want to recognize and express my gratitude to co-authors (Theo Moraes, Petter Brodin, Lucie Rodriguez, Padmaja Subbarao, Stuart Turvey, Elinor Simons, Piushkumar Mandhane), the entire CHILD Study team, the Canadian Microbiome Initiative 2 team, staff and students of the department of immunology, and Brenden Dufault for their contributions to and support of this research. I am grateful to the Canadian Institutes of Health Research for financially supporting my graduate training.

A special thank you to my parents, sister, and Ben Ho for their consistent care and support. I don’t have words that capture the gratitude I feel.

Sarah, Narges, Testimony, Huda, Courtney, Nyambura, Leo, Rilwan, Andrea, Spencer, Tim, Michelle – how lucky am I to have met you all. Thank you for your friendships, the memories, the vibes, the lessons, and for enriching my life in Winnipeg. Padmanie, all that X 10.

TABLE OF CONTENTS

ABSTRACT ..... *i*

ACKNOWLEDGEMENTS ..... *iii*

TABLE OF CONTENTS ..... *iv*

LIST OF ABBREVIATIONS ..... *vii*

LIST OF TABLES ..... *ix*

LIST OF FIGURES ..... *xi*

Chapter I: Introduction and Literature Review *1*

1.1. Immune system development is influenced by non-heritable exposures in early life **1**

1.2. Human breast milk supports healthy infant growth and immune system development **4**

1.3. The association between infant feeding practices and health **11**

1.4. Inflammation-associated serum biomarkers can reflect immune system activities and development **15**

1.5. Research objective, questions, and hypotheses **17**

1.5.1. Research objective 17

1.5.2. Research questions 17

1.5.3. Hypotheses 17

Chapter II: Methodology *20*

2.1. Study design and population **20**

2.2. CHILD Cohort Study questionnaire data **23**

2.2.1. Infant feeding practices subject to analysis 23

2.2.2. Population characteristics evaluated for inclusion as covariates in analysis 23

2.3. Participant exclusion criteria **33**

2.4. Infant serum collection 34

2.5. Infant serum inflammation-associated biomarker quantification 34

2.6. Data cleaning, transformation, analysis, and visualization 37

Chapter III: Results 41

3.1. Study population demographic characteristics 41

3.1.1. Population characteristics evaluated for inclusion as covariates in analysis 41

3.1.2. Infant feeding practice characteristics 46

3.2. Inflammation-associated biomarker distributions 49

3.3. Investigating the association between infant current HMF status and inflammation-associated biomarker levels 54

3.3.1. Serum biomarker levels differ according to current HMF status 54

3.3.2. Inflammation-associated serum biomarker measures can predict infant current HMF status 56

3.4. Investigating the association between history of HMF and inflammation-associated biomarker levels 60

3.5. Current HMF status, but not history of HMF, accounts for inflammation-associated biomarker variation 66

Chapter IV: Discussion 69

4.1. Interpreting associations between infant current HMF status and inflammation-associated serum biomarkers 69

4.2. Interpreting associations of infant history of HMF and inflammation-associated serum biomarkers 79

4.3. Infant feeding practices are associated with overall inflammation-associated biomarker variation 82

4.4. Overall implications of HMF on infant immune system activities and development 83

Chapter V: Strengths, Limitations, and Future Directions 88

5.1. Strengths **88**

5.2. Limitations **89**

5.3. Future Directions **93**

Chapter VI: Conclusion ***97***

Supplementary Files ***99***

References ***151***

LIST OF ABBREVIATIONS

HM	Human milk
HMF	Human milk feeding
TGF	Transforming growth factor
IL	Interleukin
IGF	Insulin-like growth factor
EGF	Epithelial growth factor
GCSF	Granulocyte colony-stimulating factor
IBD	Inflammatory bowel disease
FDR	False-discovery rate
SD	Standard deviation
IQR	Interquartile range
LOD	Limit of detection
PEA	Proximity extension assay
TNF-α	Tumor necrosis factor alpha
TLR	Toll like receptor
R0R**γ**t+ Treg	Retinoic acid receptor-related orphan receptor gamma expressing regulatory T cell
RDA	Redundancy analysis
Ig	Immunoglobulin
4E-BP1	Eukaryotic translation initiation factor 4E-binding protein 1
ADA	Adenosine Deaminase
ARTN	Artemin
AXIN1	Axin-1
β-NGF	Beta-nerve growth factor
CASP-8	Caspase-8
CCL	C-C motif chemokine
CD244	Natural killer cell receptor 2B4
CD40	CD40L receptor
CD5	T-cell surface glycoprotein CD5
CD6	T cell surface glycoprotein CD6 isoform
CD8A	T-cell surface glycoprotein CD8 alpha chain
CDCP1	CUB domain-containing protein 1
CSF-1	Macrophage colony-stimulating factor 1
CST5	Cystatin D
CX3CL1	Fractalkine
CXCL	C-X-C motif chemokine
DNER	Delta and Notch-like epidermal growth factor-related receptor
EN-RAGE	Protein S100-A12
FGF	Fibroblast growth factor
Flt3L	Fms-related tyrosine kinase 3 ligand
GDNF	Glial cell line-derived neurotrophic factor
HGF	Hepatocyte growth factor
IFN-**γ**	Interferon gamma

LAP TGF-β-1	Latency-associated peptide transforming growth factor beta-1
LIF	Leukemia inhibitory factor
LIFR	Leukemia inhibitory factor receptor
MCP	Monocyte chemotactic protein
MMP	Matrix metalloproteinase
NRTN	Neurturin
NT-3	Neurotrophin-3
OPG	Osteoprotegerin
OSM	Oncostatin-M
PD-L1	Programmed cell death 1 ligand 1
SCF	Stem cell factor
SIRT2	SIR2-like protein 2
SLAMF1	Signaling lymphocytic activation molecule
ST1A1	Sulfotransferase 1A1
STAMBP	STAM-binding protein
TGF-α	Transforming growth factor alpha
TNF	Tumor necrosis factor
TNFB	TNF-beta
TNFRSF9	Tumor necrosis factor receptor superfamily member 9
TNFSF14	Tumor necrosis factor ligand superfamily member 14
TRAIL	TNF-related apoptosis-inducing ligand
TRANCE	TNF-related activation-induced cytokine
TSLP	Thymic stromal lymphopoietin
TWEAK	Tumor necrosis factor (Ligand) superfamily, member 12
uPA	Urokinase-type plasminogen activator
VEGFA	Vascular endothelial growth factor-A
RAGE	Receptor for advanced glycation end products

LIST OF TABLES

Table 1. Infant feeding practice variables investigated in this study. 24

Table 2. Demographic variables evaluated for and/or included in study analyses. 26

Table 3. Population characteristics of the full one-year-old study population (n=605) and subset not currently HMF (n=347). 43

Table 4. Infant feeding practice characteristics of the full one-year-old study population (n=605) and subset not currently HMF (n=347). 47

Table 5. Olink Target 96 Inflammation panel biomarker descriptive statistics for one-year-old CHILD cohort infants (full study population, n=605). 51

Table 6. Associations of infant, household, study, and family variables with the cumulative variation of Olink biomarker measures in one-year-old CHILD cohort infants (full study population, n=605). 67

Supplementary Table 1. Results from a multi-step forward selection analysis completed using the 'step' R function. 110

Supplementary Table 2. Linear regression associations of infant serum biomarker levels with current HMF status among one-year-old CHILD cohort infants (full study population, n=605). 111

Supplementary Table 3. Logistic regression associations of infant serum biomarker levels with current HMF status among one-year-old CHILD cohort infants (full study population, n=605).. 113

Supplementary Table 4. Evaluating AUC value differences between univariable and multivariable logistic regression models. 115

Supplementary Table 5. Linear regression associations of infant serum biomarker levels with continuous HMF duration among one-year-old CHILD cohort infants (not currently HMF subset, n=347). 116

Supplementary Table 6. Linear regression associations of infant serum biomarker levels with continuous exclusive HMF duration among one-year-old CHILD cohort infants (not currently HMF subset, n=347). 118

Supplementary Table 7. Linear regression associations of infant serum biomarker levels with categorical HMF duration (infants grouped in two-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). 120

Supplementary Table 8. Linear regression associations of infant serum biomarker levels with categorical HMF duration (infants grouped in three-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). 128

Supplementary Table 9. Linear regression associations of infant serum biomarker levels with categorical exclusive HMF duration (infants grouped in four-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347).…..... 134

Supplementary Table 10. Linear regression associations of infant serum biomarker levels with categorical HMF duration (infants grouped in two-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). 138

Supplementary Table 11. Linear regression associations of infant serum biomarker levels with categorical exclusive HMF duration (infants grouped in three-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347).…..... 142

Supplementary Table 12. Linear regression associations of infant serum biomarker levels with HMF method at three months among one-year-old CHILD cohort infants (not currently HMF subset, n=347).…..... 145

LIST OF FIGURES

Figure 1. Schematic illustrating the relationship between infant feeding practices and the development of the immune system in the first year of life. 19

Figure 2. One-year-old CHILD infants selected for Olink Target 96 Inflammation panel serum biomarker quantification and statistical analysis. 22

Figure 3. Standardized normalized protein expression (NPX) of inflammation-associated serum biomarkers among one-year-old CHILD cohort infants (full study population, n=605). 50

Figure 4. Associations between current HMF status and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (full study population, n=605). 55

Figure 5. Associations of infant serum biomarker levels with current HMF status in one-year-old CHILD cohort infants (full study population, n=605). 58

Figure 6. Associations of CCL20, CD244, CXCL6, EN-RAGE, FGF-21, and all five biomarkers collectively, with current HMF status of one-year-old CHILD cohort infants (full study population, n=605). 59

Figure 7. Associations of both continuous HMF duration and continuous exclusive HMF duration with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). 62

Figure 8. Associations between categorical HMF duration (grouped into four-month intervals) and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). 63

Figure 9. The relationship of IL-7 with time since HMF cessation for CHILD cohort infants <14 months of age (n=599). 64

Figure 10. Associations between HMF method at three months of age and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347).. 65

Figure 11. Summary of biomarker associations with current HMF status and potential implications for infant immune system activities and overall health. 87

Supplementary Figure 1. Time until blood sample centrifugation varies among study sites and is associated with inflammation-associated serum biomarker levels in one-year-old CHILD cohort infants (full study population, n=605). 99

Supplementary Figure 2. Exclusion criteria for Olink Target 96 Inflammation panel quantified biomarkers included in main study analyses. 100

Supplementary Figure 3. Associations of biomarker presence/absence with infant feeding practice variables among one-year-old CHILD cohort infants (full study population, n=605)...101

Supplementary Figure 4. Spearman correlation and hierarchical clustering analysis among all inflammation-associated biomarkers in one-year-old CHILD cohort infants (full study population, n=605).. 102

Supplementary Figure 5. Demographic variables associated with inflammation-associated serum biomarker levels in one-year-old CHILD cohort infants (full study population, n=605)..... 103

Supplementary Figure 6. Spearman correlation associations between current HMF status and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (full study population, n=605), sorted according to hierarchical clustering of biomarkers..... 104

Supplementary Figure 7. Associations of all biomarker-derived principal components with current HMF status of one-year-old CHILD cohort infants (full study population, n=605). 105

Supplementary Figure 8. Associations of categorical HMF duration (grouped into two-month intervals) with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). 106

Supplementary Figure 9. Associations of categorical HMF duration (grouped into three-month intervals) with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). 107

Supplementary Figure 10. Associations of categorical exclusive HMF duration (grouped into two-month intervals) with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). 108

Supplementary Figure 11. Associations between of exclusive HMF duration (grouped into three-month intervals) and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). 109

Chapter I: Introduction and Literature Review

Portions of this chapter have been adapted from Ames et al., 2023 - *Comparing early life nutritional sources and human milk feeding practices: personalized and dynamic nutrition supports infant gut microbiome development and immune system maturation*.[1] Including this published article is permitted in accordance with Taylor & Francis copyright guidelines.[2]

1.1. Immune system development is influenced by non-heritable exposures in early life

Immune system components (e.g. immune cells, epithelial barriers, mucosal site structures) are immature, or differentially adapted, at birth.[3,4] Compared to adults, neonatal neutrophils, monocytes, and dendritic cells have reduced functional capacity to prevent and clear pathogenic infections.[5–7] Activated and functional T and B cells are detected around 12 weeks after birth, but at this stage they are more likely to induce antigen tolerance rather than clearing the antigen from the infant system.[8–10] Unlike their immunologically mature counterparts, neonatal T helper cell responses are biased towards a Th2, or anti-inflammatory, phenotype. This Th2 bias reduces risk of a damaging inflammatory response and explains the reduced antigen responsiveness, but increased susceptibility to infection and allergic reaction, observed in neonates, compared to adults.[11,12] The transition from Th2 to pro-inflammatory Th1 phenotype bias has not been well described; however, this transition is thought to provide an infant with more antigen-clearance ability and occurs with maturation of immune cells.[11] Furthermore, intestinal barriers have increased permeability for up to six months postnatally, allowing ingested macromolecules, including immunoglobulins (Igs), to translocate across the immature intestinal epithelium.[4,13] In parallel, the infant microbiome rapidly matures in the first few weeks and months of life. Gut microbiota play a key role in shaping the immune system by protecting the infant from harmful

pathogens, facilitating mucosal immune site structure (e.g. epithelial cells, immune cells) stimulation, and inducing antigen tolerance.[14]

In 1989, Strachan proposed that increased microbial exposure in early life (via unhygienic contact with older siblings) may protect children from developing immune hypersensitivities later in life.[15] This 'hygiene hypothesis' formed the basis for studying the influence of non-heritable factors, such as environmental microbiota exposures, environmental antigen exposures (e.g. pollutants, pets), infections, vaccine administration, and oral or ingested exposures (e.g. antibiotics, **nutritional source)** on the maturation of the gut microbiome and infant immune system toward the composition and capabilities of a healthy adult.[16–18]

Generally, environmental exposures are thought to influence immune system development by modulating the infant microbiome,[1,19] inducing immune system structure-associated epigenetic modifications,[19] or stimulating immune system structures (e.g. receptors, cells, epithelial barriers) directly.[20] For example, air pollution exposure has been shown to alter the airway microbiome – a process with consequences for short-chain fatty acid (SCFA) production and downstream antigen-induced pro-inflammatory responses in the lung.[21] Air pollutants (e.g. particulate matter, ozone) have also been shown to change dendritic cell, innate lymphoid cell, and T cell gene expression by perturbing epigenetic enzyme activity and expression.[21] Furthermore, airway pollutants can provoke pro-inflammatory responses, enhance Th2 and Th17 differentiation and proliferation,[22] and stimulate allergic airway inflammation associated toll-like receptor 2 and 4 signaling.[21] Furry pets and older siblings are factors associated with increased infant gut microbiome diversity and antigen (e.g. secretoglobins, lipocalins)[23] exposure in early life.[24] Neonatal T cells are more tolerogenic than their adult

counterparts; therefore, are thought to establish a tolerant, rather than a pathogenic and inflammatory, immune response to harmless microbes and antigens.[25,26] Similarly, infection incidence, vaccine administration, and other methods of antigen or microbial exposure (e.g. daycare, food) in infancy stimulate an immune response and the generation of a memory immune cell repertoire (e.g. memory Tregs, memory effector cells) that can dictate the type of immune response (e.g. tolerant or pathogenic) upon antigen re-exposure.[26,27]

Early life nutrition (e.g. human milk, formula) has also been shown to regulate gut microbiome maturation and introduce food antigens to an infant.[1] The timing of introduction to allergenic foods is also important: for example, early introduction of peanuts to infants at risk of peanut allergy has been shown to decrease the frequency of peanut allergy, suggesting that introduction of non-microbial antigens in early life has consequences for health outcomes.[28] Further associations of early life nutrition and immune system development will be discussed in section 1.2.

The perturbation or lack of early life microbial exposure also has consequences for immune system development. Germ-free animals models have many immune system associated physiological differences – including differences in intestinal epithelial cell morphology, and spleen, thymus, lymph node, and gut-associate lymphoid structure development - compared to animal models with conventional commensal microbe exposures.[29] Furthermore, early-life antibiotic induced gut microbiome dysbiosis has been associated with increased allergen-driven Th2/Th17 immune pathway activities[29] and increased risk of developing asthma and allergic disease in childhood.[30]

Overall, non-heritable factors may influence gut microbiome and immune system development, as well as contribute to the variation in immune system composition and functions observed among humans throughout life.[31] This section introduces evidence that briefly highlights some known associations between environmental exposures and immunity; however, the influence of non-heritable factors may change depending on developmental stage and there remains a need to determine the full extent to which non-heritable factors influence early life immune system development. Understanding how non-heritable factors influence immune system activities and development can help us i) avoid negative health trajectories induced by non-heritable factors or mitigate the impact of these exposures, and ii) understand how to provide infants with the best start to life. This study sought to further our understanding of the relationship between **early life nutrition** and immune system development and activity.

1.2. Human breast milk supports healthy infant growth and immune system development

Infant nutritional source has been shown to influence immune system activities and development, as reviewed below.[32] Common forms of early life nutrition include human milk (HM), donor HM, and formula. HM satisfies infant nutritional requirements (except vitamin K and D) and contains protective and immunomodulatory components (e.g. immune cells, immunoglobulins, cytokines, chemokines, prebiotic oligosaccharides) that adapt dynamically to infant needs.[10] Furthermore, human milk feeding (HMF) has been associated with protecting against respiratory and gastrointestinal tract infections, developing overweight/obesity, diabetes, allergy, and inflammatory bowel disease (IBD).[1]

Immunomodulatory components within HM are thought to support and assist immune system structure (e.g. immune cells, mucosal immune site components) development.

Additionally, HM provides substrates that select for beneficial ingested microbiota to colonize the gut.[1] This section introduces HM components that have been associated with supporting immune system activities or development. The dynamic changes in HM composition that occur throughout lactation and in response to infant infection are also discussed.

Immune cells (i.e. leukocytes) within HM include lymphocytes (T and B cells), monocytes, macrophages, neutrophils, and innate lymphoid cells.[1] The buffering capacity of HM allows these cells to survive within the infant gut.[33] Furthermore, immune cells can infiltrate the permeable neonatal intestinal barrier, allowing them to become activated and motile in the infant.[34] HM supplied cytotoxic T cells and plasma B cells have been shown to elicit cytotoxic effects and secrete IgG in infants, respectively, which may compensate for the decreased activity of immature immune cells in infancy.[35,36] HM macrophages are phagocytic, secrete cytolytic and inflammatory mediators, and express activation markers (e.g. CD11c) in infants.[37] HM plasma B cells produce immunoglobulins, which in turn have roles in blocking pathogenic infection, regulating gut inflammation, and promoting antigen tolerance.[38,39] These associations identify roles for HM provided immune cells in influencing the development of immune system components; however, further research is required to determine the extent to which ingested HM components permeate the intestinal barrier and contribute to the activities and development of the infant immune system.[1]

Signaling proteins and bioactive enzymes within HM include cytokines, chemokines, growth factors, receptors, and other immune system associated biomolecules. This includes fibroblast growth factor 21 (FGF-21), chemokine ligand 20 (CCL20), chemokine ligand 6 (CXCL6), cluster of differentiation 244 (CD244), transforming growth factor-ß1 (TGF-ß1), TGF-ß2, interleukins IL-10, IL-6, IL-7, IL-1ß, insulin-like growth factor-1 (IGF-1), tumor

necrosis factor-α (TNF-α), and granulocyte colony-stimulating factor (GCSF).[10,40] These signaling proteins can act locally in the intestine by binding cell surface receptors, or systemically by permeating the intestinal barrier.[40]

HM signaling proteins are associated with the development of the intestinal environment, gut microbiome, and overall immune system. For instance, HM proteins can induce the differentiation of naïve T cells to antigen-specific Tregs that help maintain intestinal homeostasis, induce tolerance, and regulate inflammation (i.e. TGF-ß, IL-10, IL-6, and IL-1ß).[41,42] HM proteins have also been associated with neonatal gut microbial colonization and composition (TGF-ß1, TGF-ß2),[43,44] the inhibition of pro-inflammatory cytokine production in intestinal epithelia (TGF-ß1),[43,44] and intestinal epithelial cell repair and development (TGF-ß1, GCSF, IGF-1).[43–45]

TNF-α is an inflammatory cytokine normally produced by macrophages/monocytes during acute inflammation and plays a role in immune cell activation, migration, and proliferation.[46,47] Interestingly, TNF-α levels in HM fed directly from the breast increase when the feeding infant is mounting an immune response to an infection – a dynamic function that is not possible in donor HM or formula, and is likely disrupted in pumped and bottled (expressed) HM.[46]

HM is the main source of lactoferrin in HM-fed neonates.[48] This antimicrobial enzyme contributes to selective infant gut colonization and can prevent pathogenic intestinal bacterial growth by i) chelating iron with a high affinity, and ii) altering gram-negative bacterial outer membranes.[49,50] Low lactoferrin levels in early life may increase infant susceptibility to aberrant gut microbiome development, sepsis, necrotizing enterocolitis and enteric infections, as well as diabetes and obesity in later life.[48,50]

Immunoglobulins (Igs) - including IgA, soluble IgA [SIgA], IgG, IgM, IgE, and IgD – are present in HM, where they resist infant digestion and maintain function in infants.[51] These functions are especially critical during the early neonatal period because Ig-containing and producing host cells are not present at birth; appearing between 10 days to eight weeks of age depending on Ig isotype.[52,53] Igs transferred in milk can support innate immunity by conferring the same function as host-made Igs (i.e. providing 'passive' immunity) and by indirectly influencing gut microbiome development, as described below.[39]

SIgA is the most abundant Ig in HM and is capable of binding to antigens present on toxins, viruses, and both commensal and pathogenic microbes.[39,54] SIgA-microbe interactions contribute to 'beneficial' early life microbe (e.g. bifidobacteria, lactobacilli) colonization and maintenance within the infant gut.[54,55] SIgA-microbe interactions are also associated with the prevention of both commensal and pathogenic gut microbe translocation across the mucosal epithelium.[39]

Furthermore, HM IgG and IgA have been shown to dampen mucosal T helper cell responses in mice, limiting adaptive immune responses to commensal antigens.[56] Verhasselt et al.[57] have also proposed that HM IgG-antigen immune complexes can transfer across intestinal barriers and mediate inflammatory responses by promoting the formation of infant Tregs. HM Ig-associated microbiota exclusion and immune system regulation promotes intestinal homeostasis and helps prevent excessive immune stimulation as the infant gut is colonized by microbes.[39]

Microbes are present in HM. HM shares taxa (e.g. bifidobacteria) with microbes known to populate the infant gut in early life, suggesting HM microbes may contribute to infant gut

microbiome colonization.[58–60] Expressed HM has a different microbial profile than HM fed directly from the breast, suggesting the method of HMF (directly at the breast vs. pumped and bottled) is a key factor influencing HM microbiota composition, presumably due to the contribution of exogenous bacteria (e.g. from the infant oral cavity and/or pumping equipment).[61,62] Relatively little is known about the relationship of HMF method, breast pump cleaning practices, and milk storage conditions with infant immune system development.[63,64]

Prebiotic oligosaccharides are compounds that are fermented by beneficial microbiota and stimulate their growth. HM oligosaccharides, the third most abundant component of HM, serve as prebiotics to infant gut microbes including bifidobacteria and other select taxa. HM oligosaccharides can act as soluble decoy receptors that bind to pathogenic bacteria and reduce infection risk. Human milk oligosaccharides can also impact intestinal epithelial cell surface glycan expression, lymphocyte maturation, and selectin-mediated cell-cell interactions that may reduce gut mucosa leukocyte infiltration and activation.[65]

Fatty acid (FA) bound triacylglycerols make up fat globules in HM. Mature HM FA content consists of <1% short-chain FAs, ~12% medium-chain FAs, ~82% long-chain FAs, and ~1% "essential" polyunsaturated long-chain FAs that must be acquired from an individual's diet.[66,67] HM FAs serve as a major energy source for the infant and contribute to essential neurological and immune system development, as well as gut microbiota colonization in early life.[68,69]

FAs are antimicrobial – their amphiphilic properties allow them to disrupt or remodel microbial cell membranes by acting as a detergent and solubilizing cell membrane materials, or by inserting themselves into microbial cell membranes.[67,70] These mechanisms lead to the inhibition of microbial growth, observed *in vitro* when microbial taxa such as *Lactobacillus*,

Bifidobacterium, *Escherichia*, and *Clostridium* are cultured with medium-chain or long-chain polyunsaturated FAs.[69,71,72] This evidence suggests that HM-derived long and medium-chain FAs may contribute to the regulation of microbial growth in the infant gut.[67]

HM FAs have been associated with infant immune function. Essential polyunsaturated long-chain FAs present in HM, including arachidonic acid and docosahexaenoic acid, induce anti-inflammatory cytokine expression and Treg activation.[1,73] In addition, short-chain FAs in HM can serve as energy sources for epithelial cells and stimulate lamina propria Treg proliferation and anti-inflammatory cytokine expression.[74]

Postbiotics are non-viable microbes (intact or broken) and/or microbial components (e.g. cell wall fragments, microbial cell fractions, short-chain fatty acids, enzymes, vitamins) that confer a health benefit on the host.[75,76] Postbiotics are present in HM and have some similar functions to probiotics; for example, they can adhere to the gut mucosa, bind to cell receptors, transduce receptor signals, and exclude pathogens from colonizing the gut microbiome.[77] However, they do not actively metabolize prebiotic substrates.[77] In gnotobiotic mice, *Bifidobacterium breve* postbiotics have been shown to suppress pro-inflammatory cytokine production in the spleen, although live strains had greater impact on the regulation of intestinal metabolism.[78] Mice receiving infant formula supplemented with postbiotics derived from *Bifidobacterium breve* and *Streptococcus thermophilus* show prolonged dendritic cell survival and maturation, improved epithelial barrier function, and increased anti-inflammatory cytokine (i.e. IL-10) production.[75] Additionally, metabolic products released by *Lactobacillus paracasei* fermentation, when added to formula, have been shown to inhibit immune cell inflammation and can protect against colitis in mice.[75,79] Further research is needed to determine if similar postbiotic effects are seen in humans.

HM contains over 1400 unique epigenetic associated **MicroRNA**s (miRNAs). These non-coding RNA sequences bind to specific complementary sequences and induce translational repression, as well as mRNA deadenylation and decapping.[80] The expression of over 4000 CpG sites, including sites associated with Treg and granulocyte proliferation, have been associated with HM miRNAs.[1] HM miRNA-induced gene expression silencing may be associated with differential infant immune system development; however, this has not yet been studied comprehensively.

HM has been shown to adapt to the immunological needs of the infant. For example, macrophage and TNF-α levels within HM have been shown to increase when nursing infants are mounting an immune response against an infection, even when the lactating parent is asymptomatic.[46] Riskin et al. hypothesize that this dynamic ability is facilitated by a bi-directional exchange of immune factors that occurs through direct suckling at the breast.[46] Expressed HM does not appear to adapt in this manner, presumably because it is collected without direct infant contact and/or due to storage practices that may change its bioactive profile.[46,81] Furthermore, HM composition changes that occur as milk matures over lactation are thought to accommodate infant immunological needs at different developmental stages.[1]

Existing HM immunomodulatory research has generally focused on elucidating i) associations between HMF and infant health outcomes, and ii) the potential contribution of individual HM components to immunity. Research investigating the role of individual HM components in immunity often use animal models or in vitro methods; therefore, there remains a need to investigate the contributions of HM immunomodulatory components in human infant immunity. Furthermore, HM immunomodulatory research commonly focuses on components within HM and fails to capture potential associations of HMF with other immune system

components (e.g. immune cells, bioactive molecules) and general processes (e.g. inflammation). This study addresses these gaps in knowledge by investigating associations between HMF and an expansive array of immune system biomarkers that provide an indication of many distinct immune system activities (e.g. inflammation, immune cell proliferation), and not just the roles of individual HM components in immunity, in human infants.

1.3. The association between infant feeding practices and health

HM appears to support infants in avoiding potentially damaging inflammatory responses in early life. HM composition can adapt to an infant's needs and may gradually allow an infant to 'gain more responsibility' and independence in regulating its own health.[1] Furthermore, the ability of HM to 'train' immune cells to tolerate harmless antigens and seed the gut microbiome may help infants begin life on a healthy trajectory. Despite this noted phenomenon, the majority of studies investigating HM immunomodulatory abilities do not account for nuances in infant feeding practices – including current HMF and history of HMF (HMF duration, exclusive HMF duration, and HMF method (i.e. feeding from the breast or with pumped and bottled milk).

The World Health Organization recommends exclusive HMF for the first six months of life, and complementary feeding for up to two years, or as long as both the mother and infant wish to continue.[82] A 2017-2018 Canadian community health survey found 91% of Canadian parents start out HMF, but only 35% of these parents did it exclusively for at least six months, and 38% of these parents stopped all HMF before the infant reached six months of age. The mean HMF duration was 9.1 ± 7.5 months and 31.1% of Canadian parents reported HMF at 12 months of age or beyond. This Canadian community health survey did not capture HMF method data.[83]

The relationship of these infant feeding practices with infant immune system activities and development are relatively understudied. This section outlines why understanding these relationships are important for advancing our understanding of HM immunomodulatory capabilities.

Current HMF supports infant immunity. For example, animal model studies have shown murine milk immune cells can permeate pup digestive tracts and act in sites including lymph nodes, spleen, and liver.[34] Furthermore, the ability of HM Igs to provide 'passive immunity' to infants is well-known.[1] Despite these associations, the full extent to which current HMF influences infant immune system activities is unknown. Determining if current HMF i) induces distinct changes in immune system-associated biological processes, and ii) influences the levels of an expansive selection of immune system associated components, including components that are not found in HM, are gaps in knowledge examined in this current study. Investigating the relationship between current HMF and infant immune system activities will help uncover HM mechanisms that have developed to support infant health. Understanding this relationship can further inform how to provide the best start to life for infants and how alternative forms of nutrition can be improved to support infant health. Furthermore, HMF research commonly studies low weight preterm infants and is conducted in the context of negative infant health conditions such as allergy, asthma, and necrotizing enterocolitis.[84,85] Understanding the association of current HMF with healthy infant immunity is another important direction for future research and was a focus of this current study.

Exclusive HMF duration and **HMF duration** have been associated with supporting infant metabolic regulation,[86] brain development,[87] and infant health outcomes.[88]

Exclusive HMF duration is defined as the length of time an infant receives only HM and no other food or drink. This variable also reflects the age at which alternative nutrition sources (formula or foods) are introduced. Exclusive HMF duration has been negatively associated with the likelihood of negative health conditions in infancy, such as respiratory and gastrointestinal infection,[89] diarrhea,[90] and type 1 diabetes.[87] Furthermore, exclusive HMF duration has been positively associated with Bayley Scales of Infant Development scores – a test of memory language, and motor skills - at 14 months and 18 months of age, problem-solving abilities in two- and three-year-old children, and intelligence scores from ages 1 to 7.[87]

HMF duration is defined as the length of time an infant receives any HM. HMF duration has been negatively associated with fasting insulin concentrations and insulin resistance in five-year-old chilren.[91] Prolonged HMF has been shown to induce long-lasting physiological changes in liver-to-hypothalamus communication and hypothalamic metabolic regulation, which may underly the association between HMF and reduced likelihood of obesity and overweight in adolescence.[86,92] HMF duration has also been inversely associated with the likelihood of developing asthma, allergic disease (i.e. eczema, allergic rhinitis), and colitis in childhood.[88,91]

The mechanisms underlying beneficial associations of HMF duration and exclusive HMF duration are hardly understood. We speculate exclusive exposure (exclusive HMF duration), as well as continued exposure (HMF duration) to HM nutrients, immunomodulatory components, and dynamic ability, may have implications for infant immune system structure (e.g. immune cells, mucosal immune site components, epithelial barriers) development or biological process activities. For example, the positive association between exclusive HMF duration and both thymus size and T cell number may explain the negative association between exclusive HMF duration and incidence of respiratory infections.[93–96] Investigating the relationships of HMF

duration and exclusive HMF duration with immune system development (e.g. changes in mucosal immune site structure, immune cell and bioactive component composition, localization, and activities) is required to uncover the mechanisms of these protective associations, and is a focus of this current study. Furthermore, the dose-dependency of HM immunomodulatory abilities is not clear. Investigating the relationship of HMF duration and exclusive HMF duration with immune system development will help elucidate i) the dose-dependency and kinetics of HM immunomodulatory abilities and protective associations, and ii) the association between HM and physiological immune system component (e.g. immune cells, mucosal immune site structures) development.

Infant HMF method, in this current study, refers to the infant nutritional source (e.g. formula, HM) and method in which nutrition is administered (e.g. receiving HM directly from the breast, or pumped and bottled milk). HMF method has been associated with infant immune system activity and development. Microbiota present in expressed HM is enriched with potential pathogens and depleted in Bifidobacteria, in comparison to direct HM.[61] Furthermore, and as previously mentioned, TNF-α and macrophage levels within direct HM have been shown to increase when nursing infants are mounting an immune response against an infection, even when the lactating parent is asymptomatic.[46] Expressed HM does not appear to adapt in this manner, indicating a bi-directional exchange of immune factors is happening with direct suckling at the breast. Infant formula satisfies infant nutritional components but lacks hundreds of other HM molecules, including ones associated with infant immunity. Formula feeding has been associated with an increased risk of an infant developing necrotizing enterocolitis, respiratory infections, asthma, obesity, diabetes, and IBD, compared to exclusive HMF.[1] These associations indicate infants receiving formula may have long-lasting differences in immune system activities and

development, in comparison to infants receiving HM. Investigating the relationship between early life HMF method and immune system development is required to determine the implications of feeding method associated HM abilities on infant health and is a focus of this current study.

In summary, infant feeding practices have been associated with infant immune system activity, development, and health outcomes. Despite this, the mechanisms underlying these associations are not well understood. Furthermore, the infant feeding practices mentioned above are not often measured or accounted for in HM research. Furthering our understanding of the association between infant feeding practices and immune system activity and development is an important direction for HM research.

1.4. Inflammation-associated serum biomarkers can reflect immune system activities and development

Gerard Eberl's essay on immunity by equilibrium suggests the immune system is in a constant state of dynamic equilibrium in which immune system-associated components, the microbial environment, and the internal milieu in a given tissue dictate if immune component-antigen interactions lead to tolerance, protective immunity, or inflammatory pathology.[97,98] This suggests immune system associated component levels may provide an indication of immune system activity or state. Blood contains immune cells, cytokines, and other immune-associated biomarkers that can provide a global representation of immune system state at a given time; therefore, investigating a comprehensive set of immune system associated blood components may uncover how immune system activities and development change in response to different exposures or perturbations.[31,99] For example, the immune system maturation associated transition

from predominantly Th2 to predominately Th1 may be reflected by relative levels of IFN-γ – a cytokine representative of the inflammatory Th1 immunity – and IL-4 – a cytokine representative of the anti-inflammatory Th2 immunity.[100,101] Furthermore, investigating cytokine levels can indicate immune cell proliferation (IL-2 for B and T cells), differentiation (GCSF for monocytes and dendritic cells), activation (IL-1α for antigen presenting cells and T cells), or inhibition (IL-10 and TGF-β for T cells) in a given tissue or systemically.[98] These examples support the use of inflammation-associated biomarkers in comparing immune system activities, states, and development in infants.

Investigating a variety of inflammation-associated serum biomarkers provides this study with power to determine associations of infant feeding practices with a spectrum of inflammation and immune system associated processes. The Olink Target 96 Inflammation panel measures an extensive selection of inflammatory-associated serum proteins. Previous studies have used the Olink Target 96 Inflammation panel to investigate biomarker diagnostic potential,[102] develop our understanding of immune system activity differences among disease states,[103] develop mechanistic disease development and progression hypotheses,[102] provide an indication of systemic biological process activity (e.g. inflammation, metabolism), and inform future research targets and experiment development.[104] This study utilizes the diverse capabilities of Olink Target 96 Inflammation panel measures in one-year-old infants to further our understanding of the relationship of infant feeding practices with infant immune system development and activity. To our knowledge, no prior research has investigated associations of non-heritable factors with Olink Target 96 Inflammation panel measured serum biomarkers in healthy infants.

1.5. Research objective, questions, and hypotheses

1.5.1. Research objective

To investigate the association of current HMF status and history of HMF (including HMF duration, exclusive HMF duration, and HMF method at three months of age) with inflammation-associated biomarkers measured in serum collected from healthy one-year-old infants (**Figure 1**).

1.5.2. Research questions

- Are current HMF status, HMF duration, exclusive HMF duration, and HMF method at three months of age associated with inflammation-associated serum biomarker levels at one year of age?
- If so, how strong are these relationships and which biomarkers are most associated with infant feeding practices?
- Is overall biomarker variation associated with infant feeding practices, and if so, what is the effect size in comparison to other demographic variables?

1.5.3. Hypotheses

<u>General:</u>

Infant feeding practices (current HMF status, HMF duration, exclusive HMF duration, HMF method at three months of age) are associated with some inflammation-associated biomarker levels.

Specific:

- Associations between inflammation-associated biomarkers and current HMF status will suggest current HMF status influences HMF-dependent immune system activities.
- Associations between inflammation-associated biomarkers and history of HMF will suggest that HM feeding supports immune system development and has a lasting influence on immune system activities.
- The proportion of overall biomarker variation accounted for by infant feeding practice variables will be significant and have a comparable effect size to demographic variables commonly accounted for in infant serum proteomics (e.g. sex, infant age).

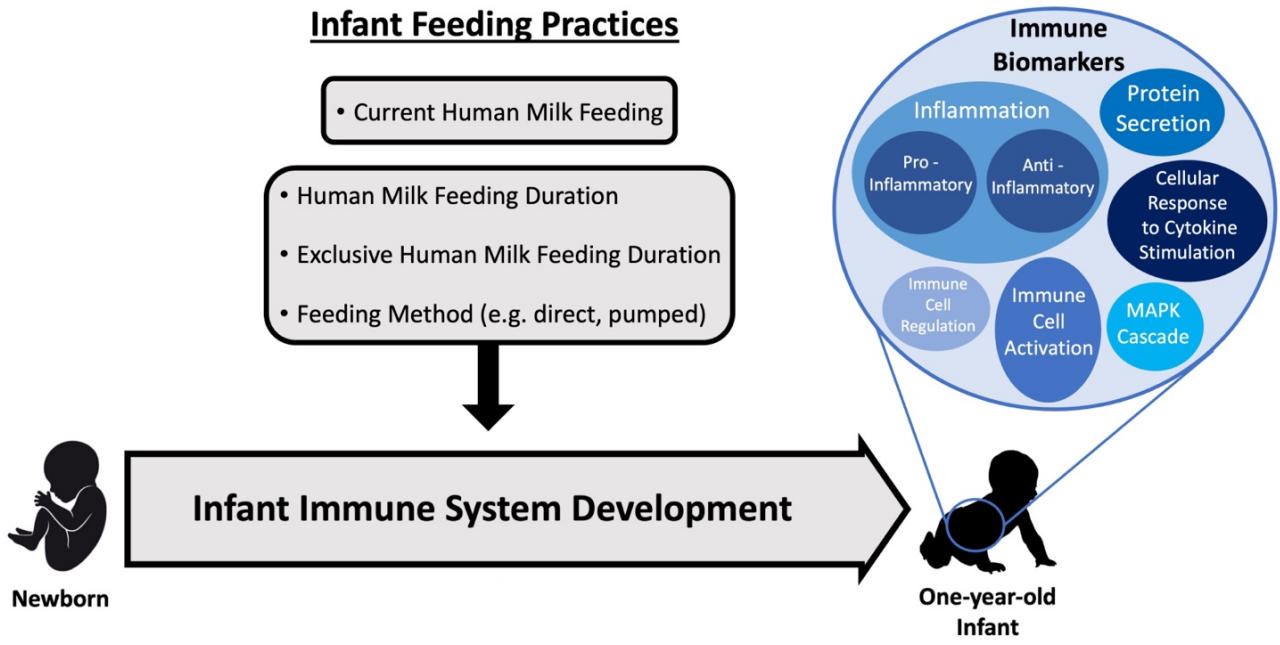


Figure 1. Schematic illustrating the relationship between infant feeding practices and the development of the immune system in the first year of life.

Chapter II: Methodology

2.1. Study design and population

Questionnaire data and biological samples from the Canadian Healthy Infant Longitudinal Development (CHILD) Cohort Study were used in this current study. CHILD is an ongoing, prospective, longitudinal, general population birth cohort study that recruited over 3600 pregnant mothers from Vancouver (British Columbia), Edmonton (Alberta), Winnipeg, Morden, Winkler (Manitoba), and Toronto (Ontario) between 2009 and 2012.[105] The original objective of the CHILD Cohort Study was to advance knowledge on how genetic, environmental, and host factors (*in utero* and postpartum) interact with the developing fetus and infant to alter risk of atopic disease such as asthma and allergy.[106] To address this objective, CHILD collected infant and parent demographic, environmental, and health-related information using longitudinal study questionnaires and clinical assessments. Skin prick tests were completed for infants and parents.[106] Biological samples, such as cord blood, house dust, breast milk, parent's blood, and children's blood, nasal swabs, urine, and stool were also collected from CHILD families.[106] The CHILD Cohort Study excluded premature infants, children born with major congenital abnormalities or respiratory distress syndrome, families that expected to move away from the recruitment area within one year post-recruitment, parents pregnant with more than one baby, parents that had in-vitro fertilization pregnancies, and children expected to spend less than 80% of their time in the primary home.[107]

The wealth of data and biological samples collected through CHILD has enabled researchers to address gaps in knowledge for the intended fields of allergy and asthma, as well as fields such as psychology and microbiology.[105] At the time of writing this thesis, CHILD

participants remain engaged in the study (e.g. completed questionnaires and provided dried blood spot samples for the CHILD COVID-19 Add-on study between 2021-2022, participating in the 13-year visits) and researchers continue to utilize CHILD questionnaire and biological sample data to address gaps in knowledge associated with the developmental origins of health and disease.

This thesis research investigated a subset of 670 CHILD Cohort Study infants, using data collected in the first year of life. This subset was chosen by Canadian Microbiome Initiative 2: Research Teams, "Causational Roles of the Gut Microbiome in Childhood Asthma: Leveraging the CHILD Cohort," grant investigators, in collaboration with the Biological Samples Committee - a sub-committee of CHILD co-investigators - based on the availability of i) blood serum collected from infant participants during the one-year CHILD clinic visit (2010-2013), and ii) infant metagenomic data at both three months and one year of age (**Figure 2**).

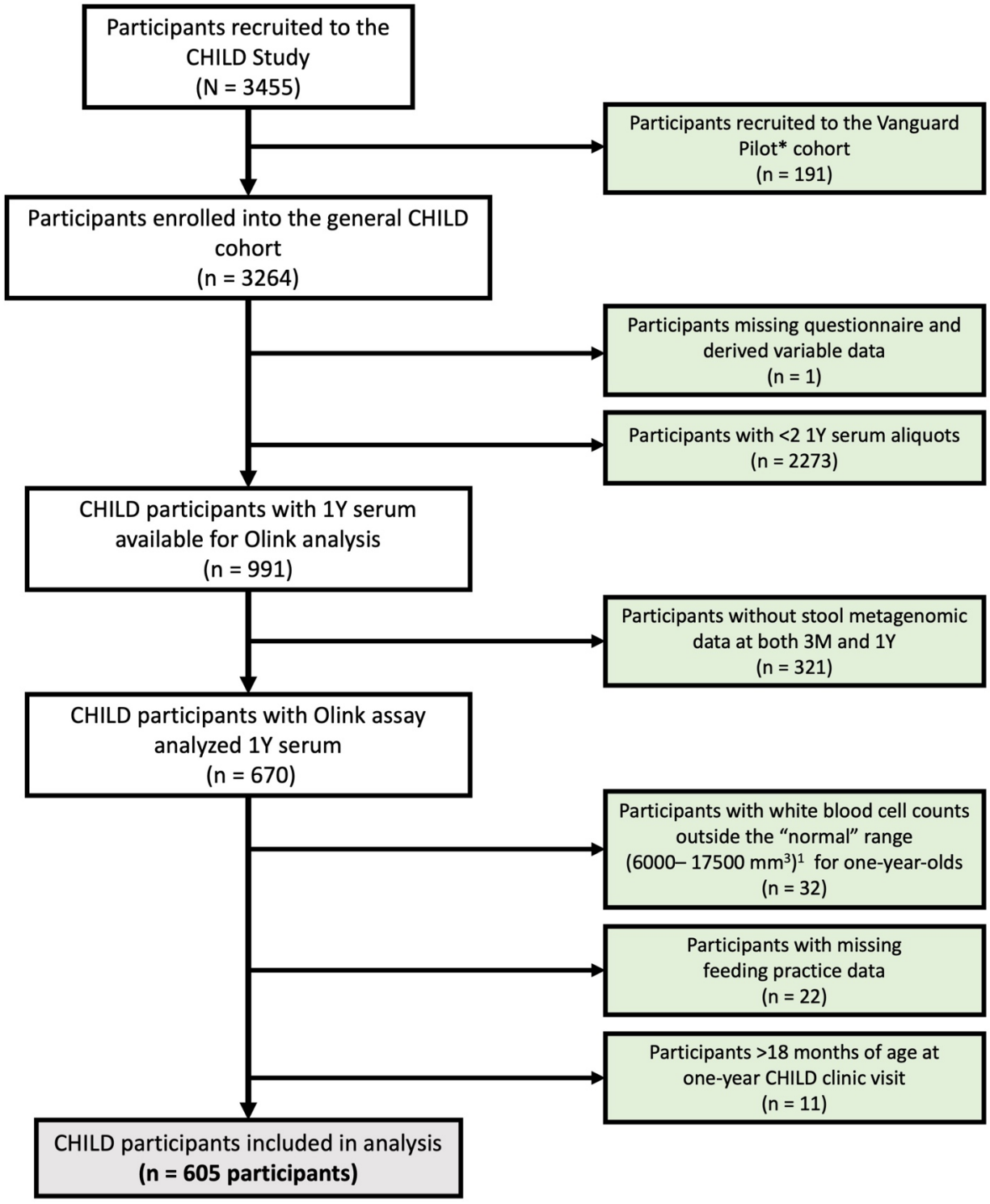


Figure 2. One-year-old CHILD infants selected for Olink Target 96 Inflammation panel serum biomarker quantification and statistical analysis. *Vanguard Pilot study participants were used to test exposure assessment approaches. [1]Nathan DG et al. 1987.

2.2. CHILD Cohort Study questionnaire data

This study used CHILD Cohort Study questionnaires completed by parent participants at recruitment (18-weeks gestation), 36-weeks gestation, and three months, six months, one year and three years postpartum.[106,107] Child birth chart data was collected from hospital reports. The wide range of data captured with these CHILD questionnaires are shown in **Table 1** and **Table 2.**

2.2.1. Infant feeding practices subject to analysis

Infant feeding practice variables investigated in this current study include infant HMF status at one-year blood sample collection ("current HMF status"), HMF duration, exclusive HMF duration, and HMF method at three months of age. Variable definitions, categories, source, and derivation details are in **Table 1**.

2.2.2. Population characteristics evaluated for inclusion as covariates in analysis

Demographic characteristics potentially related to overall infant development, infant immune system development, allergy and asthma incidence, inflammation-associated biomarker levels, and serum sample quality were captured in CHILD questionnaires or hospital child birth charts. Demographic characteristics in **Table 2** were either used directly (as a main outcome variable or covariate), indirectly (to derive variables used as a main outcome variable or covariate) or were evaluated but did not pass model building criteria in analysis. The scientific rationale for potentially including each demographic characteristic in analyses, as well as variable derivation information, are also in **Table 2.**

Table 1. Infant feeding practice variables investigated in this study.

	Definition and Categories	Source and Derivation	Original Questionnaire Wording
Current HMF Status			
HMF status at blood sample collection	• HMF at blood sample collection *(Complete HMF cessation occurred after one-year CHILD visit)* • Not HMF at blood sample collection *(Complete HMF cessation occurred before one-year CHILD visit)*	Infant birth date (*child birth chart*), one-year blood sample collection date (*one-year blood sample collection form*) and report of complete HMF cessation (*three-month; six-month; one-year questionnaires*) were used to derive this variable.	If you are not currently breastfeeding, how old was your child when you stopped breastfeeding?
History of HMF			
HMF duration	Infant age at earliest report of HMF cessation, in months Evaluated in continuous and categorical formats Categorical variables: • Two-month HMF intervals: 0, >0-≤2, 2-≤4, 4-≤6, 6-≤8, 8-≤10, >10 • Three-month HMF intervals: 0, >0-≤3, 3-≤6, 6-≤9, >9 • Four-month HMF intervals: 0, >0-≤4, 4-≤8, >8	Parent's report of complete HMF feeding cessation (*three-month; six-month; one-year questionnaires*) was used to derive this variable. The minimum known HMF duration was used when complete HMF cessation was unreported. Infant age at one-year blood sample collection was used as HMF duration value if an infant was HMF at blood sample collection.	If you are not currently breastfeeding, how old was your child when you stopped breastfeeding?
Exclusive HMF duration	Infant age at first introduction to formula or solid food, in months Evaluated in continuous and categorical formats Categorical variables: • Two-month exclusive HMF intervals: 0, >0-≤2, 2-≤4, >4	Parent's report of first introduction to formula or solid food (*child birth chart; three-month; six-month; one-year questionnaires*) were used to derive this variable.	Was the mother breastfeeding in the hospital? Are you currently giving your child any infant formula? How old was your child when you started giving him/her any type of infant formula?

	• Three-month exclusive HMF intervals: 0, >0-≤3, >4		Indicate which foods you have fed your child and at what age you INTRODUCED this food type to your child.
HMF method at three months of age	• Formula feeding only • HMF and formula feeding • HMF directly from the breast and through pumped and bottled milk • Direct HMF only	Parents report of breastfeeding, bottle feeding, and formula feeding *(three-month questionnaire)* was used to derive this variable.	Did you breastfeed your child for any duration (more than a few days) since birth? - If yes, are you currently breastfeeding your child (whether or not feedings are supplemented)? When breastfeeding since birth, did you use a breast pump to express the milk? On average, how many servings of breast milk expressed with a pump did you feed your child in the last two weeks? Are you currently giving your child any infant formula?

HMF, human milk feeding

Table 2. Demographic variables evaluated for and/or included in study analyses.

	Definition and Categories	Source and Derivation	Inclusion Rationale	Original Questionnaire Wording
Infant Variables				
Biological sex	• Male • Female	Hospital report of biological sex (*child birth chart*) was used to extract this variable.	Infant biological sex is associated with inflammation associated biomarkers, immune components,[108] and immune responses.[109]	NA
Birth weight	Infant birth weight, in grams	Hospital report of birth weight (*child birth chart*) was used to extract this variable.	Birth weight has a positive association with food allergy risk.[110]	NA
Age at blood sample collection	The time between date of birth and date of blood sample collection, in months	Hospital report of birth date (*child birth chart*) and one-year blood sample collection date (*one-year blood sample collection form*) were used to derive this variable.	The first 1000 days of life is considered a critical period in which immune system components develop and mature.[111]	NA
Gestational age	Infant gestational age at birth, in weeks	Hospital report of gestational age (*child birth chart*) was used to extract this variable.	Gestational age is positively associated with allergic rhinitis risk in young adulthood.[112]	NA
Infant antibiotic use in the first year of life	• Yes (*Antibiotic exposure in the first year of life, after birth)* • No (*No antibiotic exposure in the first year of life, after birth)*	Parent's report of antibiotic consumption (*three-month; six-month; one-year questionnaires*) were used to derive this variable.	Antibiotic exposure has been associated with microbiota dysbiosis and alteration in bacterial immune response.[113]	Did your baby take ANY prescribed or over-the-counter medications during this time period? - Brand name - Generic name - Type of medication Did your baby take another medication during this time period? - Brand name - Generic name - Type of medication

Positive skin prick test at one year of age	• Yes (*Positive test for at least one food or inhalant allergen)* • No (*No positive test results for food or inhalant allergen)*	Skin prick test (*at one-year CHILD visit*) results were used to derive this variable. Allergens included A.tenuis, cat, dog, D. pteronyssinus, D. farina, cockroach, peanut, milk, egg, and soy.	Allergic disease has been associated with an overreactive immune responses to 'harmless' antigens.[114]	NA
Received all routine provincial vaccinations at one year of age	• Yes • No	Parent's report of vaccinations received by an infant (*three-month; six-month; one-year questionnaires*) were used to derive this variable.	Vaccination stimulates the development of antigen-specific immune defenses.[115]	Which of the following vaccinations has your baby received since birth? - Routine provincial vaccinations at 2 months of age - Routine provincial vaccinations at 4 months of age - Routine provincial vaccinations at 6 months of age - Routine provincial vaccinations at 12 months of age - No vaccinations
Birth delivery method	• Caesarean section • Vaginal	Hospital report of method of delivery (*child birth chart)* was used to extract this variable.	Birth delivery method has been associated with bacterial richness and diversity.[116] Caesarean section delivery has been positively associated with asthma risk in childhood, in comparison to vaginal delivery.[117]	Method of delivery: - Vaginal unassisted - Vaginal forceps assisted - Vaginal vacuum extracted - Assisted breech (normal delivery often with forceps) - Breech extraction (rare/emergency when baby remains in uterus) - Elective caesarean section - Caesarean section (during labour - Emergency caesarean section (during labour) - Emergency caesarean section (without labour)

				- Not recorded - Other, specify:
Infant Feeding Practice Variables				
Age at first introduction to formula	Infant age when first fed baby formula, in months	Parent's report of first introduction to formula (*three-month; six-month; one-year questionnaires*) were used to derive this variable.	Formula feeding has been associated with differences in infant gut microbiome composition, antigen exposure, and allergic disease risk, compared to HMF.[118–120]	Are you currently giving your child any infant formula? How old was your child when you started giving him/her any type of infant formula?
Age at first introduction to solids	Infant age when first fed solid food, in months	Parent's report of first introduction to solid food (*three-month; six-month; one-year questionnaires*) were used to derive this variable.	The introduction of solid food induces gut microbiome composition changes and Treg proliferation in infants.[118,119,121]	Indicate which foods you have fed your child and at what age you INTRODUCED this food type to your child.
Time since HMF cessation	The time between HMF cessation and blood sample draw, in months	Parent's report of complete HMF cessation (*three-month; six-month; one-year questionnaires)* and CHILD technician reported blood sample draw (*one-year CHILD visit)* was used to derive this variable.	Time since HMF cessation may be associated with inflammation-associated serum biomarker levels.	If you are not currently breastfeeding, how old was your child when you stopped breastfeeding?
Household Variables				
Number of different pollution sources within 100m of infant home	• 0 • 1 • 2 • 3+	Parent's report of pollution sources (*one-year questionnaire*) was used to derive this variable.	Pollutants negatively impact respiratory immune responses to pathogens.[122]	Is your home within 100 metres of any of the following? (100 meters is the length of a football field) - Major highways/arteries - Body of waters - Factories - Farms - Large parking lots - Major/prolonged construction activities
Older siblings	• 0 • 1 • 2+	Parent's report of older siblings (*18-week gestation questionnaire; child birth*	The presence of older siblings has been associated with increased gut	Do you have any OTHER children conceived and delivered with your

		chart) was used to derive this variable.	microbiome diversity and decreased allergy risk.[123]	present baby's biological father or from any previous relationships? Do you have a second/third/fourth child conceived and delivered with your baby's biological father or from any previous relationships? Total number of pregnancies, including present pregnancy - Living children (not including child who is participating in the CHILD Study)
Household income	• $0 - $49 999 • $50 000 – $79 999 • $80 000 – $99 999 • $100 000 – $149 999 • Over $150 000 • Prefer not to say	Parent's report of household income (*one-year questionnaire)* was used to derive this variable.	Socioeconomic status has been negatively associated with innate immune responsiveness.[124]	What is the best estimate of the total income, before taxes and deductions, of all household members, from all sources in the past 12 months?
Household pets with fur	• Yes • No	Parent's report of household cats, dogs, or other pets with fur (*one-year questionnaire)* were used to derive this variable.	Furry pet exposure has been associated with risk of developing atopy-related disease in early childhood.[125]	Have you had any furry PETs in the last year?
Study Variables				
Time until blood sample centrifugation	The time between blood sample draw and blood sample processing, in hours	CHILD technicians report of blood sample collection time and date (*one-year CHILD visit*) and blood sample centrifugation time and date (*one-year CHILD visit*) were used to derive this variable.	Time until blood sample centrifugation has been associated with blood serum component stability and analytical measurability.[126]	NA
Study site	• Vancouver • Edmonton • Manitoba • Toronto	Enrollment site (*18-week gestation questionnaire)* was used to extract this variable.	Study site differences in serum collection methodology and/or geographic factors may be	NA

			associated with serum biomarker levels.	
Family Variables				
Maternal age at time of delivery	Mother's age at time of delivery, in years	Infant birth date (*child birth chart)* and mothers birth date (*18-week gestation questionnaire)* were used to derive this variable.	Maternal age at infant birth has been associated with T cell subset composition[127] and infant's risk of hypertensive disorders and gestational diabetes mellitus.[128]	NA
Maternal marital status	• Married or common law • Never been married, divorced, or separated	Parent's report of maternal marital status (*18-week gestation questionnaire)* was used to extract this variable.	Marital status has been associated with infant mortality and low birthweight.[129]	NA
Maternal years of education	Maternal years of education, in years	Parent's report of maternal years of education (*18-week gestation questionnaire)* was used to extract this variable.	Maternal years of education has been positively associated with the risk of low birth weight and preterm birth.[130]	How many years of education have you had?
Maternal race	• Asian • White • First Nations • Other	Parent's report of maternal ethnic or cultural group (*18-week gestation questionnaire)* was used to derive this variable.	Race has been associated with innate immune system response profile.[131]	To which ethnic or cultural group did your parents belong?
Maternal cigarette smoking status	• Yes • No	Parent's report of maternal cigarette smoking status (*18-week gestation questionnaire)* was used to derive this variable.	Prenatal smoking exposure has been associated with neonatal inflammation.[132]	DURING this pregnancy, did you completely stop smoking? At the present time, how often do you smoke?
Maternal second-hand smoke exposure	• Yes • No	Parent's report of maternal second-hand smoke exposure status (*18-week gestation questionnaire)* was used to derive this variable.	Maternal second-hand smoke exposure has been associated with reduced birth weight.[133]	Does anyone smoke inside your home? Does anybody, at present, smoke at your home?
Daily maternal alcohol consumption	Daily maternal alcohol consumption, in grams	Parent's report of maternal alcohol consumption (*18-week gestation questionnaire)* was used to derive this variable.	Maternal alcohol consumption during pregnancy has been associated with the disruption of fetal immune system	How often did you drink these beverages? - Beer (all types) - Red wine - White or rosé wine

			development, infection risk, and disease in neonates.[134]	- Coolers and wine coolers - Liquor and mixed drinks What was the serving size?
Maternal diet quality	Maternal diet quality, reflected by healthy eating index[135] score	Food composition tables from the Nutrition Coding Center nutrient database were used to derive this variable from a validated food frequency questionnaire (*18-week gestation; 36-week gestation questionnaires*).[136]	Maternal diet has been associated with infant epigenetic signatures, as well as infant allergy and infection risk.[137]	NA
Maternal pre-pregnancy body mass index	Maternal body mass index, in kg/m^2	Parent's report of pre-pregnancy maternal weight (*three-year questionnaire)*, or measured weight one year after birth (if mother could not recall pre-pregnancy weight) (*one-year mother spirometry measurement*) or imputed pre-pregnancy weight (if neither measure was available) and maternal height (*one-year spirometry measurement)* was used to derive this variable.	Maternal BMI has been associated with offspring incidence of cardiovascular disease, diabetes, and asthma.[138]	Does mother recall her weight when she became pregnant with the study child? - If yes, what was her approximate weight?
Maternal atopy (positive skin prick test)	• Yes (*Positive test for at least one food or inhalant allergen)* • No (*No positive test results for food or inhalant allergen)*	Skin prick test (*at one-year CHILD visit*) results were used to derive this variable. Allergens included A.tenuis, cat, dog, D. pteronyssinus, D. farina, cockroach, peanut, milk, egg, and soy.	Maternal allergy is associated with increased offspring allergy risk.[139]	NA
Paternal atopy (positive skin prick test)	• Yes (*Positive test for at least one food or inhalant allergen)*	Skin prick test (*at one-year CHILD visit*) results were used to derive this variable. Allergens included A.tenuis, cat, dog, D. pteronyssinus, D.	Paternal allergy is associated with increased offspring allergy risk. This association is weaker than the association between maternal	NA

	• No (*No positive test results for food or inhalant allergen)*	farina, cockroach, peanut, milk, egg, and soy.	allergy and risk of allergy in offspring.[140]

HMF, human milk feeding

2.3. Participant exclusion criteria

Sixty-five infants were excluded from analysis presented in this thesis (**Figure 2**). Infants were excluded from analysis if they met any of the following criteria:

1. Were outside the 'normal' white blood cell range for one-year-old infants (6000-17500 mm^3)[141,142] (n=32). White blood cell counts outside this range have been associated with active infection or cancer.[141]
2. Had missing HMF status at blood sample collection data (n=22).
3. Had their one-year CHILD clinic visit blood sample collection after 18 months of age (n=11).

Remaining infants (n=605) were included in analyses for investigating HMF status at blood sample collection. Infants who were currently HMF at time of blood sample collection (n=258) were excluded from analyses investigating history of HMF (HMF duration, exclusive HMF duration, HMF method at three months of age), as current HMF status was shown to have a strong confounding effect on the relationship between history of HMF variables and serum biomarker levels.

2.4. Infant serum collection

Infant blood serum was collected during one-year (mean age: 12.6 ± 1.4 months) CHILD clinic visits (2010-2013). Approximately 6 mL of blood was collected from infants with 21- to 25-gauge butterfly needles. On average, 3.0 mL of heparinized blood (anti-coagulated) and 2.25 mL non-heparinized blood were collected from infants at this visit.[106] Serum samples (two 0.3 mL aliquots) were collected by centrifuging (1000xg at room temperature for 10 minutes) heparinized blood after sample collection (median time until blood sample centrifugation: 2.2 (0.8-17.6 interquartile range (IQR)) hours) (**Supplementary Figure 1)** and immediately stored locally at -80°C.[106] Samples were then shipped to a long-term central storage site (-80°C, CRLB-Gem Lab & Biobank, Hamilton, ON) until serum biological molecule (biomarker) quantification was performed in 2021.[106]

2.5. Infant serum inflammation-associated biomarker quantification

Relative levels of 92 inflammation-associated biomarkers were quantified in infant serum (n=670, 40-100 μL for each sample) using the Target 96 Inflammation panel from Olink Proteomics ® (Uppsala, Sweden), performed at the Clinical Research Laboratory and Biobank – Genetic and Molecular Epidemiology Laboratory (Hamilton General Hospital, ON).

This Olink panel utilizes proximity extension assay (PEA) dual-recognition immunoassay technology to simultaneously measure *relative* biomarker levels in serum. 92 analyte-specific antibody pairs labelled with matched DNA oligonucleotides were added to serum samples on the panel. Antibody pairs that bind to their respective target proteins underwent a proximity-dependent DNA polymerization event in which antibody-attached DNA oligonucleotides hybridized to become a template/reporter sequence for DNA polymerase and polymerase chain

reaction (PCR) amplification. The hybridized double-stranded DNA template, or 'barcode', is unique for each biomarker target; therefore, amplicons (DNA amplification products) generated from each biomarker-antibody-oligonucleotide template were distinguished and quantified at the same time using quantitative real-time PCR (qPCR). qPCR read-out was performed using a Fluidigm® Biomark™ system.[143,144]

The Olink Target 96 Inflammation panel has a built-in quality control system that used three types of internal controls and two types of sample controls. **Internal controls** include incubation, extension, and detection controls. These internal controls were added to each serum sample and are designed to monitor PEA steps. Incubation controls are two different non-human antigens that are measured in the PEA. These controls are designed to monitor intra-assay technical variation in all PEA steps. The extension control is an antibody coupled to a unique pair of DNA-tags. This control should give a constant signal and is designed to monitor and allow for adjustment of DNA reporter sequence extension and amplification variation. The detection control is a double-stranded DNA amplicon that does not require proximity binding or extension to generate a detectable signal. This control monitors PEA amplification and detection steps.[145] **Sample controls** include inter-plate and negative controls. Sample controls were added to separate wells on each Olink plate. Inter-plate controls are pools of all 92 antibody pairs in fixed proximity. These controls are designed to give a high signal for all biomarkers. Inter-plate controls are added to three wells on each plate and are used to adjust for variation between runs and plates. Negative controls consist of buffer and are included in triplicate on each plate to monitor background noise generated when complementary DNA-tags come in close proximity without binding to target biomarkers. The mean + 3 standard deviations (SDs) of these negative controls was set as the arbitrary limit of detection (LOD) for each plate.[145]

Olink reports biomarker levels using normalized protein expression (NPX) units – an arbitrary unit on a log2 scale. NPX values are relative and specific to each individual biomarker, meaning different biomarkers with the same NPX value do not necessarily have the same absolute serum concentration. Biomarker NPX is calculated using an algorithm that incorporates extension, inter-plate, and negative control values, as well as the number of real-time qPCR cycles required for a unique antibody-oligonucleotide-based amplicon to reach the fluorescent signal threshold line of the Fluidigm® Biomark™ system.[143] Research detailing the accuracy, precision, and characteristics of this panel can be found on the manufacturer's website.[146]

An Intensity normalization process was used to account for systematic non-biological variation added to a dataset during data acquisition (i.e. batch effects) that arise from using multiple plates.[147] Intensity normalization is based on the assumption that, on average, there is no difference between median signals among plates. The intensity normalization process used in this current study included i) calculating the overall median for all samples and plates, ii) calculating each individual plate median value, iii) subtracting individual plate medians from all values on respective plates, and iv) adding the overall median to all values.[145] Additional batch effects (e.g. variation associated with oligonucleotide hybridization time) were removed with the Limma R package.[148] Operator error was evaluated by determining if samples with shared columns or rows deviate from remaining samples on a plate. Outliers were defined as samples more than three SDs from the interquartile range of all samples and more than three SDs from the mean of all biomarker medians. No operator error effects or outlier serum samples were found. Biomarkers with >50% of samples below the LOD (n=16 biomarkers) were subsequently excluded from analyses (**Supplementary Figure 2)**.[149] Values below the LOD for remaining biomarkers (n=76) were replaced by the LOD value of each respective plate. A logistic

regression analysis did not identify any significant associations between biomarker presence/absence and any infant feeding practices investigated in this study (**Supplementary Figure 3)** Outlier detection, batch effect removal, and LOD replacement were completed by project collaborators Lucie Rodriguez and Petter Brodin. The names of all biomarkers quantified by this panel, including biomarkers that were excluded from analysis, are found in **Table 5**.

2.6. Data cleaning, transformation, analysis, and visualization

All data cleaning, analysis, and visualization was performed in R version 4.0.5: A language and environment for statistical computing using R Studio version 2021.09.2+382 (R Core Team, Vienna, Austria, http://www.R-project.org/).[150] R packages used included dplyr,[151] tidyr,[152] lm,[153] glm,[154] tidyverse,[155] and vegan.[156] The R package ggplot2 was used to visualize all results and data.[157]

Missing data was removed from statistical analyses. Biomarker NPX measures were converted to Z-scores to make analysis results more comparable across biomarkers This standardization process resulted in each biomarker having a mean NPX of zero and SD of one.

The Benjamini-Hochberg method was used to account for multiple comparisons and false-discovery rate (FDR) in all statistical analyses.[158] Unless otherwise mentioned, $p<0.05$ was considered statistically significant. Normally distributed continuous demographic characteristics were summarized using mean and SDs and non-normally distributed continuous demographic characteristics were summarized using median and IQRs.

Linear Regression:

The associations between infant feeding practices (continuous or categorical independent variables) and standardized serum biomarker levels (continuous dependent variables) at one year of age were determined using linear regression. Linear regression models estimate differences in the dependent variable for different levels of the independent variables (either 'per unit increase' for continuous variables, or relative to the chosen reference group for categorical variables).[159] The benefit of using linear regression to investigate categorical variables, in comparison to a t-test or ANOVA, is that it can account for covariates.[159]

Linear regression models were created using each infant feeding practice, individually, as independent variables predicting each standardized biomarker level. Current HMF status (binary), HMF duration (grouped in intervals of two months, three months, and four months), exclusive HMF duration (grouped in intervals of two months and three months), and HMF method at three months (four categories) were evaluated in linear regression models as categorical independent variables. HMF duration and exclusive HMF duration were additionally assessed as continuous independent variables. Spearman correlation coefficient informed hierarchical clustering analysis (**Supplementary Figure 4)** was used to inform biomarker order in a linear regression analysis using current HMF status as an independent variable. Results were obtained for univariable models and for multivariable models adjusting for covariates.

Regression model covariate selection:

Covariates evaluated in multivariable regression models were chosen based on literature and a forward stepwise covariate selection process. Increasing the number of independent variables increases the risk of overfitting and multicollinearity; therefore, a 'simplest is best' model building approach was used in this current study.[160] Infant sex and study site were chosen

to be included in analyses *a priori*. Infant sex is commonly included in research utilizing the Olink Target 96 Inflammation panel, as sex differences have been reported for several inflammation-associated biomarker levels.[161,162] Blood sampling methodology and storage are known to affect biomarker stability[126,163] and are suspected to vary slightly among CHILD study sites.

A multi-step forward stepwise model building process was used to identify which demographic characteristics (listed in **Table 2**) were MOST justifiable for inclusion in regression models. First, univariable linear regression was used to investigate associations of demographic characteristics with serum biomarker levels. Characteristics with a linear regression FDR-corrected p-value < 0.05 for one or more biomarkers were then evaluated for inclusion in linear regression models using the *step* R function.[164] The *step* function adds variables to linear regression models one by one, beginning with the variable demonstrating the lowest univariate model p-value, until no variables remain, or until all remaining variables have a p-value larger than the specified threshold of 0.15.[165] In this study, the *step* function was used to determine what characteristics would be added to models using current HMF status as an independent predictor of serum biomarkers found to have significant associations with current HMF status in univariable regression analysis**.** A demographic characteristic was selected for inclusion in multivariable regression analysis if it was added to, or met the forward stepwise selection criteria, for at least five of seven biomarker models. The final multivariable linear regression models included **infant sex**, **study site**, and **time until blood sample centrifugation**. Univariable and multivariable linear regression assumptions of multicollinearity and homoscedasticity were tested for and met.

Logistic Regression:

To further explore the relationship of current HMF status with infant immune system activity and development, the extent to which inflammation-associated biomarkers can individually and collectively predict infant current HMF status was determined with logistic regression models. Covariate adjustments were applied as described above. All biomarkers significantly associated with current HMF status in individual multivariable logistic regression were added to one multi-biomarker logistic regression model.

Receiver operating characteristic curves and respective area under the receiver operating characteristic curve (AUC) values were generated and calculated, for all logistic regression models using the pROC and plot.roc R functions, respectively.[166,167] The ability of a logistic regression model to use independent predictors (inflammation-associated biomarkers) to correctly predict or discriminate a dependent variable (current HMF status) is reflected by AUC. An AUC value has a positive relationship with model performance; therefore, a higher AUC indicates more distinction among inflammation-associated biomarker levels.[168] The roc.test R function used delong and bootstrap methods to test for AUC value differences between individual biomarker univariable and multivariable logistic regression models.[166] Univariable and multivariable logistic regression assumptions of multicollinearity were tested for and met.

Redundancy Analysis:

Redundancy analysis (RDA) was performed to indicate the proportion of all included inflammation-associated biomarker (n=75) variance explained by infant feeding practice variables, as well as other demographic variables. The complete biomarker profile (n=75), except FGF-5 (contained 46 NA values), was included in this analysis.

Chapter III: Results

3.1. Study population demographic characteristics

We studied 605 one-year-old CHILD infants ("full study population") to investigate the association between current HMF status and inflammation-associated serum biomarker levels. A subset of infants not currently HMF (n=347, 57.4% of the study population) was used to investigate associations with history of HMF variables (HMF duration, exclusive HMF duration, and HMF method at three months of age).

3.1.1. Population characteristics evaluated for inclusion as covariates in analysis

Hospital reports and repeated CHILD questionnaires provided data describing study population demographic characteristics. These demographic characteristic variables were evaluated for inclusion as covariates in statistical analysis.

As shown in **Table 3,** the median age at the time of blood sample collection was 12 months (IQR 12.0-13.0). Full study population infants (57.4% female) were originally enrolled at the Vancouver (37.4%), Edmonton (22.3%), Toronto (35.2%), and Manitoba (5.1%) CHILD study sites. The majority of these infants had relatively high earning households (29.3% - $150,000 or over; 29.9% - $100,000-$149,999). Mothers were predominantly white (74.6%) and partnered upon study enrollment (95.2%). The majority (70.0%) of participant blood samples were centrifuged on the same day of blood sample collection, though a large range was observed in time to centrifugation (median: 2.17 hours (IQR: 0.83 – 17.58)) (**Supplementary Figure 1**). The full study population stopped receiving any HM a median of 2 months (IQR: 0-6.0) before the one-year CHILD clinic visit (time since HMF cessation). Demographics were similar in the

subset of infants not currently HMF, except for sex (43.2% female), and time since HMF cessation (5.0 [3.0-9.0] months). **Table 3** outlines the distribution of additional descriptive characteristics for both the full study population and subset not currently HMF.

Table 3. Population characteristics of the full one-year-old study population (n=605) and subset not currently HMF (n=347). These characteristics were evaluated for inclusion as covariates in analysis.

	Full Study Population (n=605)		Not Currently HMF Subset (n=347)	
	n	Mean ± SD, Median (IQR), or (%)	n	Mean ± SD, Median (IQR), or (%)
Infant Variables				
Biological sex				
Male	258	(42.6)	197	(56.8)
Female	347	(57.4)	150	(43.2)
Birth weight, grams	601	3440 (3140-3760)	345	3510 (3140-3780)
Age at blood sample collection, months	605	12.0 (12.0-13.0)	347	12.0 (12.0-13.0)
Gestational age, weeks	600	39.0 (38.0-40.0)	344	39.0 (38.0-40.0)
Infant antibiotic use in the first year of life				
Yes	123	(20.3)	85	(24.5)
No	482	(79.7)	262	(75.5)
Positive skin prick test at one year of age				
Yes	92	(15.3)	50	(14.5)
No	509	(84.7)	294	(85.5)
Missing	4	—	3	—
Received all routine provincial vaccinations at one year of age[1]				
Yes	199	(36.7)	123	(40.6)
No	343	(63.3)	180	(59.4)
Missing	63	—	44	—
Birth delivery method				
Caesarean section	147	(24.5)	91	(26.4)
Vaginal	454	(75.5)	254	(75.6)
Missing	4	—	2	—
Infant Feeding Practice Variables				
Age at first introduction to formula, months	352	1.3 (0-5.0)	269	1.0 (0-4.0)
Age at first introduction to solids, months	589	5.0 (4.5-6.0)	335	5.0 (4.5-5.0)
Time since HMF cessation, months	605	2.0 (0-6.0)	347	5.0 (3.0-9.0)
Household Variables				
Number of different pollution sources within 100m of infant home*				

0	7	(1.3)	6	(2.0)
1	415	(77.1)	234	(77.5)
2	76	(14.1)	42	(13.9)
3+	40	(7.4)	20	(6.6)
Missing	67	—	45	—
Older siblings				
0	319	(52.7)	181	(52.2)
1	219	(36.2)	125	(36.0)
2+	67	(11.1)	41	(11.8)
Household income*				
$0 - $49,999	36	(6.1)	22	(6.5)
$50,000 - $79,999	77	(13.0)	42	(12.4)
$80,000 - $99,999	74	(12.5)	42	(12.4)
$100,000 - $149,999	177	(29.9)	105	(31.1)
$150,000 or over	174	(29.3)	102	(30.2)
Prefer not to say	55	(9.3)	25	(7.4)
Missing	12	—	9	—
Household pets with fur*				
Yes	326	(60.6)	180	(59.6)
No	212	(39.4)	122	(40.4)
Not Applicable or Missing	67	—	45	—
Study Variables				
Time until blood sample centrifugation, hours	605	2.2 (0.8-17.6)	347	2.6 (0.8-17.8)
Study site				
Vancouver	226	(37.4)	105	(30.3)
Edmonton	135	(22.3)	87	(25.1)
Manitoba	31	(5.1)	15	(4.3)
Toronto	213	(35.2)	140	(40.3)
Family Variables				
Maternal age at time of delivery, years	603	34.0 (31.0-37.0)	346	34.0 (31.0-37.0)
Maternal marital status**				
Married or common law	518	(95.2)	289	(94.1)
Never been married, divorced, or separated	26	(4.8)	18	(5.9)
Missing	61	—	40	—
Maternal years of education**, years	593	17.0 (16.0-19.0)	338	17.0 (15.0-18.0)
Maternal race				

Asian	109	(18.0)	62	(17.9)
White	445	(73.6)	255	(73.5)
First Nations	16	(2.6)	9	(2.6)
Other	35	(5.8)	21	(6.0)
Maternal cigarette smoking status**				
Yes	51	(8.6)	34	(10.0)
No	544	(91.4)	305	(90.0)
Missing	10	—	8	—
Maternal second-hand smoke exposure**				
Yes	60	(10.1)	36	(10.6)
No	535	(89.9)	303	(89.4)
Missing	10	—	8	—
Daily maternal alcohol consumption**, grams	559	0.02 (0.01-0.05)	316	0.02 (0.01-0.05)
Maternal diet quality*, healthy eating index score	559	75.1 (69.4-80.0)	316	74.2 (68.5-79.3)
Maternal body mass index*, kg/m^2	589	22.7 (20.8-25.8)	337	22.9 (21.0-26.9)
Maternal atopy (positive skin prick test)*				
Yes	395	(65.8)	228	(66.3)
No	205	(34.2)	116	(33.7)
Missing	5	—	3	—
Paternal atopy (positive skin prick test)*				
Yes	340	(70.4)	187	(69.5)
No	143	(29.6)	82	(30.5)
Missing	122	—	78	—

Participants with missing data (marked with a —) were not included in percentage calculations. *Data collected from the one-year CHILD questionnaire. **Data collected from the 18-week gestation questionnaire. [1]We suspect many infants have **not yet** received all provincial routine vaccinations at one year of age.

In univariable regression analyses, 16 of the demographic characteristics in **Table 3** were significantly associated with at least one inflammation-associated biomarker (infant sex, age at first introduction to solids, age at first introduction to formula, age at blood sample collection, time since HMF cessation and vaccination; maternal age, race, atopy, body mass index, alcohol consumption, years of education, and marital status; paternal atopy; household pets; study site; time until blood sample centrifugation) (**Supplementary Figure 5**). Of the associated

demographic characteristics, time until blood sample centrifugation was the lone variable that satisfied forward stepwise selection requirements, warranting its addition to all regression models in subsequent analyses (**Supplementary Table 1, Supplementary Figure 1).** We additionally included sex and study site in multivariable regression models based on literature and suspected study site methodology variation, respectively.

3.1.2. Infant feeding practice characteristics

As shown in **Table 4,** in the full study population, the median duration of HMF was 11.0 months (IQR: 7.0-12.0) and 4.5 months (IQR: 0.8-5.0) for exclusive HMF. In the subset not currently HMF, the median duration of HMF was 8.0 months (IQR: 4.0-10.0) and 2.0 months (IQR: 0.3-4.5) for exclusive HMF. 18 infants did not receive any HM before their one-year CHILD clinic visit. Approximately half of the full population were exclusively receiving HM at three months of age (53.7%). At three months of age, more infants were fed a combination of HM directly from the breast and pumped milk from bottles (35.4%), than exclusively from the breast (28.3%). Remaining infants received a combination of HM and formula (24.6%), or exclusively formula (10.9%). Unsurprisingly, infants not currently HMF had relatively lower rates of exclusive HMF (45.6%) and relatively lower rates of exclusive HMF from the breast (17.6%) or direct and expressed HMF (28.0%), as well as relatively higher rates of receiving a combination of HM and formula (34.3%) and exclusive formula feeding (19.0%) at three months of age.

Table 4. Infant feeding practice characteristics of the full one-year-old study population (n=605) and subset not currently HMF (n=347).

	Full Study Population (n=605)		Not Currently HMF Subset (n=347)	
	n	Mean ± SD, Median (IQR), or (%)	n	Mean ± SD, Median (IQR), or (%)
Current HM Feeding Status				
HMF at blood sample collection[1]				
Yes	258	(42.6)	0	(0)
No	347	(57.4)	347	(100)
History of HMF				
HMF duration[2]				
Continuous HMF Duration, months	605	11.0 (7.0-12.0)	347	8.0 (4.0-10.0)
Categorical HMF duration (two-month intervals)				
0	18	(3.0)	18	(5.2)
0 - ≤2	39	(6.4)	39	(11.2)
2 - ≤4	32	(5.3)	32	(9.2)
4 - ≤6	49	(8.1)	49	(14.1)
6 - ≤8	68	(11.2)	68	(19.6)
8 - ≤10	64	(10.6)	63	(18.2)
>10	335	(55.4)	78	(22.5)
Categorical HMF duration (three-month intervals)				
0	18	(3.0)	18	(5.2)
0 - ≤3	61	(10.1)	61	(17.6)
3 - ≤6	59	(9.8)	59	(17.0)
6 - ≤9	103	(17.0)	103	(29.7)
>9	364	(60.2)	106	(30.5)
Categorical HMF duration (four-month intervals)				
0	18	(3.0)	18	(5.2)
0 - ≤4	71	(11.7)	71	(20.5)
4 - ≤8	117	(19.3)	117	(33.7)
>8	399	(66.0)	141	(40.6)
Exclusive HMF duration				
Continuous exclusive HMF duration, months	596	4.5 (0.8-5.0)	342	2 (0.3-4.5)

Categorical exclusive HMF duration (two-month intervals)				
0	89	(14.9)	78	(22.8)
0 - ≤2	121	(20.3)	103	(30.1)
2 - ≤4	81	(13.6)	54	(15.8)
>4	305	(51.2)	107	(31.3)
Missing	9	—	5	—
Categorical exclusive HMF duration (three-month intervals)				
0	89	(14.9)	78	(22.8)
0 - ≤3	146	(24.5)	120	(35.1)
>3	361	(60.6)	144	(42.1)
Missing	9	—	5	—
HMF method at three months of age				
Formula feeding only	66	(10.9)	66	(19.0)
HMF and formula feeding	149	(24.6)	119	(34.3)
HMF directly from the breast and through pumped and bottled milk	214	(35.4)	97	(28.0)
Direct HMF only	171	(28.3)	61	(17.6)
Missing	5	—	4	—

[1]Blood sample collection completed at the one-year CHILD clinic visit. [2]Duration at the time of one-year CHILD clinic visit.

3.2. Inflammation-associated biomarker distributions

Olink biomarker measures were standardized (converted to z-scores) to enhance biomarker analysis comparison. Histogram review and Kolmogorov-Smirnov test results of standardized biomarker measures indicate the majority (49/76 - 65%) of biomarkers were approximately normally distributed (**Figure 3, Table 5**).

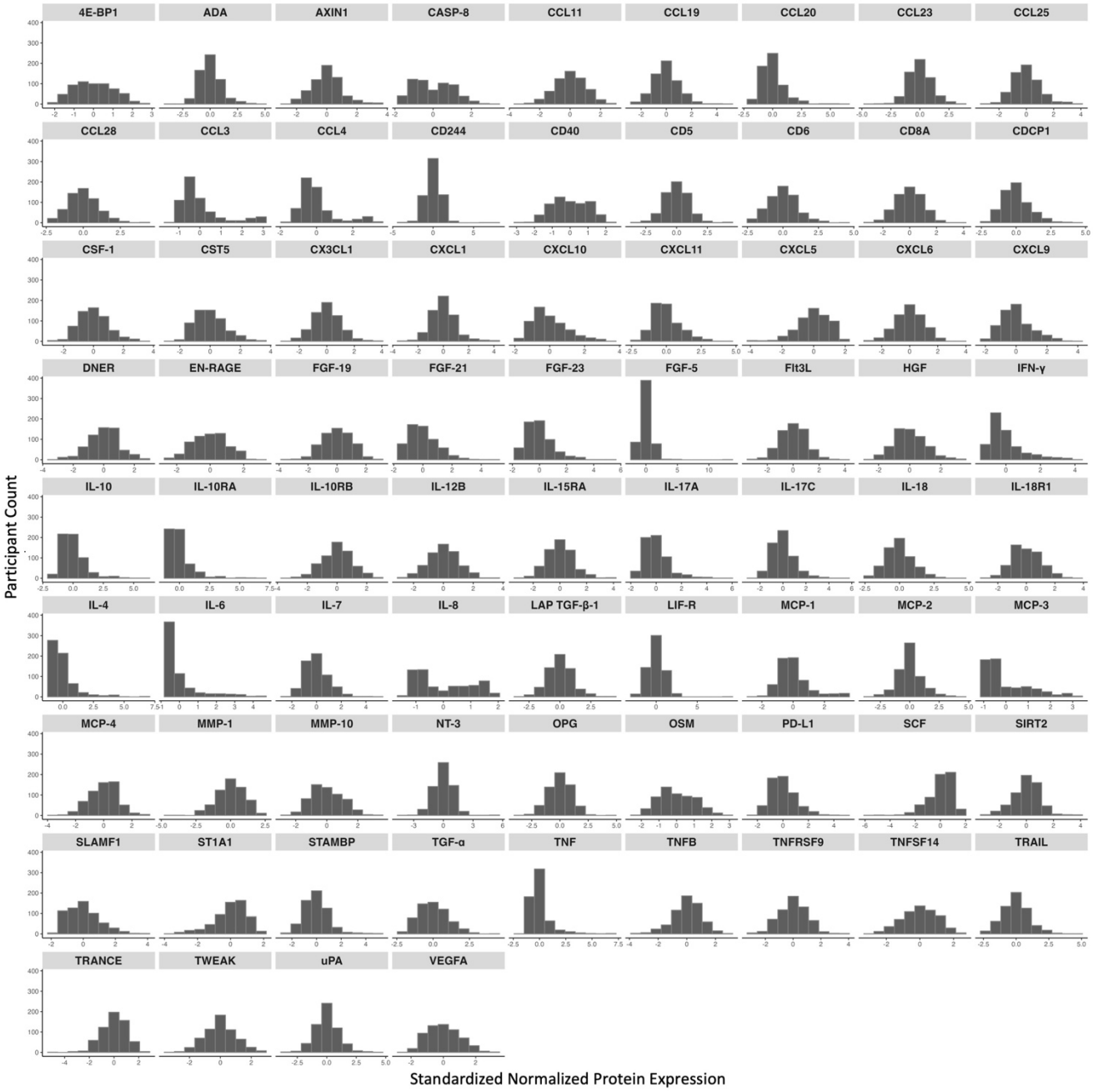


Figure 3. Standardized normalized protein expression (NPX) of inflammation-associated serum biomarkers among one-year-old CHILD cohort infants (full study population, n=605). Biomarkers were measured using the Olink Target 96 Inflammation panel. Full biomarker names can be found in **Table 5**.

Table 5. Olink Target 96 Inflammation panel biomarker descriptive statistics for one-year-old CHILD cohort infants (full study population, n=605).

Abbreviation	Biomarker name	Mean ± SD or Median (IQR)	Range	Kolmogorov-Smirnov Normality Test P-values
4E-BP1	Eukaryotic translation initiation factor 4E-binding protein 1	8.68 ± 1.16	6.11 - 11.58	0.11
ADA	Adenosine Deaminase	5.79 ± 0.45	4.03 - 7.76	0.10
ARTN	Artemin	—	—	—
AXIN1	Axin-1	3.90 ± 0.81	1.91 - 6.85	0.20
β-NGF	Beta-nerve growth factor	—	—	—
CASP-8	**Caspase-8**	**3.13 (2.27 – 4.11)**	**1.31 - 6.50**	**<0.01**
CCL11	Eotaxin	7.62 ± 0.41	6.32 - 8.77	0.99
CCL19	C-C motif chemokine 19	9.65 ± 0.66	7.80 - 12.58	0.26
CCL20	**C-C motif chemokine 20**	**8.04 (7.56 – 8.55)**	**6.40 - 13.66**	**<0.01**
CCL23	C-C motif chemokine 23	9.71 ± 0.46	7.61 - 11.26	0.26
CCL25	C-C motif chemokine 25	6.37 ± 0.49	4.92 - 8.19	0.11
CCL28	C-C motif chemokine 28	2.36 ± 0.49	1.29 - 4.32	0.43
CCL3	**C-C motif chemokine 3**	**6.76 (6.06 – 7.95)**	**4.61 - 13.83**	**<0.01**
CCL4	**C-C motif chemokine 4**	**7.82 (7.39 – 8.44)**	**6.12 - 12.72**	**<0.01**
CD244	Natural killer cell receptor 2B4	6.07 ± 0.36	4.76 - 8.91	0.40
CD40	CD40L receptor	11.68 ± 0.55	10.10 - 12.94	0.11
CD5	T-cell surface glycoprotein CD5	6.61 ± 0.31	5.63 - 7.93	0.79
CD6	T cell surface glycoprotein CD6 isoform	7.09 ± 0.50	5.82 - 9.08	0.64
CD8A	T-cell surface glycoprotein CD8 alpha chain	9.82 ± 0.55	7.93 - 11.70	0.99
CDCP1	**CUB domain-containing protein 1**	**1.64 (1.42 – 1.92)**	**0.66 - 3.31**	**0.01**
CSF-1	Macrophage colony-stimulating factor 1	9.80 ± 0.21	9.16 - 10.46	0.43
CST5	Cystatin D	6.31 ± 0.60	4.89 - 8.55	0.11
CX3CL1	Fractalkine	3.72 ± 0.34	2.76 - 5.05	0.75
CXCL1	C-X-C motif chemokine 1	11.14 ± 0.62	9.33 - 13.86	0.07
CXCL10	**C-X-C motif chemokine 10**	**10.04 (9.41 – 10.91)**	**8.15 - 14.25**	**<0.01**
CXCL11	**C-X-C motif chemokine 11**	**8.11 (7.54 – 8.90)**	**5.87 - 13.02**	**<0.01**
CXCL5	C-X-C motif chemokine 5	12.60 ± 0.60	10.27 - 13.76	0.39
CXCL6	C-X-C motif chemokine 6	9.67 ± 0.58	7.87 - 11.68	0.98
CXCL9	**C-X-C motif chemokine 9**	**6.89 (6.41 – 7.53)**	**5.20 - 10.59**	**<0.01**
DNER	Delta and Notch-like epidermal growth factor-related receptor	9.20 ± 0.16	8.70 - 9.68	0.67
EN-RAGE	Protein S100-A12	6.51 ± 1.06	3.64 - 9.45	0.81
FGF-19	Fibroblast growth factor 19	8.24 ± 1.04	4.55 - 11.12	0.81
FGF-21	**Fibroblast growth factor 21**	**2.53 (1.76 – 3.45)**	**0.71 - 8.71**	**0.01**
FGF-23	**Fibroblast growth factor 23**	**0.67 (0.49 – 0.93)**	**0.09 - 2.80**	**<0.01**
FGF-5*	**Fibroblast growth factor 5**	**0.72 (0.60 – 0.84)**	**0.24 – 3.80**	**<0.01**

Flt3L	Fms-related tyrosine kinase 3 ligand	8.16 ± 0.38	6.91 - 9.65	0.99
GDNF	Glial cell line-derived neurotrophic factor	—	—	
HGF	Hepatocyte growth factor	9.01 ± 0.47	7.79 - 10.59	0.36
IFN-γ	**Interferon gamma**	**7.75 (7.25 – 8.73)**	**6.13 - 14.19**	**<0.01**
IL-1α	Interleukin-1 alpha	—	—	
IL-10	**Interleukin-10**	**4.49 (4.14 – 5.06)**	**3.20 - 9.64**	**<0.01**
IL-10RA	**Interleukin-10 receptor subunit alpha**	**0.90 (0.64 – 1.27)**	**0.41 - 5.70**	**<0.01**
IL-10RB	Interleukin-10 receptor subunit beta	6.19 ± 0.31	5.33 - 6.78	0.83
IL-12B	Interleukin-12 subunit beta	7.65 ± 0.45	6.37 - 9.18	0.81
IL-13	Interleukin-13	—	—	
IL-15RA	Interleukin-15 receptor subunit alpha	1.30 ± 0.29	0.36 - 2.36	0.75
IL-17A	**Interleukin-17A**	**2.39 (2.01 – 2.93)**	**0.99 - 6.96**	**<0.01**
IL-17C	**Interleukin-17C**	**3.62 (1.95 – 8.25)**	**1.95 - 8.25**	**0.02**
IL-18	Interleukin-18	8.79 ± 0.60	7.36 - 11.35	0.18
IL-18R1	Interleukin-18 receptor 1	8.10 ± 0.37	7.12 - 9.51	0.23
IL-2	Interleukin-2	—	—	—
IL-20	Interleukin-20	—	—	—
IL-20RA	Interleukin-20 receptor subunit alpha	—	—	—
IL-22-RA1	Interleukin-22 receptor subunit alpha-1	—	—	—
IL-24	Interleukin-24	—	—	—
IL-2RB	Interleukin-2 receptor subunit beta	—	—	—
IL-33	Interleukin-33	—	—	—
IL-4	**Interleukin-4**	**0.56 (0.42 – 0.86)**	**0.35 - 4.53**	**<0.01**
IL-5	Interleukin-5	—	—	—
IL-6	**Interleukin-6**	**1.80 (1.37 – 2.91)**	**1.00 - 12.83**	**<0.01**
IL-7	Interleukin-7	2.28 ± 0.43	1.31 - 4.50	0.11
IL-8	**Interleukin-8**	**9.12 (6.24 – 12.14)**	**4.38 - 15.08**	**<0.01**
LAP TGF-β-1	Latency-associated peptide transforming growth factor beta-1	7.04 ± 0.37	5.85 - 8.63	0.76
LIF	Leukemia inhibitory factor	—	—	—
LIFR	Leukemia inhibitory factor receptor	3.64 ± 0.22	3.11 - 5.56	0.47
MCP-1	**Monocyte chemotactic protein 1**	**12.44 (12.06 – 12.88)**	**10.74 - 15.46**	**<0.01**
MCP-2	**Monocyte chemotactic protein 2**	**8.79 (8.37 – 9.35)**	**5.98 - 13.27**	**<0.01**
MCP-3	**Monocyte chemotactic protein 3**	**2.74 (2.07 – 5.60)**	**1.10 - 11.79**	**<0.01**
MCP-4	Monocyte chemotactic protein 4	14.80 ± 0.59	12.71 - 16.54	0.79
MMP-1	Matrix metalloproteinase-1	14.23 ± 0.88	10.61 - 16.43	0.81

MMP-10	Matrix metalloproteinase-10	9.58 ± 0.75	7.52 - 11.99	0.20
NRTN	Neurturin	—	—	—
NT-3	Neurotrophin-3	2.35 ± 0.29	1.28 – 4.00	0.59
OPG	Osteoprotegerin	9.96 ± 0.30	8.96 - 11.43	0.98
OSM	**Oncostatin-M**	**6.94 (5.81 – 8.41)**	**3.57 - 11.95**	**0.01**
PD-L1	**Programmed cell death 1 ligand 1**	**4.89 (4.69 – 5.15)**	**4.03 - 6.77**	**0.03**
SCF	**Stem cell factor**	**9.07 (8.75 – 9.33)**	**6.25 - 9.86**	**<0.01**
SIRT2	SIR2-like protein 2	5.27 ± 0.88	2.78 - 8.73	0.11
SLAMF1	Signaling lymphocytic activation molecule	1.56 ± 0.32	1.03 - 2.85	0.11
ST1A1	**Sulfotransferase 1A1**	**5.01 (4.33 – 5.54)**	**1.22 - 6.84**	**0.01**
STAMBP	STAM-binding protein	5.09 ± 0.72	3.30 - 8.71	0.05
TGF-α	Transforming growth factor alpha	3.85 ± 0.61	2.41 - 6.28	0.39
TNF	**Tumor necrosis factor**	**3.48 (3.18 – 3.83)**	**2.26 - 9.39**	**<0.01**
TNFB	TNF-beta	6.20 ± 0.45	4.61 - 7.53	0.11
TNFRSF9	Tumor necrosis factor receptor superfamily member 9	8.20 ± 0.29	7.24 - 9.17	0.99
TNFSF14	Tumor necrosis factor ligand superfamily member 14	6.85 ± 0.91	4.31 - 9.29	0.52
TRAIL	TNF-related apoptosis-inducing ligand	7.60 ± 0.32	6.81 - 9.08	0.44
TRANCE	TNF-related activation-induced cytokine	6.20 ± 0.52	3.61 - 7.53	0.28
TSLP	Thymic stromal lymphopoietin	—	—	—
TWEAK	Tumor necrosis factor (Ligand) superfamily, member 12	9.06 ± 0.29	8.14 - 9.84	0.71
uPA	Urokinase-type plasminogen activator	10.23 ± 0.30	9.10 - 11.40	0.19
VEGFA	Vascular endothelial growth factor-A	11.51 ± 0.61	9.87 - 13.33	0.14

*45 participant samples had NA values for FGF-5. Untransformed normalized protein expression (NPX) data was used to obtain mean or median values and data range. Standardized NPX data was used to obtain Kolmogorov-Smirnov normality test results. NPX values cannot be compared between biomarkers. The Benjamini-Hochberg method was used in the FDR p-value correction of Kolmogorov-Smirnov test results. Bolded results had FDR-corrected Kolmogorov-Smirnov test p-values<0.05 indicating non-normality. Biomarkers highlighted in grey had >50% of participant samples below the limit of detection and were excluded from analysis.

3.3. Investigating the association between infant current HMF status and inflammation-associated biomarker levels

3.3.1. Serum biomarker levels differ according to current HMF status

Serum biomarker level differences between current HMF status groups were determined by using current HMF status to predict serum biomarker levels in univariable linear regression. Of the 76 biomarkers tested, six (CCL20, CD244, CXCL6, FGF-21, IL-10RB, and TRANCE) were significantly higher in HMF infants, and one (EN-RAGE) was significantly lower (all FDR p-values <0.05) (**Figure 4, Supplementary Table 2).** The strongest association, or largest difference in biomarker level according to current HMF status, was observed for FGF-21 (mean 0.32 +/- 1.06 standardized NPX in currently HMF infants vs -0.23 +/- 0.89 in not currently HMF infants, FDR-p<0.001; standardized β-coefficient 0.56, 95% CI: 0.40 – 0.71), with other standardized β-coefficients ranging from -0.29 to 0.36. Notably, IL-10RB, TRANCE, and EN-RAGE became marginally associated with current HMF status (adjusted p-values 0.06, 0.07, and 0.12 respectively) after adjusting for covariates (time until blood sample centrifugation, sex, and study site) (**Figure 4A, Supplementary Table 2)**, suggesting potential confounding of these relationships. No biomarkers became significant (p>0.05 → p<0.05) upon covariate adjustment. The FGF-21 standardized β-coefficient remained highest among all significant biomarkers after covariate adjustment (0.56, 95% CI: 0.41 – 0.72). Ordering biomarkers according to hierarchical clustering analysis results (**Supplementary Figure 4)** show current HMF status may be associated with biomarker clusters (**Supplementary Figure 6).**

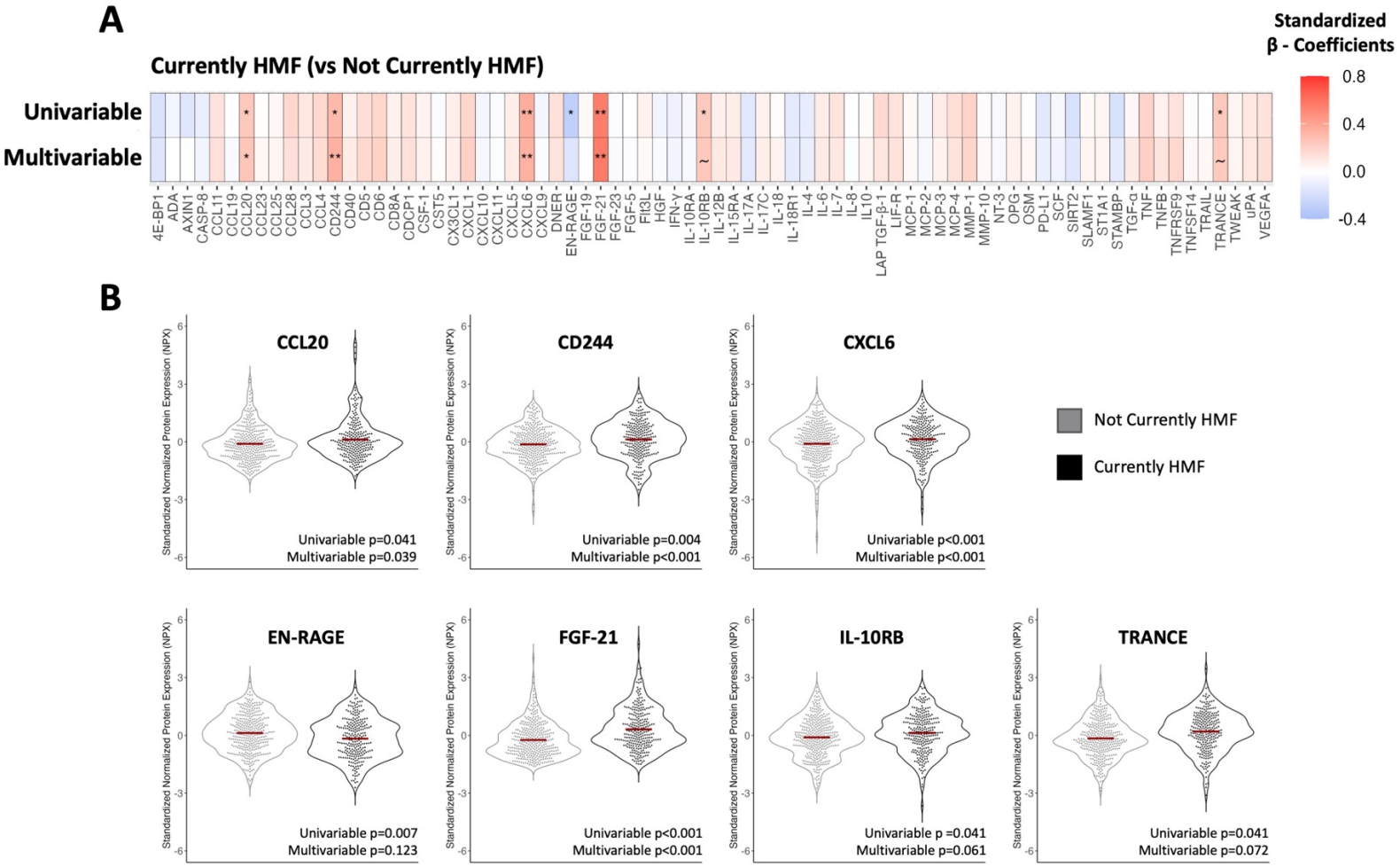


Figure 4. Associations between current HMF status and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (full study population, n=605). (A) Standardized β-coefficients obtained from univariable and multivariable (adjusted for time until blood sample centrifugation, study site, and infant sex) linear regression models that used infant current HMF status to predict serum biomarker level. All p-values were FDR-corrected using the Benjamini-Hochberg method. ~p<0.1, *p<0.05, **p<0.01. **(B)** Differences in standardized NPX biomarker measures for biomarkers with significant results in univariable or multivariable regression models.

3.3.2. Inflammation-associated serum biomarker measures can predict infant current HMF status

Serum biomarker level differences between current HMF status groups were further investigated by evaluating the extent to which serum biomarkers can correctly predict infant current HMF status. This was evaluated using logistic regression models and corresponding receiver operating characteristic (ROC) curves. As expected, based on linear regression results, CCL20, CD244, CXCL6, EN-RAGE, and FGF-21 serum levels were significant predictors of infant current HMF status in univariable logistic regression models (**Figure 5, Supplementary Table 3**). FGF-21 had the highest odds ratio (1.71, 95% CI: 1.38 – 2.12) of all measured biomarkers – indicating a one standard deviation increase in serum FGF-21 level leads to a 1.7-fold increased likelihood of an infant currently receiving HM. All significant biomarkers (in univariable logistic regression), except EN-RAGE, had an odds ratio >1, indicating an increase in biomarker level is associated with current HMF status. CXCL6 and EN-RAGE were no longer significantly associated with current HMF status after adjusting for covariates. No biomarkers became significant ($p>0.05 \rightarrow p<0.05$) upon covariate adjustment.

FGF-21 had the highest univariable logistic regression model area under the ROC curve (AUC) value (0.69, 95% CI: 0.62 – 0.77) of all measured biomarkers (**Figure 6**). This biomarker AUC is considered "poor/fair" at predicting current HMF status, according to a guide on using biomarkers in diagnostic testing.[169] This indicates FGF-21 serum levels are best at correctly predicting an infant's current HMF status, among all measured biomarkers. The AUC value for all significant biomarker logistic regression models, except CCL20, decreased upon covariate adjustment. Differences in multivariable and univariable model AUC values were not significant for any biomarkers (**Supplementary Table 4**). A logistic regression model incorporating the five

biomarkers significant in univariable logistic regression to predict infant current HMF status had an AUC value (univariable: 0.74 (95% CI: 0.66-0.81); multivariable: 0.70 (95% CI: 0.62-0.78)) higher than the best independent biomarker model AUC value (FGF-21 – univariable: 0.69 (95% CI: 0.62-0.77); multivariable: 0.67 (95% CI: 0.59-0.75)). This AUC is considered "fair" and indicates biomarkers have partially independent predictive abilities and are collectively better at predicting current HMF status, than any biomarker alone. A logistic regression model using all principal components derived from a principal component analysis of all 76 biomarkers to predict infant current HMF status had an AUC value (univariable: 0.63 (95% CI: 0.55-0.72); multivariable: 0.63 (95% CI: 0.54-0.71) lower than the logistic regression model that used all five significant biomarkers as independent predictors of infant current HMF status (**Supplementary Figure 7)**.

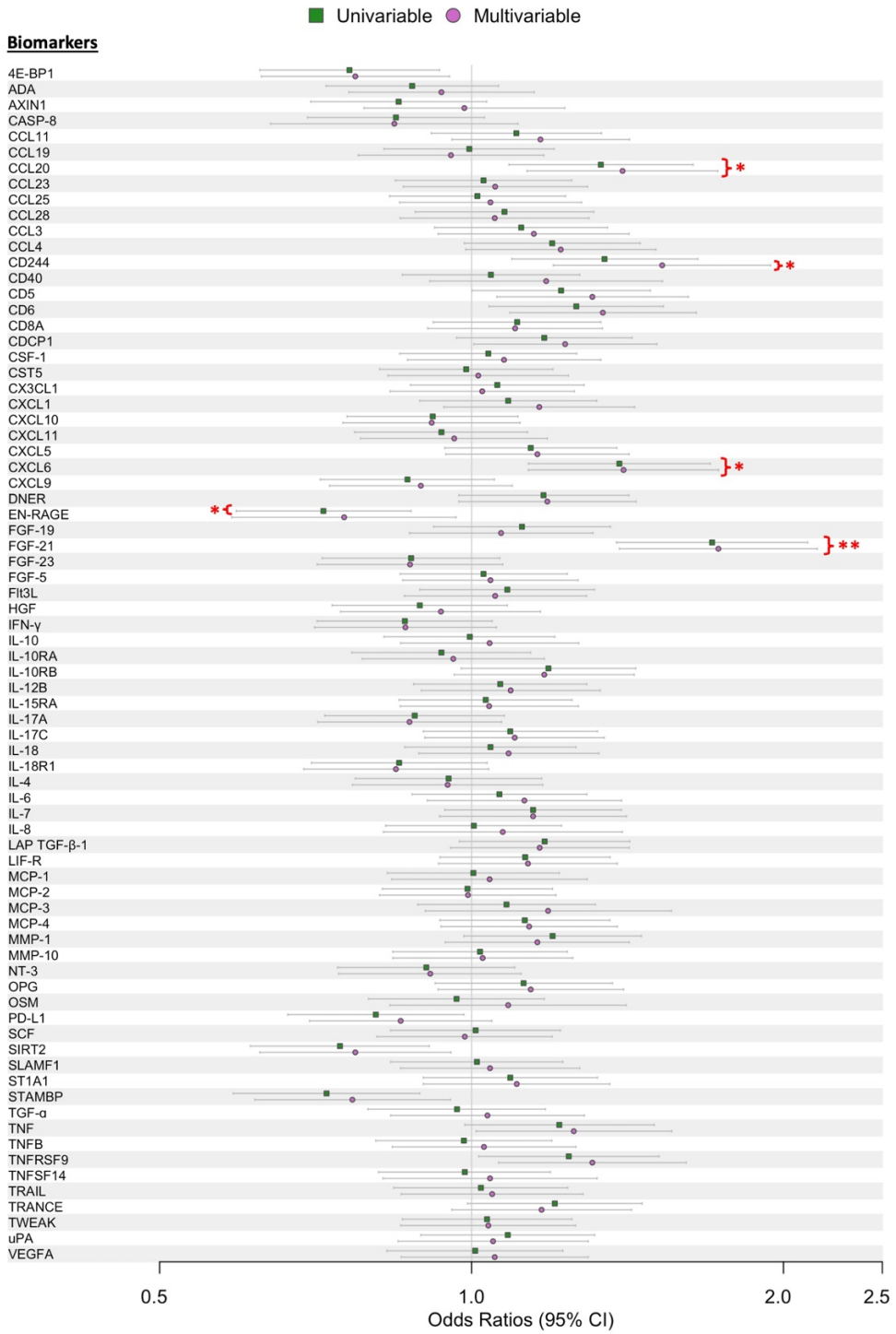


Figure 5. Associations of infant serum biomarker levels with current HMF status in one-year-old CHILD cohort infants (full study population, n=605). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) logistic regression models that use biomarker levels, independently, to predict infant current HMF status. The not currently HMF group was used as reference. Odds ratios are per one standard deviation increase of standardized biomarker level. The Benjamini-Hochberg method was used for FDR p-value correction. *p<0.05, **p<0.01.

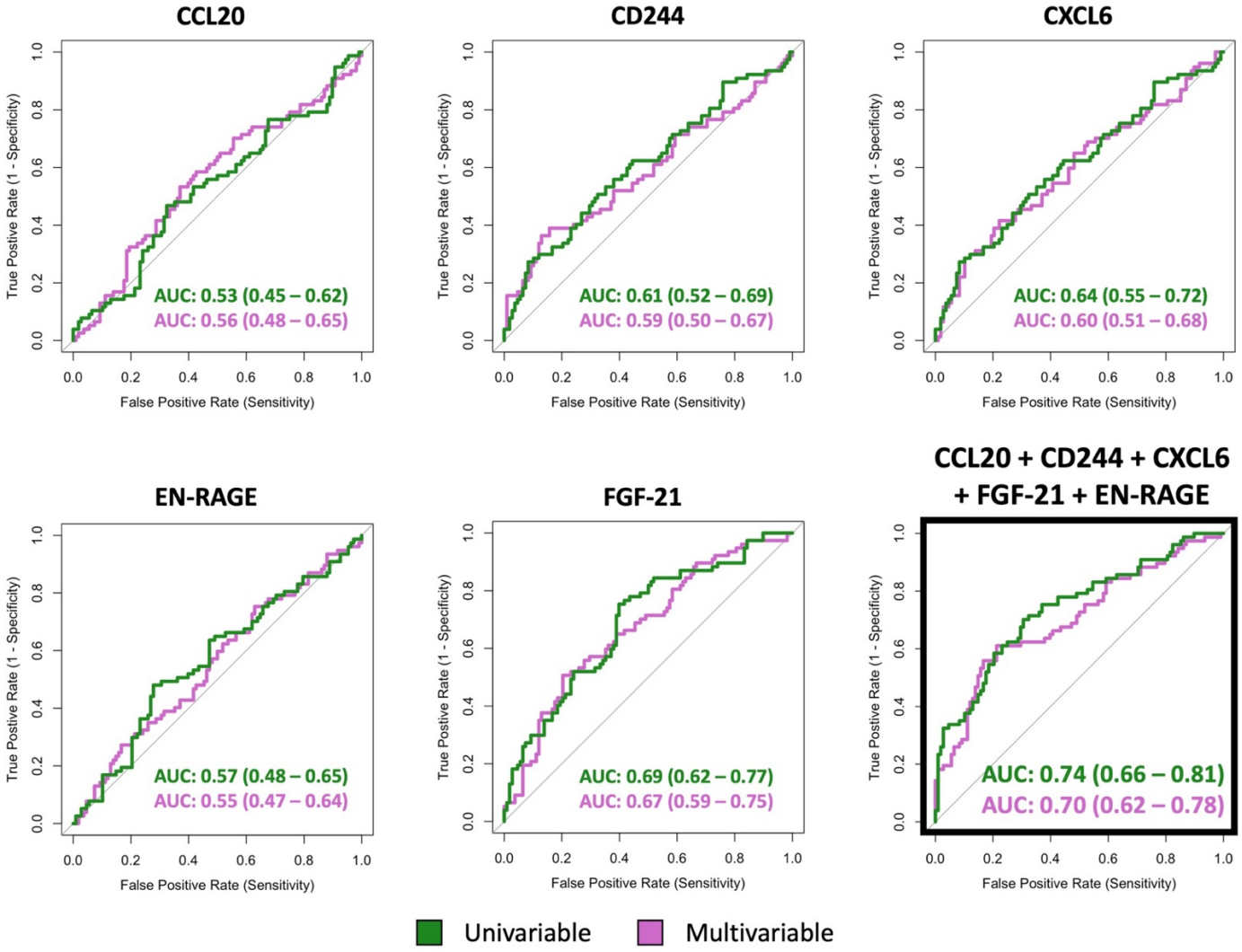


Figure 6. Associations of CCL20, CD244, CXCL6, EN-RAGE, FGF-21, and all five biomarkers collectively, with current HMF status of one-year-old CHILD cohort infants (full study population, n=605). Figures show receiver operating characteristic (ROC) curves and respective area under the ROC curve (AUC) values for logistic regression models that used biomarkers (CCL20, CD244, CXCL6, EN-RAGE and FGF-21), individually and together, to predict infant current HMF status.

3.4. Investigating the association between history of HMF and inflammation-associated biomarker levels

Similar to the investigation of current HMF status, univariable linear regression models were used to investigate the association between history of HMF (HMF duration, exclusive HMF duration, and HMF method at three months of age) and inflammation-associated biomarker levels. History of HMF variables were individually used as predictors of serum biomarker levels in these models. Exclusive HMF duration and HMF duration were evaluated in both continuous and categorical variable forms. Overall, in contrast to current HMF status, history of HMF variables had little or no association with biomarker levels.

Continuous HMF duration and exclusive HMF duration had a marginally significant ($p < 0.1$) positive association with IL-7 serum levels in univariable linear regression **(Figure 7, Supplementary Table 5, Supplementary Table 6)**. The standardized β-coefficient for IL-7 was larger for exclusive HMF duration (0.08, 95% CI: 0.03 – 0.13) compared to HMF duration (0.05, 95% CI: 0.02 – 0.07). These variables did not have any other significant or marginally significant ($p<0.1$) associations with any other measured biomarker levels in univariable linear regression. Exclusive HMF duration lost marginal significance with IL-7 ($p<0.1 \rightarrow p>0.1$) after covariates were added as predictors to linear regression models.

The two- or three-month interval categorical HMF duration variables (infants grouped in intervals of two months and three months of HMF) were not significant predictors of any measured biomarker levels in univariable or multivariable linear regression models (**Supplementary Figure 8, Supplementary Figure 9, Supplementary Table 7, Supplementary Table 8).** A significant association was observed between the four-month

categorical HMF duration variable (infants grouped in intervals of four months of HMF) and IL-7 serum levels. Mean serum IL-7 levels were lower in infants that were HMF for 0 - ≤4 months compared to infants that were HMF for >8 months HMF (univariable: standardized β: -0.56 (95% CI: -0.84 - -0.27), $p<0.05$; multivariable: standardized β: -0.59 (95% CI: -0.87 - -0.31), $p<0.01$) (**Figure 8, Supplementary Table 9).** Mean IL-7 serum levels were also lower for infants that stopped receiving HM >5 months before one-year blood draw in comparison to infants that stopped receiving HM ≤5 months before one-year blood draw and infants that were still receiving HM at one-year CHILD blood draw (**Figure 9**).

The two- or three-month interval categorical exclusive HMF duration variables (infants grouped in intervals of two months and three months of exclusive HMF) were not significant predictors of any measured biomarker levels in univariable or multivariable linear regression (**Supplementary Figure 10, Supplementary Figure 11, Supplementary Table 10, Supplementary Table 11).**

HMF method at three months of age was not a significant predictor of any measured biomarker levels in univariable or multivariable linear regression (**Figure 10, Supplementary Table 12).**

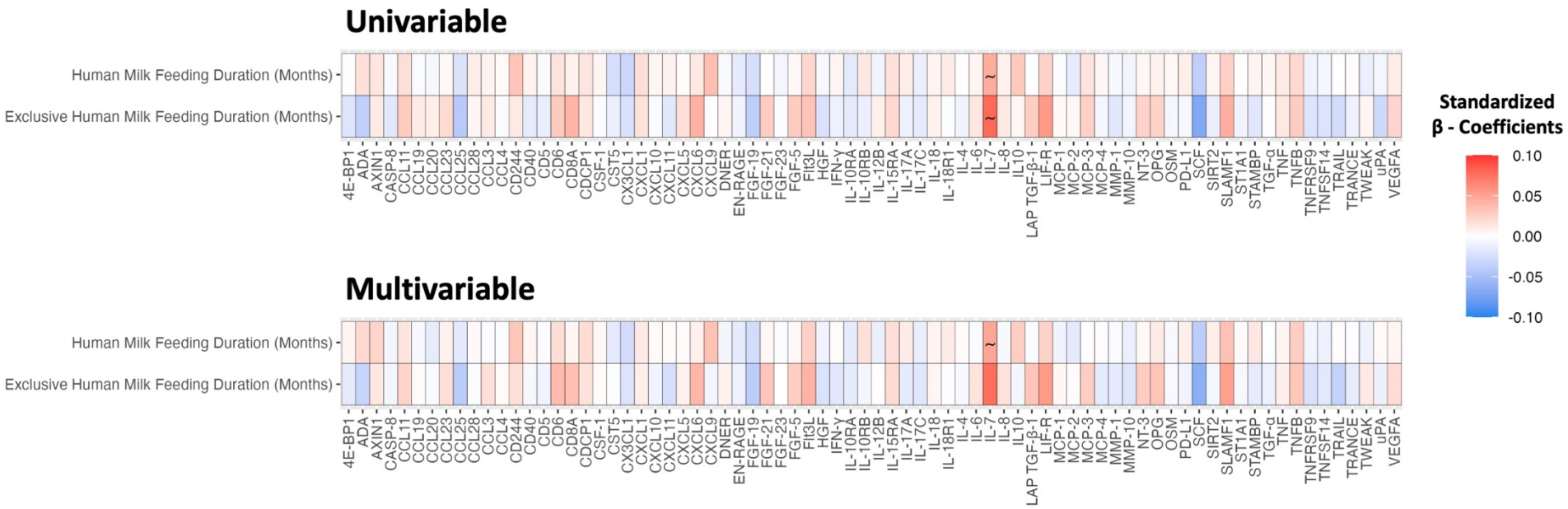


Figure 7. Associations of both continuous HMF duration and continuous exclusive HMF duration with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusted for time until blood sample centrifugation, study site, and infant sex) linear regression models predicting biomarker level using either continuous HMF duration or continuous exclusive HMF duration. All p-values were FDR-corrected using the Benjamini-Hochberg method. ~p<0.1, *p<0.05, **p<0.01.

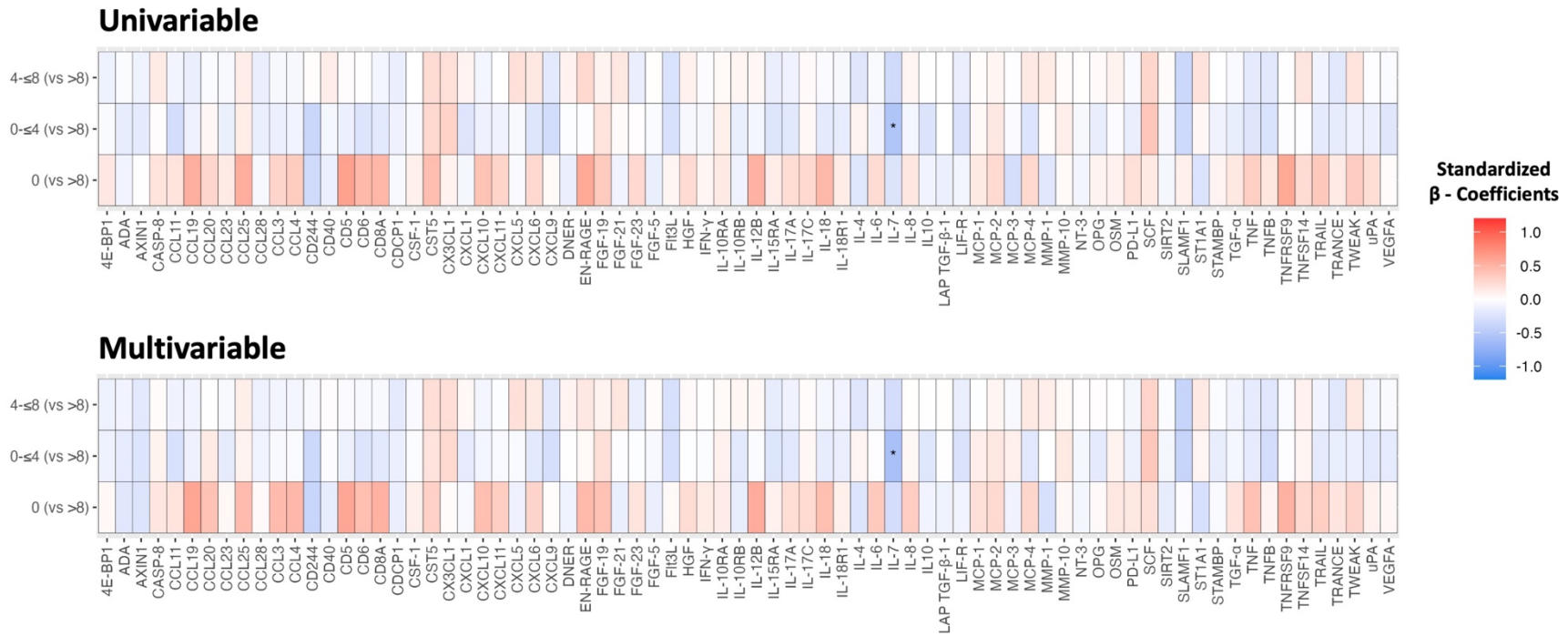


Figure 8. Associations between categorical HMF duration (grouped into four-month intervals) and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusting for time until blood sample centrifugation, study site, and sex) linear regression models that predicted individual biomarker level with categorical HMF duration (grouped into four-month intervals). The Benjamini-Hochberg method was used for FDR p-value correction. ~p<0.1, *p<0.05, **p<0.01.

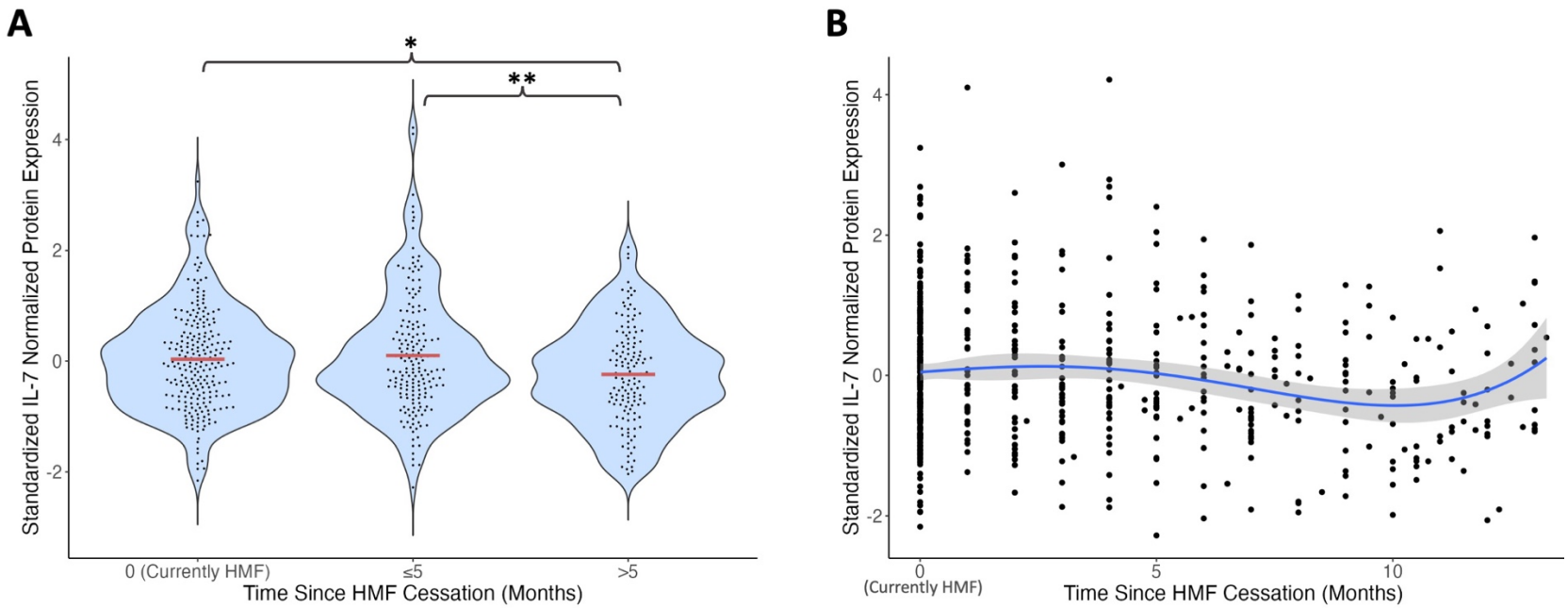


Figure 9. The relationship of IL-7 with time since HMF cessation for CHILD cohort infants <14 months of age (n=599). (A) Standardized IL-7 levels for infants receiving HM for ≤ five months, infants receiving HM for >five months, but not at blood sample collection, and infants receiving HM at blood sample collection. **(B)** Standardized IL-7 levels and time since HMF cessation of infants included in this current study. *p<0.05, **p<0.01, ANOVA and Tukey HSD test. Study infants were excluded from these figures if they were ≥ 14 months of age at the one-year CHILD clinic visit.

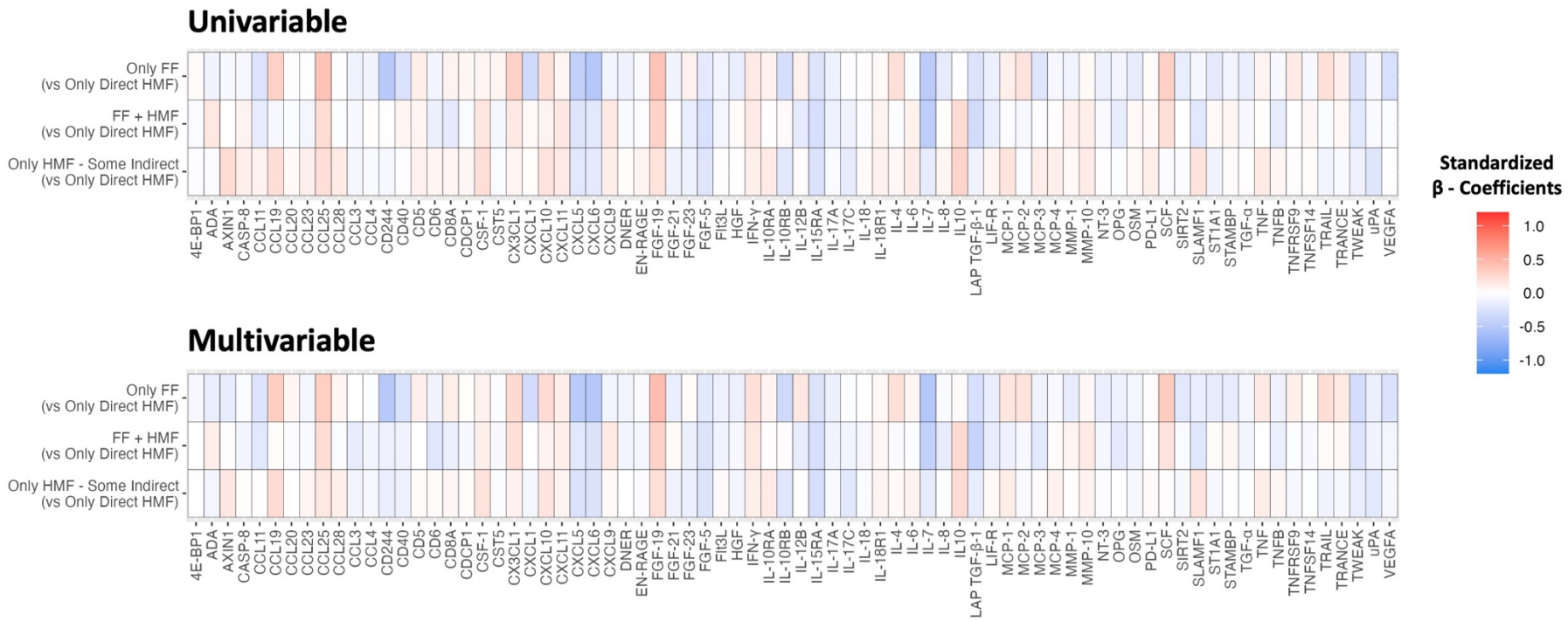


Figure 10. Associations between HMF method at three months of age and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusting for time until blood sample centrifugation, study site, and sex) linear regression models that predicted individual biomarker level with HMF method at three months of age. The Benjamini-Hochberg method was used for FDR p-value correction. ~p<0.1, *p<0.05, **p<0.01. No significant associations were observed after FDR correction.

3.5. Current HMF status, but not history of HMF, accounts for inflammation-associated biomarker variation

Redundancy analysis indicated current HMF status was significantly associated with the cumulative variation of all Olink biomarkers (R^2 - 0.48% variance explained, $p<0.05$) (**Table 6)**. This proportion was comparable to that explained by sex (R^2 - 0.40%, $p<0.05$), age at blood sample collection (R^2 - 0.42%, $p<0.05$), vaccinations (R^2 - 0.65%, $p<0.01$), age at first introduction to solids (R^2 - 0.46%, $p<0.05$), household pets with fur (R^2 - 0.44%, $p<0.01$), maternal marital status (R^2 - 0.72%, $p<0.05$), and maternal years of education (R^2 - 0.33%, $p<0.05$). History of HMF variables (HMF duration, exclusive HMF duration, and HMF method at three months of age) were not significantly associated (all $p>0.05$) with the cumulative variation of all Olink biomarkers. Notably, maternal race (R^2 – 1.21%, $p<0.01$), study site (R^2 – 2.92%, $p<0.001$) and time until blood sample centrifugation (R^2 - 6.34%, $p<0.001$) accounted for the largest proportion of all Olink biomarker variance. A redundancy analysis model that combined all variables found to be significant in univariable redundancy analysis accounted for 12.48% of all Olink biomarker variance.

Table 6. Associations of infant, household, study, and family variables with the cumulative variation of Olink biomarker measures in one-year-old CHILD cohort infants (full study population, n=605). Redundancy analysis values (R^2) indicate the percent (%) of total variation explained by each individual variable. Shading reflects magnitude of R^2. The Benjamini-Hochberg method was used for FDR p-value correction. ~p<0.10, *p<0.05, **p<0.01, ***p<0.001.

Univariable Analysis	Biomarkers (n=75)[1] R^2 (%)	p
Infant Feeding Practice Variables		
Current HMF status	0.48	*
HMF duration[2]	0.33	
Exclusive HMF duration[2]	0.28	
HMF method at three months of age[2]	0.84	
Age at first introduction to formula	0.38	
Age at first introduction to solids	0.46	*
Time since HMF cessation	0.43	*
Infant Variables		
Biological sex	0.40	*
Birth weight	0.17	
Age at blood sample collection	0.42	*
Gestational age	0.25	
Infant antibiotic use in the first year of life	0.14	
Positive skin prick test at one year of age	0.18	
Received all routine provincial vaccinations at one year of age	0.65	**
Birth delivery method	0.16	
Household Variables		
Number of different pollution sources within 100m of infant home	0.45	
Participant older siblings	0.21	
Household income	0.92	
Household pets with fur	0.44	*
Study Variables		
Time until blood sample centrifugation	6.34	***
Study site	2.28	***
Family Variables		
Maternal age at time of delivery	0.28	
Maternal marital status	0.53	**
Maternal years of education	0.33	*
Maternal race	1.21	**
Maternal cigarette smoking status	0.17	
Maternal second-hand smoking exposure	0.19	
Daily maternal alcohol consumption	0.28	
Maternal diet quality	0.18	
Maternal body mass index	0.23	
Maternal positive skin prick test	0.21	

Paternal positive skin prick test	0.18	
Multivariable Analysis		
All variables significant in univariable RDA	12.24	***

[1]FGF-5 was excluded due to NA data for 45 participant samples. [2]Investigated using the subset of infants not currently HMF (n=347).

Chapter IV: Discussion

Compared to formula feeding, human milk feeding (HMF) has been associated with a decreased risk of respiratory infections in infancy, asthma, obesity, diabetes, and inflammatory bowel disease (IBD).[1] These associations have been attributed, at least in part, to the presence of compounds within HM that are thought to support infant immune system activity and development (e.g. cytokines, chemokines, immune cells, microbiota, miRNAs, immunoglobulins, enzymes).[1] However, despite these established associations and generally accepted hypotheses, the association of HMF status and history with infant immune system activity and development is not well understood.

This thesis research investigated the association of both current HMF status (HMF at blood sample collection) and history of HMF (HMF duration, exclusive HMF duration, HMF method at three months of age) with inflammation-associated biomarker levels in one-year-old infants. This cross-sectional investigation provides insight on the potential influence of i) current HMF on immune system activities of one-year-old infants, and ii) history of HMF on immune system development in the first year of life. To our knowledge, this is the first cohort study to investigate associations between a panel of inflammation-associated serum biomarkers and these infant feeding practices.

4.1. Interpreting associations between infant current HMF status and inflammation-associated serum biomarkers

Univariable linear regression analysis results show infants receiving HM had significantly higher **CCL20, CD244, CXCL6, FGF-21, IL-10RB,** and **TRANCE** serum levels, and significantly lower **EN-RAGE** serum levels, in comparison to infants not receiving HM.

Notably, associations with **IL-10RB, TRANCE,** and **EN-RAGE** lost significance upon covariate adjustment, suggesting covariates explain some of the biomarker variation initially associated with current HMF status in univariable linear regression. These biomarkers and their biological functions are discussed individually below. While several are known to be present in HM (CCL20,[170] CD244,[1] CXCL6,[171] FGF-21[172]), it was not possible in our study to determine their origin (i.e. maternal or infant) in the serum samples analyzed. It is unknown if these HM-derived biomarkers can permeate intestinal barriers and enter the infant blood stream, although this has been observed for HM immune cells (e.g. T and B cells) and similar biomolecules (e.g. TGF-β).[1] It is important to note variation in early life intestinal barrier permeability,[1] or other early life physiology changes, may influence the degree of HM biomolecule permeation.

CCL20 (Chemokine C-C motif ligand 20) serum level was significantly higher in infants currently receiving HM. CCL20 is a chemokine constitutively expressed and regulated by the intestinal epithelium.[173] It is also present at relatively high levels, compared to other biomolecules, in HM (~200-1800 pg/mL). The concentration of CCL20 is highest in colostrum and gradually decreases until weaning.[170] Thus, maternal CCL20 derived from HM ingested by the infant may account for the higher CCL20 serum levels observed among HMF infants in our study. It is also possible that HM upregulates infant CCL20 production through upstream mechanisms, yet no research, to our knowledge, has examined this possibility.

CCL20 is the sole ligand of CCR6 – a receptor expressed on Th17 cells, Tregs, B cells, immature dendritic cells, and weakly on neutrophils.[174,175] If CCL20 is provided to an infant through HM, it can be assumed that CCL20 concentrations are high near the intestine of infants receiving HM. This indicates infants currently receiving HM may have an increased recruitment of CCR6 expressing immune cells to the gut, and subsequently, more gut antigen-immune cell

interactions.[172] An increase in the number of antigen-presenting immature dendritic cells, inflammatory effector Th17 cells, and suppressive Treg cells near the gut could have mixed outcomes for an infant. The Th17:Treg, or pro-inflammatory : anti-inflammatory activity ratio, depends on cell abundance and level of activation, as well as the milieu of cytokines and biomolecules in a given microenvironment.[176] Given the neutralizing and anti-inflammatory properties of HM,[1] I speculate an increase in immune cell recruitment to the gut of HMF infants does not have inflammatory consequences. Immature dendritic cells are known to induce immunosuppressive Treg differentiation and coinhibitory CTLA-4 or PD-1 molecule expression on activated T cells.[177] Furthermore, infants receiving HM have higher Treg levels relative to infants receiving formula.[96] This suggests that, if HM-provided CCL20 leads to an increase in the recruitment of CCR6 expressing immune cells to the gut, the resultant environment is likely to be more anti-inflammatory compared to infants not receiving HMF. To our knowledge, gut mucosal site and lamina propria inflammation-associated biomarker milieu and immune cell abundance, subtype, and activation level differences have not yet been comprehensively investigated between infants or animal models receiving and not receiving breastmilk.

Interestingly, 2'-fucosyllactose and 6'-sialyllactose – abundant HM oligosaccharides – inhibit CCL20 release in antigen-antibody complex stimulated intestinal epithelial cell lines.[178] Furthermore, *Bifidobacterium infantis,* a species enriched in the gut microbiome of HMF infants, has been shown to attenuate baseline secretion of CCL20 in human intestinal epithelial cells.[179] This suggests HM may inhibit infant epithelial cell CCL20 release while simultaneously providing an infant with CCL20. Infant CCL20 expression and subsequent immune cell migration is known to be induced by inflammatory cytokines and in response to inflammatory stimuli (e.g. lipopolysaccharide).[180,181] Furthermore, epithelial cell CCL20 release is accompanied

by the release of other pro-inflammatory biomolecules (e.g. TNF-α).[182] Given this, I speculate HM may create an environment with high HM-provided CCL20 levels, but low levels of epithelial cell inflammatory activity. This may induce recruitment, but not activation, of immune cells to the gut.

CD244 (cluster of differentiation 244, 2B4) serum level was significantly higher in infants currently receiving HM. CD244 is a signaling lymphocytic activation molecule immunoregulatory transmembrane receptor expressed on NK cells, certain T cell subsets, dendritic cells, and myeloid-derived suppressor cells.[183] Transmembrane proteins, while detectable in serum, are present in relatively low abundance compared to proteins without transmembrane components.[184] No soluble version of CD244 has been identified.
HM contains CD244 expressing lymphocytes, NK cells, dendritic cells, and myeloid-derived suppressor cells; however, the abundance of CD244-expressing cells in HM has not been studied directly.[1,185] HM immune cells have been proven capable of permeating an infant intestinal membrane[1]; therefore, the presence of HM CD244 expressing cells in an infant bloodstream may account for the higher CD244 serum levels in infants currently receiving HM. HM may also upregulate CD244 expression on existing immune cells, support the proliferation of CD244 expressing immune cells, or induce differentiation into CD244 expressing immune cells. These alternate scenarios may also explain the increase in CD244 serum level observed in infants currently receiving HM. To our knowledge, no studies have investigated these scenarios; however, infants receiving HM have a higher number of CD244 expressing Tregs, compared to infants receiving formula.[96] Determining if higher Treg, or other immune cell (e.g. NK cell), numbers are responsible for the higher CD244 serum levels in infants currently receiving HM is a direction for future research. *In vitro* studies indicate low CD244 surface levels is associated

with murine NK cell activation and high CD244 surface levels is associated with murine NK cell inhibition.[183] If HMF induces greater CD244 expression on immune cells, I speculate immune cell activities in infants currently receiving HM may be inhibited to a higher degree, relative to infants not currently receiving HM. To our knowledge, no studies have investigated differences in immune cell CD244 expression levels between infants currently receiving HM and infants not currently receiving HM.

CXCL6 (CXC ligand 6, granulocyte chemotactic peptide 2) serum level was significantly higher in infants currently receiving HM. CXCL6 is a chemokine produced by fibroblasts, chondrocytes, epithelial cells, and mesenchymal cells that binds to CXCR1 and CXCR2 expressed on neutrophils, T cells, and mast cells.[186–188] HM contains CXCL6 (<1.6-936 pg/mL)[171]; therefore, maternal CXCL6 derived from HM ingested by the infant may account for the higher CXCL6 serum levels observed among HMF infants in our study. No research, to our knowledge, has determined if HM is capable of upregulating infant CXCL6 production, although *Bifidobacterium breve*, a microbiota selectively cultivated in the gut microbiome of HMF infants, has been associated with upregulating CXCL6 gene expression in intestinal epithelial cells.[189]

In addition to its chemoattractant ability, CXCL6 promotes epithelial cell to mesenchymal cell transition.[190,191] The elevated serum CXCL6 levels in infants currently receiving HM suggests these infants may have i) more CXCR1 and CXCR2 expressing cell (e.g. neutrophil, T cell, and mast cells) migration – likely to the gut, and ii) increased epithelial cell – mesenchymal stem cell transitions, relative to infants not currently receiving HM. As mentioned previously, the recruitment of immune cells to the gut may have mixed outcomes (e.g. inflammation, tolerance induction) given the milieu and activity of cells and bioactive molecules

(e.g. cytokines, chemokines).[97] Mesenchymal stem cells are associated with organ development, tissue regeneration, and monocyte polarization toward the immunosuppressive and anti-inflammatory M2 phenotype; therefore, elevated mesenchymal stem cell numbers may lead to an increase in anti-inflammatory responses and tissue development.[186,192] Additionally, M2 macrophages secrete TGF-β – a component also contained within HM[1] – that can induce immunosuppressive Treg formation.[192] To our knowledge, no research has compared mesenchymal stem cell numbers between infants currently receiving HM and infants not currently receiving HM.

FGF-21 (fibroblast growth factor 21) serum level was significantly higher in infants currently receiving HM. FGF-21 is a peptide hormone expressed by the liver, adipocytes, pancreas, and brain.[193] HM contains FGF-21 (65-70 pg/mL)[194] ; therefore, the higher FGF-21 serum levels observed among HMF infants in our study may reflect maternal FGF-21 derived from HM ingested by the infant.[172] Hepatic FGF-21 gene expression can be induced by HM fatty acid stimulation; therefore, higher FGF-21 levels in HMF infants cannot be attributed solely to HM-derived FGF-21.[194]

Higher FGF-21 serum levels in infants receiving HM may have implications for infant metabolism. FGF-21 has been positively associated with the secretion of digestive peptides and enzymes such as gastric inhibitory polypeptide and glucagon-like peptide incretins, lactase, and maltase-glucoamylase.[172,195] FGF-21 serum levels have also been positively associated with leptin sensitivity in high-fat diet fed rats.[86] Furthermore, HM provided FGF-21, as well as hepatic FGF-21 derived from HM fatty acid stimulation, have been shown to interact with FGF-21 dependent D2R receptors on hypothalamic neurons to induce long-lasting brown adipose tissue thermogenesis – a process vital for neonates as they adapt to the extrauterine environment.[86,172]

This interaction has been associated with reduced adiposity, dyslipidemia and weight gain in mice. This evidence suggests infants receiving HM may have i) increased intestinal peptides and digestive enzymes levels, ii) increased leptin sensitivity, and iii) long-lasting increases in brown adipose tissue thermogenesis rate, relative to infants not currently HMF. These mechanisms may underlie the reduced risk of overweight and obesity associated with HMF.[1]

Higher FGF-21 serum levels in infants receiving HM may also have implications for infant immunity. FGF-21 supplementation has been associated with lymphocyte maturation in newborn rats. FGF-21 supplemented rats also showed increased IgG synthesis at 14 and 21 days old, compared to control rats. Additionally, FGF-21 supplemented rats were more Th2 biased – indicated by a lower IFN-γ (Th1 associated) : IL-4 (Th2 associated) ratio, compared to control rats.[101] FGF-21 has also been shown to reduce pro-inflammatory cytokine (i.e. IL-17, TNF-α, IL-1B, IL-6, IL-8, MMP3) production and increase anti-inflammatory cytokine (i.e. IL-10) production in rats.[100] Nakayama et al. showed FGF-21 knockout mice have a decreased number of mature thymocytes compared to control mice, suggesting FGF-21 has a role in thymocyte development. These authors also hypothesize FGF-21 may facilitate the selection or apoptosis of developing T cells.[196] This cumulative evidence indicates elevated FGF-21 may influence thymocyte composition and decrease the overall pro-inflammatory Th1-like : anti-inflammatory Th2-like activity ratio of infants receiving HM.

IL-10RB (IL-10 receptor subunit β) serum level was marginally higher in infants receiving HM. IL-10RB is a subunit of the transmembrane IL-10 receptor required for IL-10 signal transduction.[197] IL-10R is considered a vital structural component in maintaining inflammatory equilibrium and is ubiquitously expressed on most hematopoietic cell types. HM

immune cells are assumed to express this vital anti-inflammatory receptor subunit; however, HM immune cell IL-10RB expression has not yet been directly studied. These associations suggest infants receiving HM may have i) more IL-10R expressing immune cells, or ii) immune cells that express more IL-10R, relative to infants not currently HMF.

TRANCE (tumor necrosis factor-related activation-induced cytokine) serum level was marginally higher in infants receiving HM. TRANCE is a tumor necrosis factor family cytokine expressed by lymphoid organs and T cells. TRANCE binds to TRANCE-R - a receptor on mature dendritic cells - and is associated with T helper cell activity regulation and dendritic cell maturation.[198] TRANCE is also associated with bone loss and the differentiation of monocyte/macrophage lineage cells into bone resorbing osteoclasts.[199] TRANCE expression in HM has not been studied. These associations suggest infants currently receiving HM may have i) different dendritic cell induced T cell activities, ii) more osteoclasts, and iii) more well developed lymphoid tissues or T cell populations, relative to infants not currently HMF.

EN-RAGE (extracellular newly identified receptor for advanced glycation end products binding protein, S100A12) serum level was significantly **lower** in infants currently receiving HM. This was the only biomarker found at significantly lower levels in infants currently receiving HM, compared to infants not receiving HM in this study. EN-RAGE is a calcium-binding pro-inflammatory protein secreted by activated granulocytes, macrophages, and lymphocytes in response to inflammatory challenges (e.g. antigens). EN-RAGE has not, to our knowledge, been measured in HM. EN-RAGE binds to RAGE (receptor for advanced glycation end products) to induce pro-inflammatory cytokine (e.g. IL-1B, TNF-α) and adhesion molecule (e.g. ICAM-1, VCAM-1) production through intracellular signal cascade (i.e. MAP-kinase and

nuclear factor KB) activation.[200] EN-RAGE has been considered to be a non-invasive marker of gut inflammation in IBD patients;[201,202] therefore, lower EN-RAGE serum levels indicate infants currently receiving HM may have a lower degree of gut inflammation. We speculate HM antigen neutralizing, gut microbiome composition regulating, and intestinal barrier reinforcing abilities may underly this seemingly lower degree of gut inflammation.[1]

Ordering biomarkers according to hierarchical clustering analysis indicated that current HMF status may be associated with biomarker clusters (**Supplementary Figure 6).** Not all biomarkers in apparent clusters had a significant relationship with current HMF status; however, some apparent biomarker clusters share the same direction of association. This suggests a relationship of current HMF status with biomarkers found **not** significant in linear regression analysis may exist, although not captured by the analysis in this current study. For example, T cell surface glycoproteins CD5 and CD6[203] are in a cluster positively associated with current HMF status. Increased levels of these biomarkers may reflect an increase in the T cell count of infants currently HMF. CXCl1 and MCP-4 are chemokines found in HM[171,204] that are also in a cluster positively associated with current HMF status. The supplementation and subsequent increase in the level of these biomarkers in currently HMF infants may support my hypothesis that currently HMF infants may have an increased recruitment of immune cells to the gut.

Consistent with linear regression results, **CCL20, CD244, CXCL6, FGF-21,** and **EN-RAGE** were also found to be significant predictors of current HMF status in univariable logistic regression analysis. AUC values for significant biomarker univariable logistic regression models ranged from 0.53 [95% CI: 0.45-0.62] (EN-RAGE) to 0.69 [95% CI: 0.62-0.77] (FGF-21). Covariate adjustment did not meaningfully change the results. When applied to diagnostic testing, AUC values between 0.8-0.9 are considered as "good" prediction, 0.7-0.8 as "fair", 0.6-

0.7 as “poor”, and 0.5-0.6 as “fail.”[169] Thus, the individual biomarker associations identified here would all be considered either “poor” or “fail”. However, it is important to note that these guidelines are intended to classify biomarker prediction of disease states (e.g. disease or no disease) or events (e.g. mortality or no mortality).[205–207] The intention of this analysis was not to diagnose current HMF status, which does not constitute disease states, but was to gain an indication of biomarker level distinction between infant groups. Therefore, we argue the modest, yet significant biomarker model AUC values reflect a moderate and meaningful difference in biomarker serum levels according to current HMF status. Furthermore, the amount of HM ingested is certainly variable (but unfortunately not documented) among infants receiving HM in this study – suggesting the association between current HMF status and serum biomarker levels may be underestimated by this current study.

Notably, multi-biomarker logistic regression models (incorporating CCL20, CD244, CXCL6, EN-RAGE, and FGF-21) were better at predicting current HMF status (AUC: 0.74 [95% CI: 0.66-0.81]) compared to any individual biomarker alone. This indicates significant biomarkers have independent predictive abilities, meaning biomarker ability to predict current HMF status vary among infants. This may suggest significant biomarkers do not all have the same temporal relationship with current HMF status. For example, the HMF-associated serum level elevation for one biomarker may persist between HMF events, whereas the HMF-associated serum level elevation for another biomarker may only persist for a couple hours. Furthermore, the volume of HM received by an infant may mediate the association between inflammation-associated biomarkers and current HMF status. For example, infants receiving relatively large volumes of HM may display larger associations between inflammation-associated serum biomarker level and current HMF status, relative to infants receiving smaller

volumes of HM. The CHILD Cohort Study did not capture the volume of HM received or the time since receiving any HM at a resolution that will allow us to investigate these possibilities. The associations between inflammation-associated serum biomarkers and current HMF status may also vary for infants with different demographic characteristics. For example, some biomarkers may better predict current HMF status for biologically male infants compared to biologically female infants, and vice versa.

Collectively, these linear and logistic regression results suggest infant serum research investigating **CCL20, CD244, CXCL6, FGF-21,** and **EN-RAGE** should account for current HMF status. These results also suggest current HMF status may be important to account for in infant serum research investigating **IL-10RB** and **TRANCE**, and potentially other serum proteins related to immune physiology.

4.2. Interpreting associations of infant history of HMF and inflammation-associated serum biomarkers

Investigating history of HMF (HMF duration, exclusive HMF duration, HMF method at three months of age) revealed one marginally significant positive association between IL-7 and both continuous HMF duration and exclusive HMF duration variables. Comparing serum biomarker levels among categorical HMF duration groups found infants that received HM for >0-≤4 months had lower IL-7 serum levels compared to infants that received HM for >8 months.

IL-7 (interleukin 7) is produced by epithelial and stromal cells in lymphoid organs such as the thymus and bone marrow.[208] IL-7 is found in HM;[209] however, was not found to be significantly associated with current HMF status in this current study. The positive association of

IL-7 with both exclusive HMF duration and HMF duration, but not current HMF status, indicate IL-7 may remain elevated in infants or gradually decreases, for several months after HMF cessation. We found serum IL-7 level was higher in infants currently receiving HM and infants that stopped receiving HM ≤5 months ago compared to infants that stopped receiving HM >5 months ago, supporting our speculation that IL-7 persists after HMF cessation (**Figure 9A)**.

The marginally significant positive association of IL-7 with both HMF duration and exclusive HMF duration may have implications for infant immune system development. IL-7 binds to IL-7R expressed on lymphoid cells (i.e. T and B cells)[210] and is positively associated with cytotoxic T cell differentiation and peripheral naïve and central memory T cell number.[211,212] This suggests HMF duration may be associated with infant T cell repertoire and T cell count. Previous literature noting a positive association between HMF duration and absolute number of Tregs, CD4+ and CD8+ T cells supports this hypothesis.[95,96] IL-7Rα - a subunit of IL-7R - deficient mice display defects in lymph node organogenesis.[213] Furthermore, thymic indices (thymus width X largest lobe area) have been positively associated with IL-7 serum levels in two month old infants.[209] This suggests HMF duration may be associated with infant organogenesis and thymus development. Previous literature has noted a positive association between exclusive HMF duration and thymus size; however, several studies suggest the volume of HM received by an infant at time of thymus measurement underlies this finding.[93,94] Furthermore, one study found a significant difference in thymus size between infants currently receiving HM at 10 months of age and 10-month-old infants that stopped receiving HM at 8 months.[214] This indicates that, while IL-7 may be associated with thymus development, the effects of IL-7 on thymus size are not long-lasting. Regardless, literature supports the hypothesis that the marginally significant positive association of IL-7 with both HMF duration and exclusive HMF duration may mediate T

cell proliferation and thymus development. The mechanisms underlying this association could be better understood using an animal model controlling for HM dose and environmental exposures.

To our knowledge, no previous literature has suggested a mechanism by which prolonged HMF upregulates IL-7 production. Thymus stromal cells are indirectly associated with epithelial cell growth[215] and produce IL-7[210]; therefore, the increase in IL-7 may be mediated by an increase in thymus stromal cell number, or increase in IL-7 stromal cell production, that may accompany an increase in thymus size. HMF-associated thymus enlargement persists for a period after HMF cessation, but eventually subsides.[216] IL-7 follows a similar pattern – it persists at an elevated serum level for a period after HMF cessation, but eventually decreases (**Figure 9B).** This shared pattern lends support to the hypothesis that thymus stromal cells produced IL-7 may underly the positive relationship between HMF duration and serum IL-7 levels. HM may also induce IL-7 gene expression upregulation through epigenetic mechanisms.[217]

It is important to note the lack of inflammation-associated biomarkers and history of HMF associations does not indicate history of HMF variables are not associated with infant immune system development. Inflammation-associated serum biomarker levels are tightly regulated, which limits their ability to reflect differences in immune system structures (immune cells, mucosal immune sites) or biological processes, particularly in the absence of an immune challenge. Infants in this study are considered healthy; therefore, the association between history of HMF and immune system *responses* to immune challenges, such as a bacterial infection, are not captured. Furthermore, tissue-resident immune components (e.g. tissue-resident memory T cells) are not present in venous blood;[218] therefore, capturing potential infant feeding practice associated differences in tissue-resident immune component imprinting is extremely limited in

this study. This work highlights the need for mechanistic studies exploring the association between history of HMF variables and immune system responses.

4.3. Infant feeding practices are associated with overall inflammation-associated biomarker variation

Redundancy analysis (RDA) was used to investigate the association of infant feeding practice variables with all inflammation-associated serum biomarkers together as a profile or system. Investigating inflammation-associated serum biomarkers as a profile can indicate associations with the overall inflammation-associated system captured by the Olink Target 96 Inflammation panel, and not just individual biomarkers. Furthermore, variables significantly associated with the variation of the serum biomarker profile should potentially be accounted for in untargeted serum infant serum proteomics and not just in specific biomarker infant serum research.

Current HMF status was associated with a significant amount of the pooled variation from all inflammation-associated biomarker measures in RDA. Notably, the percentage of overall inflammation-associated biomarker variation explained by current HMF status (0.48%) was comparable to that explained by variables known to impact infant immune function (e.g. infant biological sex (0.40%), maternal race (1.21%), maternal body mass index (0.23%).[205,206,219] This finding provides evidence suggesting current HMF status should be accounted for in untargeted infant serum proteomics. No history of HMF variables (HMF duration, exclusive HMF duration, HMF method at three months) were associated with a significant amount of the pooled variation from all inflammation-associated biomarker measures in RDA.

4.4. Overall implications of HMF on infant immune system activities and development

Overall, the observed associations between current HMF status and inflammation-associated serum biomarker levels supports hypotheses that infants receiving HM have increased anti-inflammatory cell responses, increased antigen tolerance, and enhanced metabolism, in comparison to infants not receiving HM (**Figure 11**).[1,220]

Associations of current HMF status with CCL20, CXCL6, EN-RAGE, and FGF-21 serum biomarker levels suggest infants currently receiving HM have relatively increased **anti-inflammatory immune cell responses**. I speculate HM-provided CCL20 and CXCL6 underly the elevated levels of CCL20 and CXCL6 chemokines observed in HMF vs non-HMF infants and reflect the indicate increased recruitment of CCR6, CXCR1, and CXCR2 expressing cells (Th17 cells, Tregs, neutrophils, dendritic cells) to the gut, a process that may induce outcomes including - but not limited to -immunosuppression, immune cell proliferation, and inflammation. However, the relatively decreased level of EN-RAGE (a biomarker of gut inflammation) among HMF infants suggests that inflammation is not elevated in these infants, and if anything, gut immune cell responses are dampened or suppressed by HMF. Furthermore, elevated levels of CXCL6 and FGF-21 among HMF infants suggest they may have an increased number of anti-inflammatory immune cells (e.g. M2 macrophages, Th2 associated cells), and Th2-associated cytokines, relative to infants not receiving HM – supporting the theory that HM is associated with increased anti-inflammatory cell responses.

These findings may also suggest infants receiving HM may be more likely to develop **antigen tolerance** (a general unresponsiveness or lack of pathogenic immunity in response to antigens) than to respond with an inflammatory response. Tolerance development has been associated with the blunting of inflammatory responses to dietary antigens and commensal

microbiota, and has been associated with prevention of food allergy, type 1 diabetes, and IBD.[1,221] Tolerance is thought to be induced by immune cell inactivation or deletion, regulatory cell engagement, cell differentiation changes, or immune barrier development.[222] Gerard Eberl's essay on immunity by equilibrium states tolerance may be a reflection of the inhibition of one general type of immunity (e.g. Th1-like) by another general type (e.g. Th-like).[97] In the context of infants receiving HM, this suggests increased anti-inflammatory cell and cytokine activity may suppress pro-inflammatory immunity and increase tolerance induction rate, compared to infants not receiving HM. We speculate this HMF-associated increase in anti-inflammatory activity may be the product of continued proliferation or survival of differentially adapted and stereotypically anti-inflammatory neonatal lymphoid cells in continually HMF infants. The increase in anti-inflammatory and Th2-like activity,[1,101] but not in allergic disease incidence,[223,224] in HMF infants, suggests the mechanisms in which HMF induces this Th2-like phenotype may be independent of the mechanisms in which Th2 immunity induces allergic disease. We speculate HMF-associated Th2-like immune cells, which may be induced in HMF-associated anti-inflammatory and immunosuppressive microenvironments (perhaps near the gut), may be of a different subtype than Th2 cells typically associated with allergic disease pathogenesis. Investigating the subtype of Th2-like immune cells in HMF infants may lend evidence to inform these hypotheses.

Literature showing Tregs – the anti-inflammatory and tolerance-associated T cells – are present at higher levels in infants receiving HM, compared to infants not receiving HM, further support HM as being tolerance inducing.[96] HMF neonates have been shown to have a specific and Treg-dependent reduction and delay in proliferative T cell response to non-inherited maternal antigens.[96,220] Furthermore, TGF-β – a cytokine required for Treg induction[225] – is one

of the most abundant biomolecules present in HM,[1] suggesting T cells in HM fed infants may be more likely to differentiate into Tregs in a immunosuppressive environment. Treg subtypes associated with current HMF are still relatively unknown. Murine models have shown HMF cessation associated gut microbiota expansion induce ROR γt+ Treg proliferation. This ROR γt+ Treg proliferation was also shown to be associated with inflammatory associated disease prevention.[121] I speculate that current HMF may promote the proliferation of GATA+ Tregs – a subtype associated with development, tissue repair, anti-inflammation, and Th2 immunity.[97] Furthermore, antigen-neutralizing and gut microbiome regulating HM properties may limit antigen-immune system exposures in infants currently HMF, which may lead to T cell inactivation, Treg formation, and tolerance induction.[1]

The associations between current HMF status and FGF-21 suggest infants receiving HM may have enhanced **metabolism**. More specifically, FGF-21 serum levels have been positively associated with intestinal peptide and digestive enzyme concentration,[172] leptin sensitivity,[86] and brown adipose tissue thermogenesis.[86] These associations indicate HM fed infants may have an enhanced ability to digest foods and regulate body weight.

The elevated level of CD244 observed in infants receiving HM may have various implications for these hypotheses. For example, this result may reflect an increase in tolerance inducing and anti-inflammatory Tregs, or immune cell activity differences. Determining the mechanism underlying CD244 differences according to current HMF status is required before speculating on the implications of this result further.

Interpreting associations between history of HMF and serum biomarker levels suggests HMF duration and exclusive HMF duration may influence thymus and T cell development.

Furthermore, the lack of associations between inflammation-associated biomarker levels and history of HMF suggest that, if more associations between history of HMF and immune system development or activity exist, they are not well reflected in biomarker levels. History of HMF associations with the thymus may impact naïve T cell heterogeneity, with implications for naïve T cell phenotype, function, dynamics, and differentiation status.[226] Naïve T cells are considered relatively quiescent; therefore, naïve T cell differences may not be reflected well in serum biomarkers. Furthermore, the association of HMF and gut microbiome composition[1] indicates history of HMF may influence the maturation and development of the gut microbiome in early life. Delayed or premature gut microbiome maturation has been associated with pediatric allergic disease[227] and may influence the reactivity of immune cells to oral antigens or intestinal pathogens. Differences in reactivity may not be captured well by examining inflammation-associated serum biomarkers of healthy infants; thus, different cellular-level techniques (e.g. flow cytometry) are required for examining potential associations between history of HMF and both naïve T cell subtypes and immune system reactivity.

Study findings	Infants currently HMF (*vs not currently HMF*) have:				
	↑ CCL20	↑ CD244	↑ CXCL6	↑ FGF-21	↓ EN-RAGE
Found in human milk?	✓	✓	✓	✓	?
Potential implication(s) of serum biomarker level difference for infant immune system activities	• Increased Treg and Th17 cell migration to the gut	• Increased number of CD244 expressing immune cells or increased CD244 expression on immune cells	• Increased neutrophil, dendritic cell, T cell migration to the gut • Increased epithelial cell to mesenchymal cell transitions	• Increased brown adipose tissue thermogenesis • Increased digestive enzyme level • Decreased Th1/Th2 cytokine and cell ratio	• Decreased gut inflammation
Potential implications of serum biomarker level differences for overall infant health	• **Increased anti-inflammatory immune cell responses** • **Increased antigen tolerance** • **Enhanced metabolism**				

Figure 11. Summary of biomarker associations with current HMF status and potential implications for infant immune system activities and overall health.

Chapter V: Strengths, Limitations, and Future Directions

5.1. Strengths

The use of CHILD Cohort Study data was a key strength of this study. CHILD Cohort Study questionnaires captured and allowed for relatively undescribed, unaccounted for, and unstudied infant feeding practices to be investigated in this current study. Furthermore, CHILD cohort questionnaire and hospital report data allowed for demographic characteristics to be evaluated and, for some variables, accounted for in statistical analysis.

The relatively large number of CHILD infants (n=605) included in analysis was another strength of this study. This sample size ensured the majority of research analysis had sufficient power to account for important confounders and detect meaningful associations.

This study measured biomarker levels in serum collected from all one-year-old study infants. The collection and analysis of serum of one-year-old human infants, for this number of infants, is relatively rare in existing literature. The abundance of inflammation-associated serum biomarker measures included in this research is another strength of this study. Investigating 76 inflammation-associated biomarkers provided this study with the ability to capture potential associations of infant feeding practices with a spectrum of immune system associated biological processes. Analysing this number of serum biomarkers provided this study with power to determine associations of infant feeding practices with a spectrum of inflammatory and immune response processes.

This study investigated the association between infant feeding practices and *healthy* infant inflammation-associated serum biomarkers. The immune system activities and

development of healthy infants is relatively understudied; thus, this current study provides a unique outlook on healthy immune system variation and potential associations with infant feeding practices. Investigating healthy infants provided us with the ability to speculate on how infants may react to antigen exposure, infection, or other disease conditions.

5.2. Limitations

Limitations of the CHILD cohort population, CHILD cohort questionnaires, 'healthy' infant criteria, statistical modelling, and serum biomarker research constitute the main limitations of this current study. This section specifically outlines how these limitations may have impacted this research.

The demographic distribution of participants in this study was not entirely reflective of the demographic distribution of Canada. Study participants were predominantly White (73.6%) and generally lacked racial representation (18.0% Asian, 2.6% Indigenous/First Nations, and 5.8% other races). This study also had an over-representation of high socioeconomic status (29.9% - $100,000-$149,999; 29.3% - $150,000 or over) compared to the general Canadian population.[228] Low socioeconomic status has been associated with an increase in systemic immune activation and inflammation[124]; therefore, this study may not accurately capture socioeconomic status-immune system associations present in the general Canadian population. This study did not have an even distribution of participants from CHILD study sites (27.4% - Vancouver; 22.3% - Edmonton; 35.2% - Toronto; 5.1% - Manitoba. This indicates this study may not capture, or may have an over-representation of, study-site-specific factors that may be associated with the infant immune system (e.g. pollution levels) or serum biomarker measures. 97% of infants included in this study (n=18) received HM at some point in the first year of life.

This is not reflective of the breastfeeding initiation rate in Canada (91%)[229] and limits the statistical power of the infant group that never received HM.

The CHILD cohort did not capture information regarding the volume of HM ingested, as well as the specific length of time since an infant last received HM. Variation in HM volume ingested by each infant at one year of age may add noise to statistical analysis and 'hide' potential associations. Furthermore, the time since receiving HM, even if only a few hours, may have an influence on serum biomarker levels. Accounting for these two variables would improve study power in determining relationships of infants feeding practices with serum inflammation-associated biomarkers. This cross-sectional study could not capture potential variation in current HMF status associations that may occur with infant physiology development and immune system maturation in early life.

The complete blood count exclusion criteria implemented in this current study excludes infants showing clear signs of active, or impaired immune system function (white blood cell count <6000 or >17500 mm^3).[141] It is important to note that complete blood count measures do not capture all infant immune system challenges or health conditions; therefore, infants investigated in this current study are not guaranteed to be "healthy."

Statistical model limitations constrain the ability of study analysis to account for demographic characteristics. Adding independent variables to regression analyses increases the risk of overfitting – the phenomenon that occurs when a statistical model is fitted so well on a training dataset that it performs poorly on a testing dataset.[230] This issue forces a decision to either i) ignore risks of overfitting and include associated variables, or ii) take a 'simplest is best' model building approach and not include potentially associated variables in analysis. In the

context of this current study, taking the simplest is best model building approach avoided overfitting issues, but meant models did not include all variables that potentially account for some of the natural immune system associated variation among infants.[31] For example, medication (e.g. steroids, immunosuppressants) exposure has been associated with immune functions – including associations of glucocorticoids with Th2 biased immune cellular activities[231] and corticosteroids with leukocyte trafficking/activation[232] - suggesting infant and maternal medication exposure may influence serum biomarker levels of one-year-old infants. Another example is the time since any infection, which may influence the levels of biomarkers associated with the natural progression of infection or inflammation response (e.g. IFN-γ) and resolution (TGF-β).[233] Infection incidence may also be associated with HM intake or number of HMF sessions. CHILD did not capture theses variables at a resolution necessary to include in the analyses of this study, but they may be important for future cohorts to investigate.

Inflammation-associated serum biomarkers cannot capture or reflect all immune system associated activity, biological process, or structure differences among one-year-old infants with different infant feeding practices. Furthermore, serum biomarker level differences among infant groups do not prove specific immune system activity or developmental differences exist. In general, inflammation-associated biomarkers can be used for exploring, speculating, and identifying potential mechanisms by which infant feeding practices and both immune system activity and development are related. Follow up basic science experiments are required to verify hypotheses generated using inflammation-associated serum biomarkers.[234]

Characteristics of the Olink Target 96 Inflammation panel also limit this study. This panel reports serum biomarker levels using an arbitrary NPX unit. NPX values are relative to each individual biomarker and do not provide the absolute concentration of each biomarker in

serum. This prevents comparison of serum levels among biomarkers and restricts analysis. Furthermore, not all inflammation-associated biomarkers satisfy linear regression assumptions of normality (27/76). Non-normal distributions are commonly used in human health research[235]; nonetheless, it is important to note that the robustness and power of linear regression analyses including these biomarkers may be limited.

5.3. Future Directions

This study provides precedent and direction for future HM research that may further our understanding of topics including, but not limited to i) HM immunomodulatory abilities, ii) the temporality of HM immunomodulatory abilities, iii) the long-term effects and physiological consequences of infant feeding practice differences. This section outlines potential future directions that may further our understanding of these topics.

CHILD cohort future directions:

Determining the relationship of infant health outcomes (e.g. allergy, asthma) with infant feeding practices, and biomarkers found associated with infant feeding practices in this current study, will further our understanding of the mechanism by which infant feeding practices influence infant health. A mediation analyses could investigate the use of infant feeding practices and/or serum biomarker levels as mediators of the relationship between HMF and infant health condition risk in the CHILD cohort.

Other future directions:

This current study identified variation in the temporality of associations between inflammation-associated serum biomarkers and HMF. Studying the relationship between inflammation-associated serum biomarkers and precise time since HMF cessation or last HMF session, may further our understanding of the temporal nature of HM immunomodulatory abilities and potentially suggest mechanisms underlying long-lasting protective associations of HMF. This could be completed using a human cohort study or in animal models.

This current study found associations of inflammation-associated serum biomarkers with infant feeding practices; however, the mechanism by which many of these associations occur is unknown. For example, maternal HM-borne biomarkers may account for these associations directly, or alternatively, HM could induce changes in infant biomarker production. Determining the absolute concentration of inflammation-associated biomarkers within both HM and infant serum, and then investigating the relationship between serum and HM levels, may further our understanding of the mechanisms underlying HM-induced biomarker associations. Furthermore, a cross-fostering animal model experiment in which mice pups are nursed by green fluorescent protein expressing dams could determine if biomarkers are provided from dam milk or are produced by a pup. This research could be extrapolated to hypothesize how differences in HM stage (e.g. colostrum, early milk, mature milk) inflammation-associated biomarker levels may influence the serum inflammation-associated biomarker levels of infants receiving HM.

Investigating infant feeding practices using animal models will help determine the full extent to which infant feeding practices are associated with infant immune system activity, development, and overall health. For example, animal disease models subject to different feeding practices (e.g. pups receiving only maternal milk, pups receiving maternal milk for only the first day of life and then formula, pups receiving only formula) could be used to determine the association of infant feeding practices with disease development, severity, and progression. Animal models could also provide insight on associations of infant feeding practices with differential immune system responses to immune system challenges, such as infections in different tissues. For example, in vivo whole animal fluorescence imaging of LysM-EGFP mice – which express fluorescent neutrophils – could be used to examine neutrophilic response to infection in mice subject to different feeding practices.[236] Comparing the degree of inflammatory

response induced by different microbe or antigen doses between animals receiving maternal milk and animals not receiving maternal milk, or between animals with differences in other feeding practices, could also provide insight on HM immunomodulatory ability. Animals models could be used to investigate physiological immune system structure (e.g. mucosal immune site, immune system component composition and activities) associations with infant feeding practices. For example, an animal model could be used to further investigate the relationship of HMF duration with thymus size and cellular or biomarker level changes.[94,216]

Animal models could also be used to identify undescribed immune system differences associated with infant feeding practices. For example, flow cytometry could be used to determine differences in chemical and physical characteristics of cells or particles within mice that received different early life feeding practices. This flow cytometry investigation may also have potential to support or refute hypotheses made in this thesis. For example, flow cytometry may be able to determine if the higher level of Tregs observed in infants receiving HM express CD244 and account for higher CD244 levels observed in infants receiving HM. Furthermore, we hypothesized that infants receiving HM may have an increased recruitment of immune cells to the gut, but decreased levels of gut inflammation. Investigating gut tissue with cellular-level methods could inform these hypotheses and further our understanding of HM immunomodulatory abilities. Repeating cellular-level methods at different time points in early life may also further our understanding of how HM composition changes over time may support changes in infant immunological needs. For example, we know infants receiving HM have more Tregs,[96] compared to infants not receiving HM, but the subtype (e.g. GATA3+, RORγt+) of these Tregs, as well as potential variation in Treg subtype induced by HM in different lactation stages (e.g. colostrum, mature milk) is unknown. Determining the subtype of Treg induced by

HM at different time points may further our understanding of how i) the immune system develops in early life, and ii) how HM supports early life immune system development.

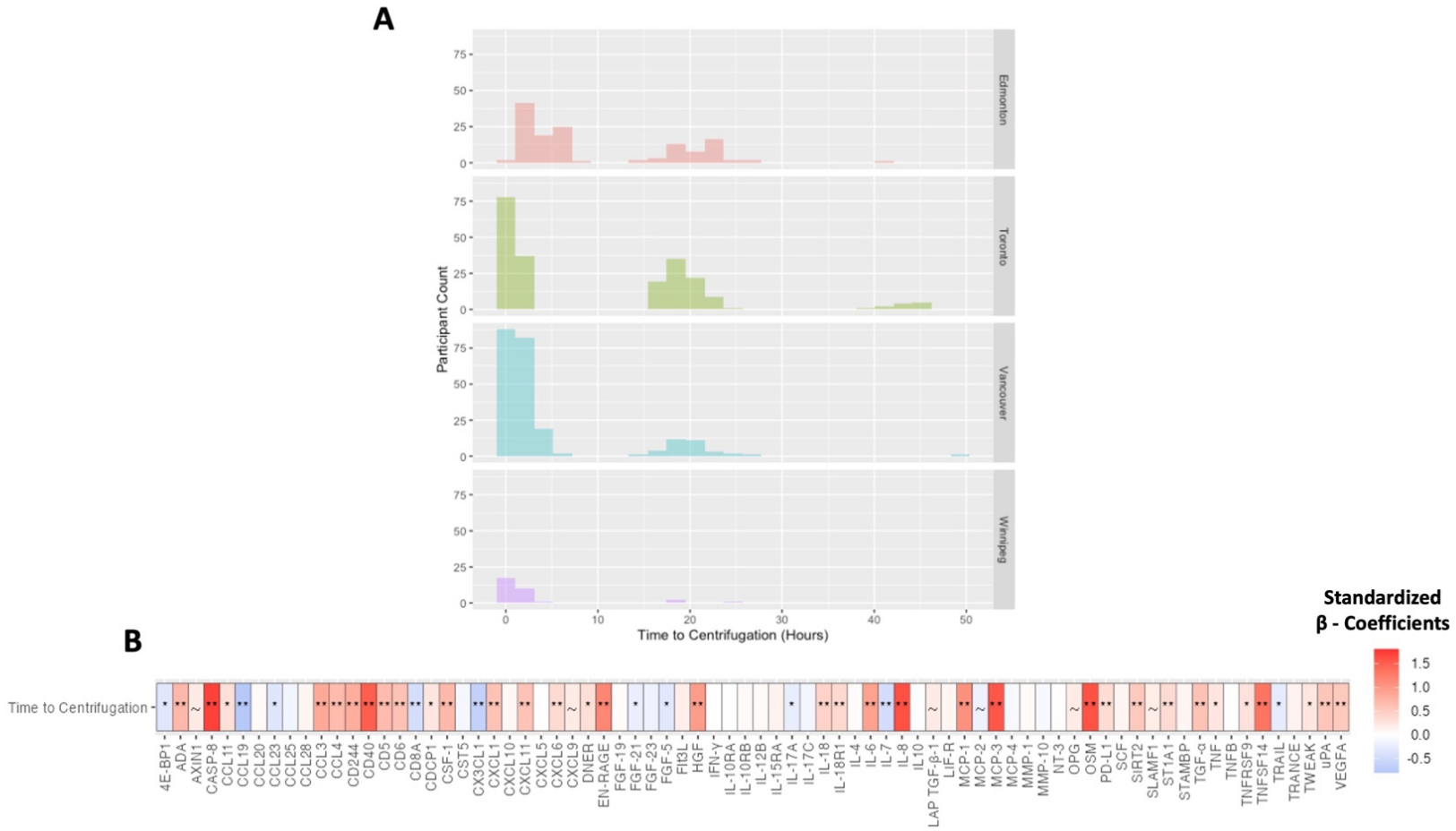
Chapter VI: Conclusion

This current study investigated the association of infant feeding practices (including current HMF status, HMF duration, exclusive HMF duration, and HMF method at three months of age) with inflammation-associated serum biomarker levels of one-year-old infants from the CHILD Cohort Study. We found significant associations of current HMF status with CCL20, CD244, CXCL6, EN-RAGE, FGF-21, and marginally significant associations with IL-10RB and TRANCE serum biomarker levels in one-year-old infants. All significantly associated biomarkers, except EN-RAGE, were higher in infants receiving HM compared to infants not receiving HM. CCL20, CD244, CXCL6, EN-RAGE, and FGF-21 were shown to have some independent ability to predict current HMF status in one-year-old infants. Considering the known biological functions and origins of these serum biomarkers, our results suggest infants receiving HM may have increased anti-inflammatory Th2-like immune responses, increased antigen tolerance, and enhanced metabolism, compared to infants not receiving HM. Investigating associations between HMF duration, exclusive HMF duration, and HMF method at three months of age revealed only one marginally significant positive association of IL-7 with both HMF duration and exclusive HMF. The persistent elevation for several months, but eventual decrease of IL-7 serum levels upon HMF cessation may underly these results. Furthermore, these positive associations suggest HMF duration and exclusive HMF duration may be associated with thymus development and infant T cell repertoire.

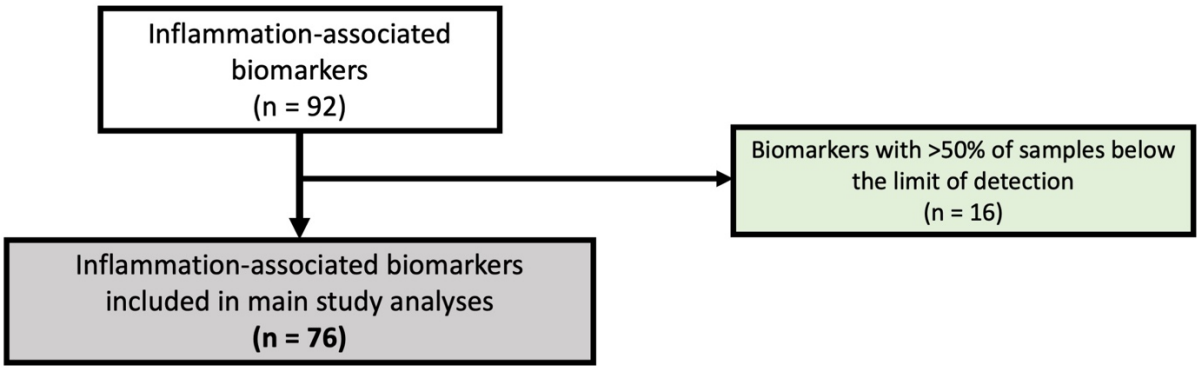
To our knowledge, this is the first study to investigate associations of current HMF status, HMF duration, exclusive HMF duration, and HMF method at three months of age with a panel of inflammation-associated serum biomarkers. This current study suggests i) infants currently

receiving HM may have differential immune system activities compared to infants not currently receiving HM, ii) history of HMF may be associated with aspects of immune system development, although these associations may not be well-reflected in inflammation-associated serum biomarkers among healthy infants, and iii) current HMF status should be accounted for in infant serum proteomics. Further investigating the association of infant feeding practices with immune system activity and development during immune challenges, in the context of disease states, and in animal models will help further develop hypotheses suggested in this study and potentially uncover further mechanisms in which nutrition influences immunity during early life. Overall, this study uncovered previously undescribed associations of HMF with early life immune system development and activity and identifies future directions further research should prioritize to further our understanding of early life immune system development and how to provide all infants with the best start to life.

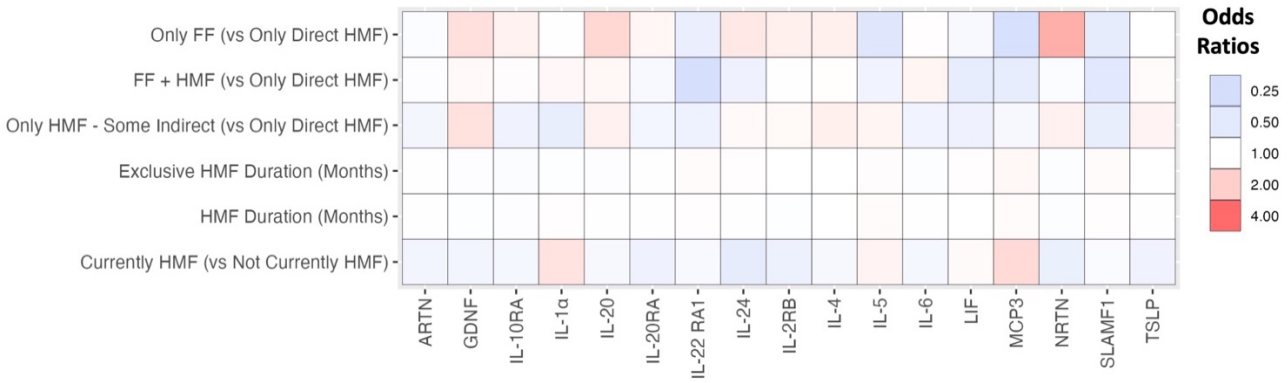
Supplementary Files



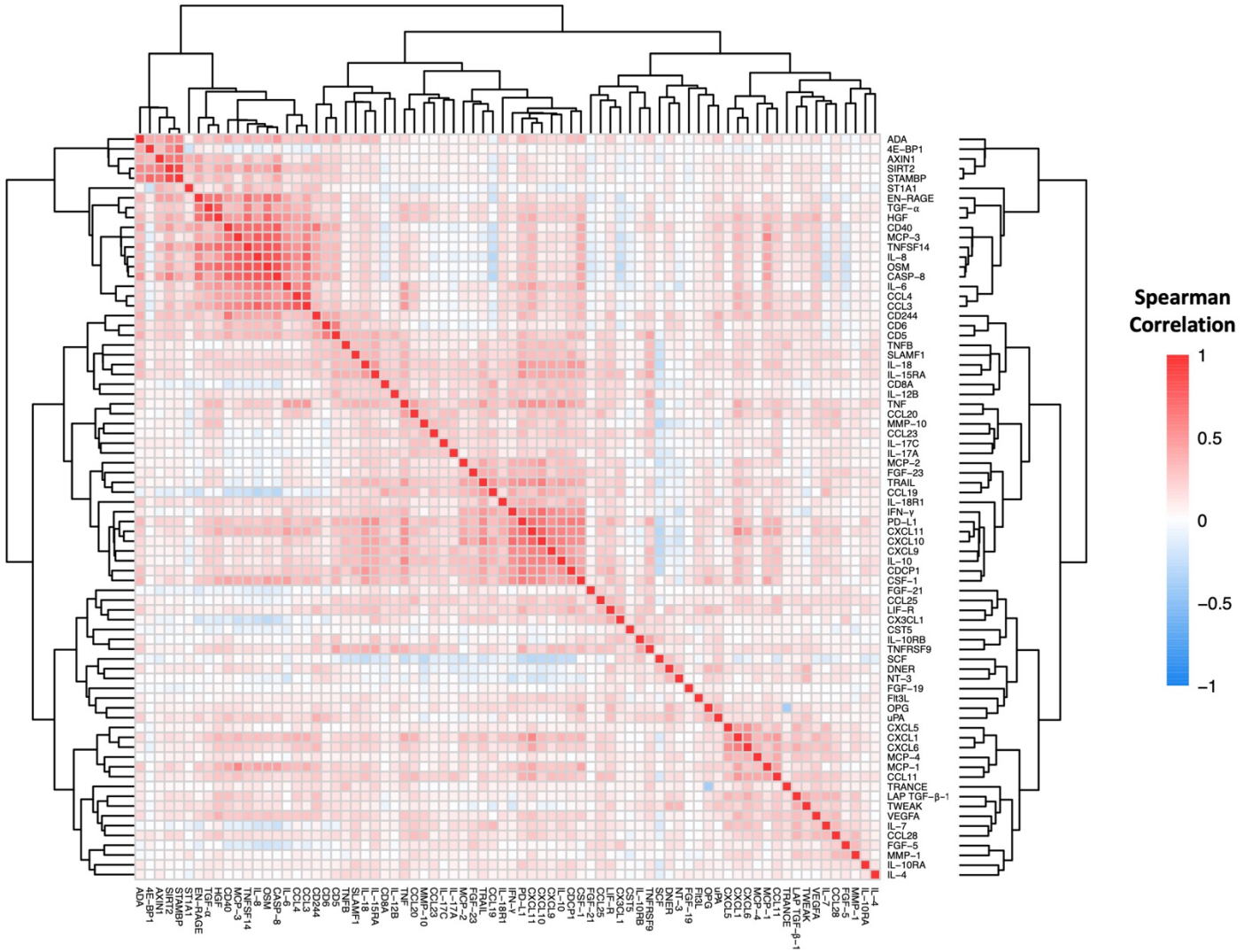
Supplementary Figure 1. Time until blood sample centrifugation varies among study sites and is associated with inflammation-associated serum biomarker levels in one-year-old CHILD cohort infants (full study population, n=605). (A) Blood sample time until centrifugation for study infants in each CHILD Cohort study site. **(B)** Linear regression associations of time until blood sample centrifugation (hours) with measured inflammation-associated serum biomarkers (standardized NPX). ~p<0.1, *p<0.05, **p<0.01.



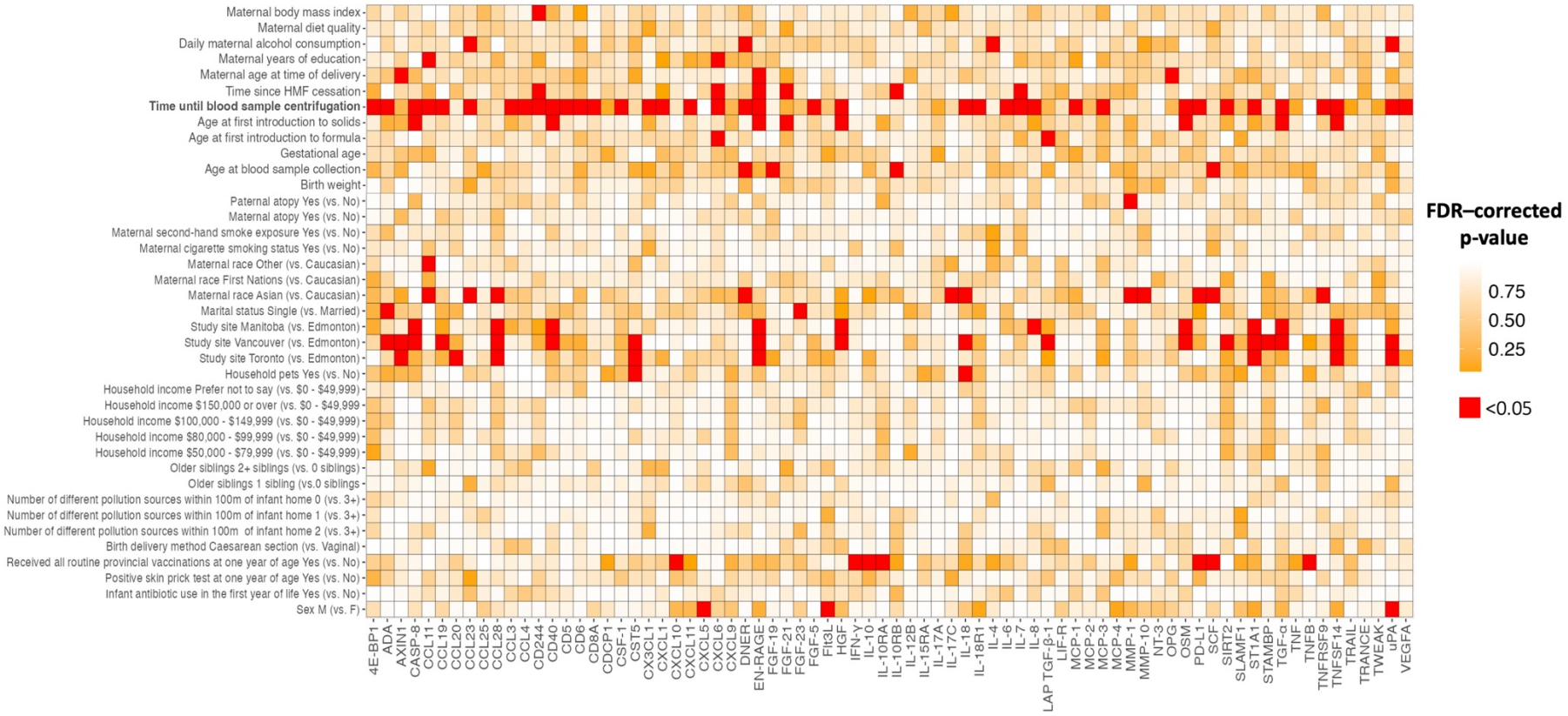
Supplementary Figure 2. Exclusion criteria for Olink Target 96 Inflammation panel quantified biomarkers included in main study analyses.



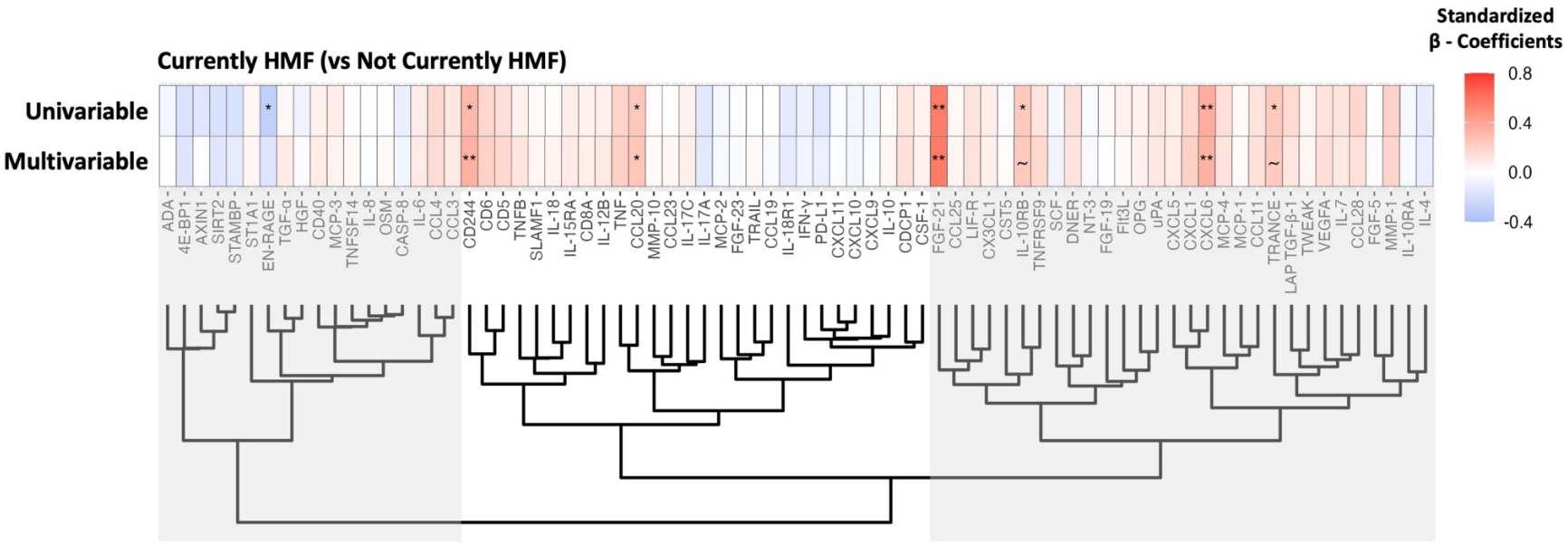
Supplementary Figure 3. Associations of biomarker presence/absence with infant feeding practice variables among one-year-old CHILD cohort infants (full study population, n=605). Logistic regression odds ratios obtained by using infant feeding practices variables, individually, to predict biomarker presence/absence. Biomarkers included in analysis had >30 infants in both present and absent groups. The Benjamini-Hochberg method was used for FDR p-value correction. No significant associations were observed.



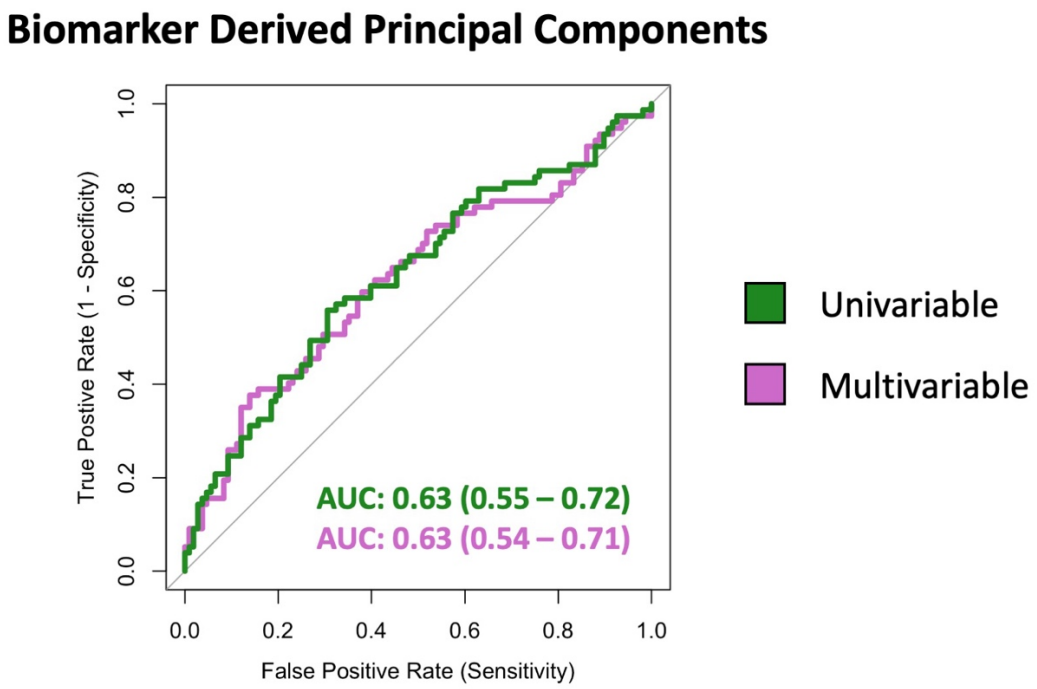
Supplementary Figure 4. Spearman correlation and hierarchical clustering analysis among all inflammation-associated biomarkers in one-year-old CHILD cohort infants (full study population, n=605). Spearman correlation coefficients were used as distance measures in hierarchical clustering analysis.



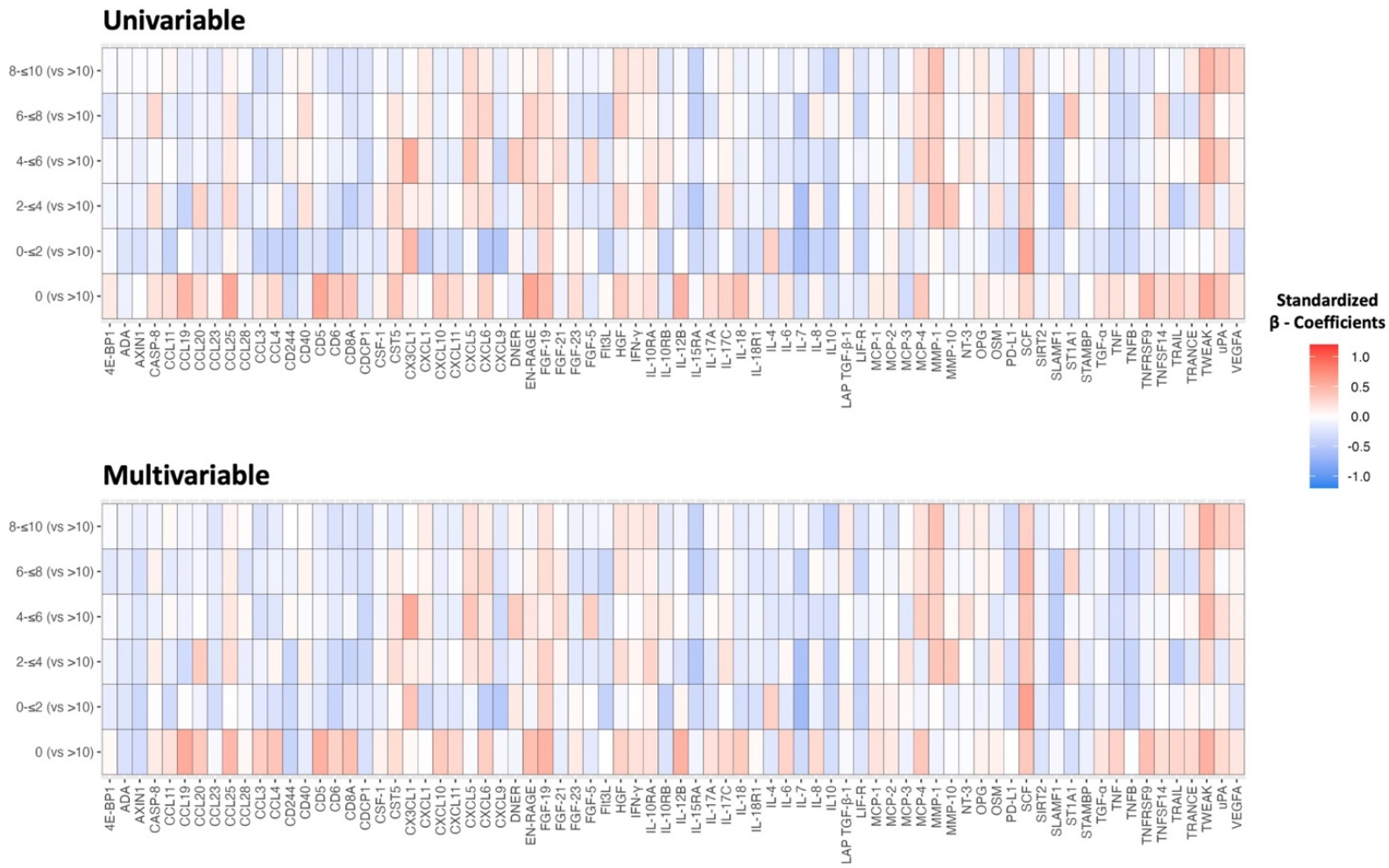
Supplementary Figure 5. Demographic variables associated with inflammation-associated serum biomarker levels in one-year-old CHILD cohort infants (full study population, n=605). Variables significantly associated with one or more serum biomarker levels were evaluated for use in the multi-step forward selection process.



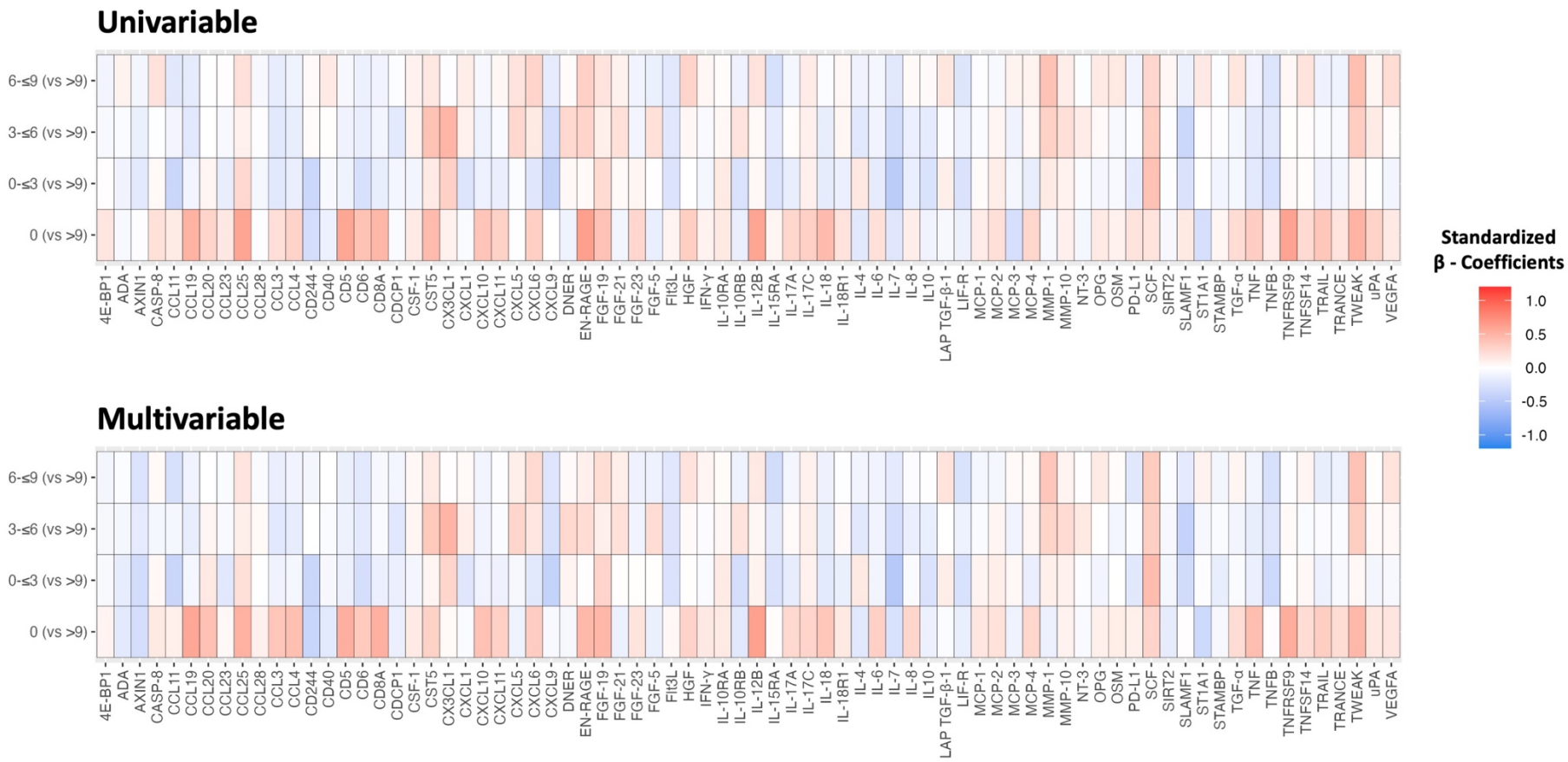
Supplementary Figure 6. Spearman correlation associations between current HMF status and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (full study population, n=605), sorted according to hierarchical clustering of biomarkers. Results are standardized β-coefficients obtained from univariable and multivariable (adjusted for time until blood sample centrifugation, study site, and infant sex) linear regression models that used infant current HMF status to predict serum biomarker level (standardized NPX). The dendrogram was obtained from spearman correlation analysis (**Supplementary Figure 4**). All p-values were FDR-corrected using the Benjamini-Hochberg method. ~p<0.1, *p<0.05, **p<0.01.



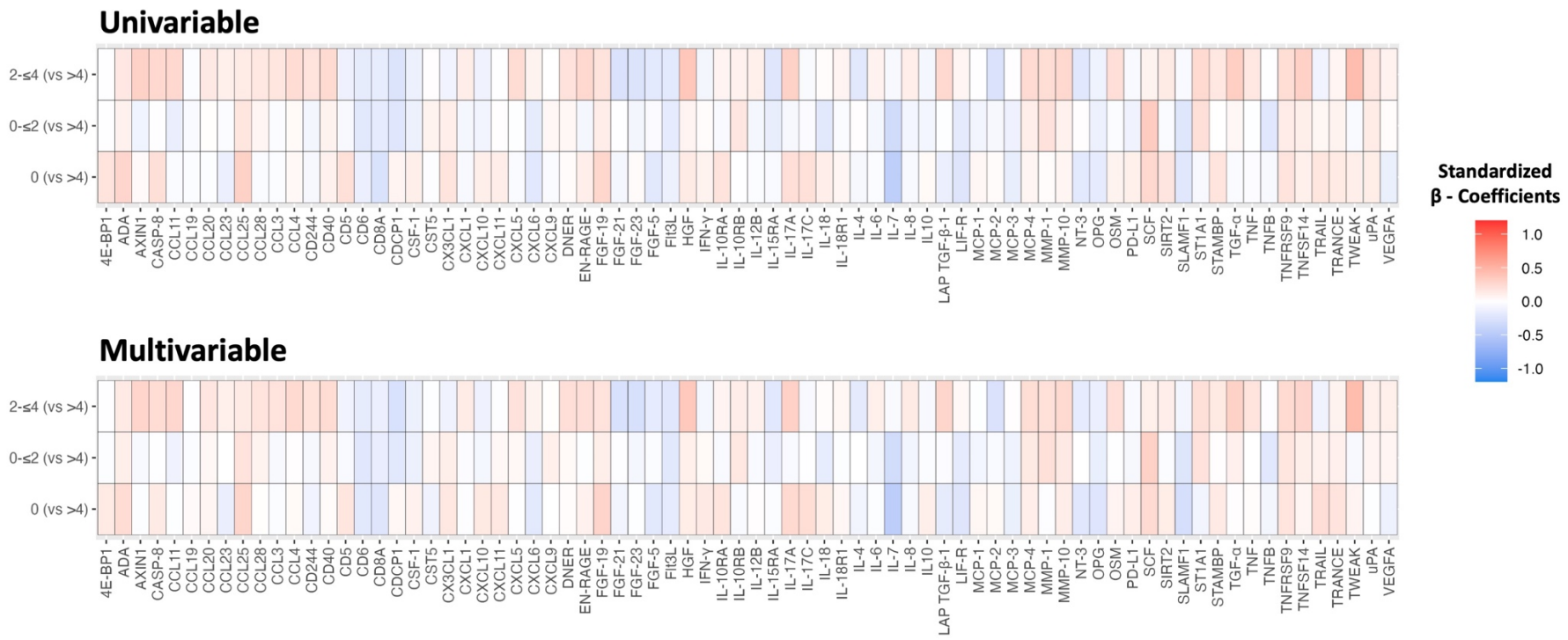
Supplementary Figure 7. Associations of all biomarker-derived principal components with current HMF status of one-year-old CHILD cohort infants (full study population, n=605). Figure shows ROC curve and respective area under the ROC curve (AUC) value for a logistic regression model that uses all principal components (n=75) derived from principal component analysis of biomarkers (excluding FGF-5) investigated in this research. FGF-5 was excluded as 46 infants had NA values for FGF-5 serum levels.



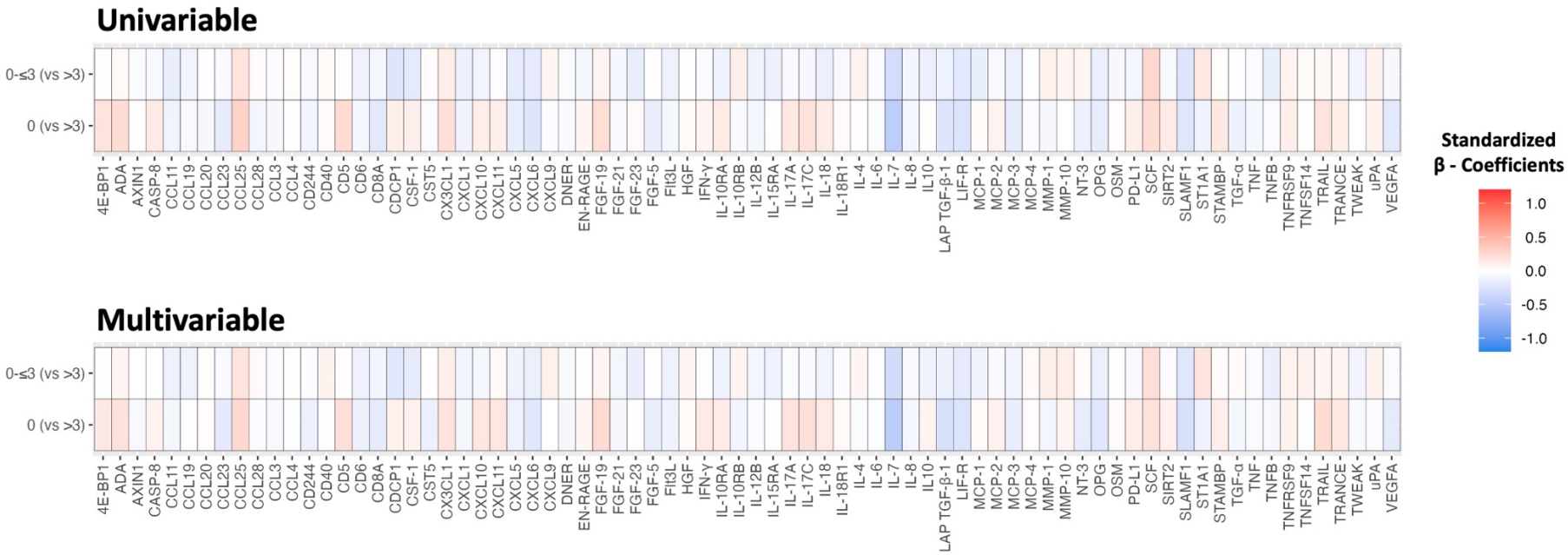
Supplementary Figure 8. Associations of categorical HMF duration (grouped into two-month intervals) with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusting for time until blood sample centrifugation, study site, and sex) linear regression models that predicted individual biomarker level (standardized NPX) with categorical HMF duration. The Benjamini-Hochberg method was used for FDR p-value correction. No significant associations were observed after FDR correction.



Supplementary Figure 9. Associations of categorical HMF duration (grouped into three-month intervals) with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusting for time until blood sample centrifugation, study site, and sex) linear regression models that predicted individual biomarker level (standardized NPX) with categorical HMF duration. The Benjamini-Hochberg method was used for FDR p-value correction. No significant associations were observed after FDR correction.



Supplementary Figure 10. Associations of categorical exclusive HMF duration (grouped into two-month intervals) with inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusting for time until blood sample centrifugation, study site, and sex) linear regression models that predicted individual biomarker level (standardized NPX) with categorical exclusive HMF duration. The Benjamini-Hochberg method was used for FDR p-value correction. No significant associations were observed after FDR correction.



Supplementary Figure 11. Associations between of exclusive HMF duration (grouped into three-month intervals) and inflammation-associated serum biomarkers measured in one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results are standardized β-coefficients obtained from univariable and multivariable (adjusting for time until blood sample centrifugation, study site, and sex) linear regression models that predicted individual biomarker level (standardized NPX) with categorical exclusive HMF duration. The Benjamini-Hochberg method was used for FDR p-value correction. No significant associations were observed after FDR correction.

Supplementary Table 1. Results from a multi-step forward selection analysis completed using the 'step' R function.

Biomarker	Variables that meet the step threshold and order	Respective AIC
CCL20	—	-121.0
	Study site	-140.7
	Time until blood sample centrifugation	-147.9
CD244	—	-697.4
	Time until blood sample centrifugation	-728.2
	Maternal BMI	-730.4
	Infant age at first introduction to solids	-732.3
	Vaccination	-733.7
CXCL6	—	-417.7
	Time until blood sample centrifugation	-425.0
	Study site	-426.9
	Sex	-428.1
EN-RAGE	—	28.1
	Time until blood centrifugation	-56.8
	Study site	-110.8
FGF-21	—	96.1
	Maternal age	84.3
	Time until blood sample centrifugation	80.9
IL-10RB	—	-1035.1
	Vaccination	-1037.5
	Maternal race	-1038.1
TRANCE	—	-470.5
	Maternal alcohol consumption	-473.6
	Maternal years of education	-475.7
	Sex	-476.2

Supplementary Table 2. Linear regression associations of infant serum biomarker levels with current HMF status among one-year-old CHILD cohort infants (full study population, n=605). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use current HMF status (Yes/No) to predict biomarker levels (standardized NPX).

Olink Biomarkers	Univariable			Multivariable		
	P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0.03	0.16	-0.174 (-0.335 - -0.013)	0.06	0.31	-0.153 (-0.314 - 0.008)
ADA	0.48	0.76	-0.058 (-0.220 - 0.103)	0.99	0.99	-0.001 (-0.158 - 0.155)
AXIN1	0.07	0.31	-0.147 (-0.309 - 0.014)	0.92	0.95	-0.007 (-0.156 - 0.141)
CASP-8	0.21	0.47	-0.103 (-0.265 - 0.058)	0.29	0.56	-0.063 (-0.179 - 0.053)
CCL11	0.13	0.38	0.124 (-0.037 - 0.286)	0.11	0.40	0.133 (-0.030 - 0.296)
CCL19	0.96	0.97	-0.004 (-0.166 - 0.157)	0.70	0.86	-0.031 (-0.186 - 0.125)
CCL20	**<0.01**	**0.04**	**0.243 (0.083 - 0.404)**	**<0.01**	**0.04**	**0.255 (0.093 - 0.417)**
CCL23	0.90	0.96	0.010 (-0.151 - 0.172)	0.65	0.84	0.038 (-0.125 - 0.200)
CCL25	0.70	0.90	0.032 (-0.130 - 0.194)	0.58	0.82	0.046 (-0.118 - 0.210)
CCL28	0.03	0.16	0.180 (0.020 - 0.341)	0.10	0.40	0.132 (-0.027 - 0.292)
CCL3	0.19	0.43	0.109 (-0.052 - 0.27)	0.25	0.53	0.090 (-0.062 - 0.242)
CCL4	0.03	0.16	0.175 (0.014 - 0.336)	0.05	0.28	0.156 (0.000 - 0.312)
CD244	**<0.01**	**<0.01**	**0.308 (0.148 - 0.468)**	**<0.01**	**<0.01**	**0.346 (0.193 - 0.499)**
CD40	0.45	0.76	0.062 (-0.099 - 0.224)	0.18	0.46	0.087 (-0.041 - 0.215)
CD5	0.08	0.31	0.145 (-0.016 - 0.306)	0.03	0.20	0.174 (0.016 - 0.331)
CD6	0.03	0.16	0.180 (0.019 - 0.341)	0.01	0.10	0.203 (0.044 - 0.361)
CD8A	0.48	0.76	0.058 (-0.104 - 0.219)	0.38	0.70	0.073 (-0.089 - 0.234)
CDCP1	0.15	0.38	0.118 (-0.043 - 0.280)	0.10	0.40	0.136 (-0.028 - 0.300)
CSF-1	0.54	0.79	0.051 (-0.111 - 0.212)	0.46	0.73	0.059 (-0.098 - 0.216)
CST5	0.80	0.94	-0.021 (-0.182 - 0.141)	0.85	0.89	0.015 (-0.147 - 0.178)
CX3CL1	0.36	0.70	0.076 (-0.086 - 0.237)	0.42	0.71	0.065 (-0.094 - 0.224)
CXCL1	0.03	0.16	0.180 (0.019 - 0.341)	0.01	0.10	0.205 (0.047 - 0.364)
CXCL10	0.51	0.77	-0.054 (-0.216 - 0.107)	0.54	0.82	-0.052 (-0.216 - 0.113)
CXCL11	0.82	0.94	-0.019 (-0.181 - 0.143)	0.85	0.89	-0.015 (-0.174 - 0.144)
CXCL5	0.38	0.72	0.072 (-0.089 - 0.234)	0.30	0.56	0.085 (-0.075 - 0.245)
CXCL6	**<0.01**	**<0.01**	**0.359 (0.200 - 0.518)**	**<0.01**	**<0.01**	**0.344 (0.184 - 0.503)**
CXCL9	0.54	0.79	-0.051 (-0.212 - 0.111)	0.81	0.88	-0.020 (-0.183 - 0.143)
DNER	0.10	0.32	0.136 (-0.025 - 0.297)	0.13	0.41	0.127 (-0.036 - 0.290)
EN-RAGE	**<0.01**	**0.01**	**-0.293 (-0.453 - -0.133)**	**0.02**	**0.12**	**-0.160 (-0.290 - -0.030)**
FGF-19	0.74	0.90	0.028 (-0.134 - 0.189)	0.99	0.99	-0.001 (-0.164 - 0.163)
FGF-21	**<0.01**	**<0.01**	**0.555 (0.399 - 0.710)**	**<0.01**	**<0.01**	**0.564 (0.405 - 0.722)**
FGF-23	0.83	0.94	-0.018 (-0.179 - 0.144)	0.76	0.87	-0.026 (-0.190 - 0.138)
FGF-5**	0.95	0.97	-0.006 (-0.174 - 0.162)	0.85	0.89	-0.016 (-0.185 - 0.153)
Flt3L	0.49	0.76	0.056 (-0.105 - 0.218)	0.75	0.87	0.027 (-0.136 - 0.189)
HGF	0.42	0.76	-0.066 (-0.227 - 0.096)	0.76	0.87	-0.024 (-0.174 - 0.127)
IFN-γ	0.34	0.67	-0.079 (-0.240 - 0.082)	0.45	0.73	-0.064 (-0.229 - 0.101)

IL-10RA	0.62	0.84	-0.041 (-0.202 - 0.121)	0.69	0.85	-0.034 (-0.199 - 0.131)
IL-10RB	**<0.01**	**0.04**	**0.237 (0.077 - 0.398)**	**<0.01**	**0.06**	**0.241 (0.077 - 0.405)**
IL-12B	0.42	0.76	0.066 (-0.096 - 0.227)	0.24	0.53	0.099 (-0.066 - 0.263)
IL-15RA	0.33	0.67	0.080 (-0.081 - 0.241)	0.27	0.54	0.093 (-0.072 - 0.257)
IL-17A	0.09	0.32	-0.139 (-0.301 - 0.022)	0.11	0.40	-0.133 (-0.297 - 0.031)
IL-17C	0.45	0.76	0.062 (-0.099 - 0.224)	0.40	0.71	0.070 (-0.095 - 0.235)
IL-18	0.87	0.96	0.013 (-0.148 - 0.175)	0.53	0.82	0.051 (-0.110 - 0.213)
IL-18R1	0.13	0.38	-0.125 (-0.286 - 0.037)	0.15	0.43	-0.120 (-0.281 - 0.042)
IL-4	0.19	0.43	-0.109 (-0.270 - 0.052)	0.22	0.51	-0.103 (-0.267 - 0.062)
IL-6	0.29	0.62	0.087 (-0.074 - 0.249)	0.22	0.51	0.094 (-0.057 - 0.246)
IL-7	0.15	0.38	0.118 (-0.043 - 0.279)	0.20	0.48	0.107 (-0.055 - 0.268)
IL-8	0.94	0.97	-0.006 (-0.167 - 0.156)	0.80	0.88	-0.015 (-0.136 - 0.105)
IL-10	0.82	0.94	0.018 (-0.143 - 0.180)	0.57	0.82	0.047 (-0.117 - 0.211)
LAP TGF-β-1	0.05	0.21	-0.041 (-0.202 - 0.121)	0.17	0.46	0.113 (-0.048 - 0.274)
LIF-R	0.14	0.38	0.237 (0.077 - 0.398)	0.13	0.41	0.129 (-0.036 - 0.293)
MCP-1	0.73	0.90	0.066 (-0.096 - 0.227)	0.78	0.88	0.021 (-0.127 - 0.168)
MCP-2	0.59	0.81	0.080 (-0.081 - 0.241)	0.63	0.83	-0.040 (-0.204 - 0.125)
MCP-3	0.31	0.66	-0.139 (-0.301 - 0.022)	0.39	0.71	0.052 (-0.067 - 0.172)
MCP-4	0.09	0.32	0.062 (-0.099 - 0.224)	0.13	0.41	0.126 (-0.037 - 0.290)
MMP-1	0.02	0.16	0.013 (-0.148 - 0.175)	0.03	0.19	0.183 (0.020 - 0.346)
MMP-10	0.88	0.96	-0.125 (-0.286 - 0.037)	0.80	0.88	0.021 (-0.144 - 0.185)
NT-3	0.68	0.89	-0.109 (-0.270 - 0.052)	0.68	0.85	-0.034 (-0.199 - 0.130)
OPG	0.49	0.76	0.087 (-0.074 - 0.249)	0.46	0.73	0.062 (-0.102 - 0.226)
OSM	0.94	0.97	0.118 (-0.043 - 0.279)	0.60	0.83	0.032 (-0.090 - 0.155)
PD-L1	0.10	0.32	-0.006 (-0.167 - 0.156)	0.26	0.53	-0.094 (-0.256 - 0.069)
SCF	0.59	0.81	0.164 (0.003 - 0.325)	0.41	0.71	-0.068 (-0.233 - 0.096)
SIRT2	0.03	0.16	0.121 (-0.040 - 0.282)	0.08	0.37	-0.143 (-0.301 - 0.016)
SLAMF1	0.78	0.94	0.028 (-0.133 - 0.190)	0.58	0.82	0.046 (-0.118 - 0.210)
ST1A1	0.64	0.85	-0.045 (-0.206 - 0.117)	0.56	0.82	0.046 (-0.110 - 0.203)
STAMBP	0.03	0.16	0.083 (-0.078 - 0.245)	0.14	0.42	-0.122 (-0.282 - 0.039)
TGF-α	0.72	0.90	0.139 (-0.022 - 0.300)	0.26	0.53	0.090 (-0.066 - 0.245)
TNF	0.02	0.16	0.197 (0.036 - 0.358)	0.01	0.10	0.211 (0.048 - 0.374)
TNFB	0.45	0.76	0.012 (-0.149 - 0.174)	0.16	0.45	0.117 (-0.046 - 0.280)
TNFRSF9	0.13	0.38	-0.034 (-0.196 - 0.128)	0.04	0.25	0.168 (0.005 - 0.331)
TNFSF14	0.88	0.96	0.056 (-0.105 - 0.218)	0.63	0.83	0.033 (-0.101 - 0.167)
TRAIL	0.99	0.99	-0.006 (-0.168 - 0.155)	0.72	0.87	0.030 (-0.133 - 0.192)
TRANCE	**<0.01**	**0.04**	**-0.137 (-0.298 - 0.024)**	**0.01**	**0.07**	**0.231 (0.068 - 0.395)**
TWEAK	0.58	0.81	-0.045 (-0.206 - 0.117)	0.63	0.83	0.041 (-0.123 - 0.205)
uPA	0.18	0.43	-0.183 (-0.344 - -0.022)	0.18	0.46	0.105 (-0.050 - 0.260)
VEGFA	0.12	0.38	0.023 (-0.138 - 0.185)	0.09	0.38	0.140 (-0.020 - 0.300)

**46 infants had an NA value for FGF-5.

Supplementary Table 3. Logistic regression associations of infant serum biomarker levels with current HMF status among one-year-old CHILD cohort infants (full study population, n=605). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) logistic regression models that use Olink biomarker levels (standardized NPX), independently, to predict infant current HMF status (Yes/No). The not currently HMF infant group was used as reference. Odds ratios are per one standard deviation increase of standardized biomarker level. The Benjamini-Hochberg method was used for FDR p-value correction. Bolded variables have a p-value <0.05.

Olink Biomarkers	Univariable				Multivariable			
	Odds Ratio (95% CI)	P-Value	FDR P-Value	Area under ROC Curve (AUC) (95% CI)	Odds Ratio (95% CI)	P-Value	FDR P-Value	Area under ROC Curve (AUC) (95% CI)
4E-BP1	0.76 (0.62 - 0.93)	<0.01	0.07	0.51 (0.42 - 0.59)	0.77 (0.63 - 0.95)	0.02	0.13	0.52 (0.43 - 0.61)
ADA	0.88 (0.72 - 1.06)	0.18	0.47	0.54 (0.45- 0.62)	0.94 (0.76 - 1.15)	0.53	0.82	0.53 (0.44 - 0.61)
AXIN1	0.85 (0.70 - 1.03)	0.10	0.35	0.55 (0.46 - 0.63)	0.98 (0.79 - 1.23)	0.89	0.90	0.54 (0.45 - 0.62)
CASP-8	0.85 (0.69 - 1.03)	0.09	0.35	0.51 (0.42 - 0.59)	0.84 (0.64 - 1.11)	0.22	0.48	0.54 (0.45 - 0.62)
CCL11	1.11 (0.91 - 1.34)	0.30	0.60	0.56 (0.47 - 0.64)	1.17 (0.96 - 1.42)	0.13	0.48	0.54 (0.45 - 0.62)
CCL19	1.00 (0.82 - 1.20)	0.96	0.97	0.52 (0.44 - 0.60)	0.96 (0.78 - 1.18)	0.67	0.82	0.53 (0.45 - 0.62)
CCL20	**1.33 (1.09 - 1.64)**	**<0.01**	**0.06**	**0.53 (0.45 - 0.62)**	**1.40 (1.13 - 1.73)**	**<0.01**	**0.04**	**0.56 (0.48 - 0.65)**
CCL23	1.03 (0.84 - 1.25)	0.79	0.97	0.49 (0.41 - 0.58)	1.05 (0.86 - 1.30)	0.61	0.82	0.53 (0.44 - 0.62)
CCL25	1.01 (0.83 - 1.23)	0.89	0.97	0.53 (0.45 - 0.62)	1.04 (0.85 - 1.28)	0.68	0.82	0.54 (0.45 - 0.62)
CCL28	1.08 (0.88 - 1.31)	0.47	0.75	0.62 (0.54 - 0.71)	1.05 (0.85 - 1.30)	0.63	0.82	0.55 (0.47 - 0.64)
CCL3	1.12 (0.92 - 1.35)	0.26	0.55	0.53 (0.44 - 0.61)	1.15 (0.93 - 1.42)	0.20	0.48	0.54 (0.45 - 0.63)
CCL4	1.20 (0.98 - 1.46)	0.07	0.34	0.55 (0.47 - 0.64)	1.22 (0.99 - 1.51)	0.07	0.35	0.55 (0.47 - 0.64)
CD244	**1.35 (1.09 - 1.66)**	**<0.01**	**0.06**	**0.61 (0.52 - 0.69)**	**1.53 (1.20 - 1.95)**	**<0.01**	**0.02**	**0.59 (0.50 - 0.67)**
CD40	1.04 (0.86 - 1.27)	0.67	0.91	0.53 (0.45 - 0.62)	1.18 (0.91 - 1.53)	0.21	0.48	0.54 (0.45 - 0.63)
CD5	1.22 (1.00 - 1.49)	0.05	0.30	0.49 (0.40 - 0.57)	1.31 (1.06 - 1.62)	0.01	0.13	0.53 (0.44 - 0.61)
CD6	1.26 (1.04 - 1.53)	0.02	0.15	0.49 (0.40 - 0.57)	1.34 (1.09 - 1.65)	0.01	0.09	0.53 (0.45 - 0.62)
CD8A	1.11 (0.92 - 1.33)	0.29	0.58	0.52 (0.44 - 0.61)	1.10 (0.91 - 1.34)	0.33	0.65	0.53 (0.44 - 0.62)
CDCP1	1.18 (0.97 - 1.43)	0.11	0.35	0.50 (0.41 - 0.59)	1.23 (1.01 - 1.51)	0.04	0.26	0.53 (0.45 - 0.62)
CSF-1	1.04 (0.85 - 1.26)	0.71	0.94	0.52 (0.44 - 0.61)	1.08 (0.87 - 1.33)	0.51	0.82	0.53 (0.45 - 0.62)
CST5	0.99 (0.82 - 1.20)	0.91	0.97	0.51 (0.43 - 0.59)	1.02 (0.83 - 1.24)	0.89	0.90	0.53 (0.45 - 0.62)
CX3CL1	1.06 (0.87 - 1.29)	0.56	0.81	0.54 (0.46 - 0.63)	1.02 (0.83 - 1.26)	0.82	0.86	0.54 (0.46 - 0.63)
CXCL1	1.09 (0.89 - 1.32)	0.42	0.71	0.60 (0.52 - 0.68)	1.16 (0.94 - 1.44)	0.16	0.48	0.57 (0.48 - 0.65)
CXCL10	0.92 (0.76 - 1.11)	0.37	0.68	0.53 (0.44 - 0.61)	0.92 (0.75 - 1.11)	0.38	0.67	0.53 (0.45 - 0.62)
CXCL11	0.94 (0.77 - 1.13)	0.49	0.77	0.55 (0.46 - 0.63)	0.96 (0.78 - 1.18)	0.71	0.82	0.53 (0.45 - 0.62)
CXCL5	1.14 (0.94 - 1.38)	0.18	0.47	0.53 (0.44 - 0.61)	1.16 (0.94 - 1.42)	0.16	0.48	0.53 (0.44 - 0.62)
CXCL6	**1.39 (1.14 - 1.70)**	**<0.01**	**0.04**	**0.64 (0.55 - 0.72)**	**1.40 (1.14 - 1.73)**	**<0.01**	**0.04**	**0.60 (0.51 - 0.68)**
CXCL9	0.87 (0.71 - 1.05)	0.15	0.45	0.57 (0.49 - 0.66)	0.89 (0.73 - 1.10)	0.28	0.58	0.52 (0.44 - 0.61)
DNER	1.17 (0.97 - 1.42)	0.10	0.35	0.53 (0.45 - 0.62)	1.18 (0.97 - 1.44)	0.09	0.47	0.54 (0.45 - 0.62)
EN-RAGE	**0.72 (0.59 - 0.87)**	**<0.01**	**0.04**	**0.57 (0.48 - 0.65)**	**0.75 (0.59 - 0.97)**	**0.03**	**0.18**	**0.55 (0.47 - 0.64)**
FGF-19	1.12 (0.92 - 1.36)	0.26	0.55	0.55 (0.47 - 0.64)	1.07 (0.87 - 1.31)	0.53	0.82	0.53 (0.44 - 0.61)
FGF-21	**1.71 (1.38 - 2.12)**	**<0.01**	**<0.01**	**0.69 (0.62 - 0.77)**	**1.73 (1.39 - 2.16)**	**<0.01**	**<0.01**	**0.67 (0.59 - 0.75)**
FGF-23	0.87 (0.72 - 1.07)	0.18	0.47	0.59 (0.48 - 0.65)	0.87 (0.71 - 1.07)	0.19	0.48	0.51 (0.43 - 0.60)

FGF-5**	1.04 (0.86 - 1.26)	0.67	0.87	0.54 (0.45 - 0.63)	1.05 (0.86 – 1.30)	0.63	0.82	0.51 (0.42 - 0.59)
Flt3L	1.08 (0.89 - 1.32)	0.42	0.71	0.51 (0.42 - 0.59)	1.05 (0.86 - 1.29)	0.61	0.82	0.53 (0.45 - 0.62)
HGF	0.89 (0.73 - 1.08)	0.25	0.55	0.51 (0.43 - 0.59)	0.93 (0.75 - 1.17)	0.55	0.82	0.54 (0.45 - 0.62)
IFN-γ	0.86 (0.71 - 1.05)	0.13	0.42	0.56 (0.48 - 0.64)	0.86 (0.71 - 1.06)	0.15	0.48	0.53 (0.44 - 0.61)
IL-10RA	0.94 (0.77 - 1.14)	0.51	0.77	0.54 (0.46 - 0.62)	0.96 (0.78 - 1.17)	0.69	0.82	0.53 (0.44 - 0.61)
IL-10RB	1.19 (0.98 - 1.44)	0.09	0.35	0.62 (0.54 - 0.70)	1.17 (0.96 - 1.44)	0.11	0.48	0.57 (0.49 - 0.66)
IL-12B	1.07 (0.88 - 1.29)	0.52	0.77	0.50 (0.41 - 0.58)	1.09 (0.89 - 1.33)	0.39	0.68	0.54 (0.45 - 0.62)
IL-15RA	1.03 (0.85 - 1.25)	0.75	0.94	0.55 (0.46 - 0.63)	1.04 (0.85 - 1.27)	0.70	0.82	0.54 (0.45 - 0.63)
IL-17A	0.88 (0.72 - 1.08)	0.22	0.51	0.55 (0.47 - 0.64)	0.87 (0.71 - 1.07)	0.19	0.48	0.54 (0.46 - 0.63)
IL-17C	1.09 (0.90 - 1.32)	0.38	0.68	0.51 (0.42 - 0.59)	1.10 (0.90 - 1.34)	0.35	0.65	0.54 (0.45 - 0.62)
IL-18	1.04 (0.86 - 1.26)	0.66	0.91	0.52 (0.44 - 0.61)	1.09 (0.89 - 1.33)	0.42	0.71	0.52 (0.44 - 0.61)
IL-18R1	0.85 (0.70 - 1.04)	0.11	0.35	0.50 (0.42 - 0.59)	0.85 (0.69 - 1.04)	0.11	0.48	0.54 (0.45 - 0.62)
IL-4	0.95 (0.77 - 1.17)	0.63	0.89	0.56 (0.47 - 0.64)	0.95 (0.77 - 1.17)	0.62	0.82	0.54 (0.45 - 0.62)
IL-6	1.06 (0.88 - 1.29)	0.53	0.78	0.50 (0.42 - 0.59)	1.13 (0.91 - 1.40)	0.28	0.58	0.54 (0.45 - 0.62)
IL-7	1.15 (0.94 - 1.40)	0.17	0.47	0.54 (0.45 - 0.62)	1.15 (0.93 - 1.41)	0.20	0.48	0.54 (0.45 - 0.63)
IL-8	1.01 (0.83 - 1.22)	0.96	0.97	0.51 (0.43 - 0.60)	1.07 (0.82 - 1.40)	0.61	0.82	0.52 (0.43 - 0.61)
IL10	1.00 (0.82 - 1.20)	0.97	0.97	0.54 (0.46 - 0.63)	1.04 (0.85 - 1.27)	0.69	0.82	0.53 (0.45 - 0.62)
LAP TGF-β-1	1.18 (0.97 - 1.42)	0.09	0.35	0.47 (0.38 - 0.55)	1.16 (0.95 - 1.42)	0.14	0.48	0.53 (0.45 - 0.62)
LIF-R	1.13 (0.93 - 1.36)	0.22	0.51	0.54 (0.45 - 0.63)	1.13 (0.93 - 1.38)	0.22	0.48	0.55 (0.46 - 0.63)
MCP-1	1.00 (0.83 - 1.22)	0.97	0.97	0.50 (0.42 - 0.59)	1.04 (0.84 - 1.29)	0.72	0.82	0.53 (0.44 - 0.61)
MCP-2	0.99 (0.82 - 1.20)	0.92	0.97	0.47 (0.38 - 0.55)	0.99 (0.82 - 1.21)	0.94	0.94	0.53 (0.45 - 0.62)
MCP-3	1.08 (0.89 - 1.32)	0.44	0.72	0.55 (0.47 - 0.64)	1.19 (0.90 - 1.56)	0.22	0.48	0.53 (0.44 - 0.61)
MCP-4	1.13 (0.93 - 1.36)	0.22	0.51	0.55 (0.47 - 0.63)	1.14 (0.93 - 1.38)	0.20	0.48	0.55 (0.46 - 0.63)
MMP-1	1.20 (0.98 - 1.46)	0.07	0.34	0.56 (0.48 - 0.65)	1.16 (0.94 - 1.42)	0.16	0.48	0.55 (0.47 - 0.64)
MMP-10	1.02 (0.84 - 1.24)	0.85	0.97	0.51 (0.43 - 0.60)	1.03 (0.84 - 1.25)	0.81	0.86	0.53 (0.44 - 0.62)
NT-3	0.90 (0.74 - 1.10)	0.31	0.60	0.53 (0.44 - 0.61)	0.91 (0.74 - 1.12)	0.37	0.67	0.53 (0.44 - 0.61)
OPG	1.12 (0.92 - 1.37)	0.25	0.55	0.51 (0.43 - 0.60)	1.14 (0.93 - 1.40)	0.21	0.48	0.53 (0.44 - 0.61)
OSM	0.97 (0.80 - 1.18)	0.74	0.94	0.51 (0.43 - 0.60)	1.09 (0.83 - 1.41)	0.55	0.82	0.53 (0.44 - 0.62)
PD-L1	0.81 (0.66 - 0.98)	0.03	0.24	0.48 (0.40 - 0.57)	0.85 (0.70 - 1.05)	0.13	0.48	0.53 (0.45 - 0.62)
SCF	1.01 (0.84 - 1.22)	0.93	0.97	0.55 (0.46 - 0.63)	0.99 (0.81 - 1.20)	0.88	0.90	0.54 (0.45 - 0.62)
SIRT2	0.75 (0.61 - 0.91)	<0.01	0.06	0.52 (0.44 - 0.61)	0.77 (0.62 - 0.96)	0.02	0.13	0.53 (0.44 - 0.62)
SLAMF1	1.01 (0.84 - 1.23)	0.91	0.97	0.51 (0.42 - 0.59)	1.04 (0.85 - 1.27)	0.68	0.82	0.54 (0.45 - 0.62)
ST1A1	1.09 (0.90 - 1.32)	0.38	0.68	0.53 (0.44 - 0.61)	1.11 (0.90 - 1.36)	0.34	0.65	0.53 (0.45 - 0.62)
STAMBP	0.72 (0.59 - 0.89)	<0.01	0.04	0.52 (0.43 - 0.60)	0.77 (0.62 - 0.95)	0.02	0.13	0.52 (0.43 - 0.61)
TGF-α	0.97 (0.79 - 1.18)	0.75	0.94	0.54 (0.45 - 0.63)	1.04 (0.84 - 1.29)	0.75	0.82	0.54 (0.46 - 0.63)
TNF	1.22 (0.99 - 1.50)	0.07	0.34	0.50 (0.42 - 0.59)	1.26 (1.01 - 1.56)	0.040	0.250	0.56 (0.47 - 0.64)
TNFB	0.98 (0.81 - 1.20)	0.87	0.97	0.55 (0.47 - 0.64)	1.03 (0.84 - 1.26)	0.79	0.86	0.54 (0.46 - 0.63)
TNFRSF9	1.24 (1.02 - 1.52)	0.03	0.24	0.53 (0.44 - 0.61)	1.31 (1.06 - 1.61)	0.01	0.13	0.52 (0.43 - 0.61)
TNFSF14	0.99 (0.81 - 1.19)	0.87	0.97	0.53 (0.44 - 0.61)	1.04 (0.82 - 1.32)	0.74	0.82	0.54 (0.45 - 0.62)
TRAIL	1.02 (0.84 - 1.24)	0.83	0.97	0.49 (0.41 - 0.57)	1.05 (0.86 - 1.28)	0.66	0.82	0.53 (0.44 - 0.61)
TRANCE	1.20 (0.99 - 1.46)	0.06	0.34	0.60 (0.52 - 0.69)	1.17 (0.96 - 1.43)	0.13	0.48	0.57 (0.48 - 0.65)
TWEAK	1.04 (0.86 - 1.25)	0.72	0.94	0.53 (0.44 - 0.61)	1.04 (0.85 - 1.26)	0.71	0.82	0.54 (0.45 - 0.62)
uPA	1.08 (0.89 - 1.32)	0.41	0.71	0.48 (0.39 - 0.57)	1.05 (0.85 - 1.30)	0.66	0.82	0.55 (0.46 - 0.63)
VEGFA	1.01 (0.83 - 1.23)	0.94	0.97	0.63 (0.55 - 0.71)	1.05 (0.86 - 1.30)	0.63	0.82	0.55 (0.46 - 0.63)

**46 infants had an NA value for FGF-5.

Supplementary Table 4. Evaluating AUC value differences between univariable and multivariable logistic regression models. Biomarkers included were shown to have a significant ability to predict infant HMF status at blood sample collection in univariable logistic regression. Multivariable models include study site, sex, and time until blood sample centrifugation. Results are p-values from DeLong's test for two correlated ROC curves. P-value<0.05 indicates AUC values are different.

Model	P-value
CCL20	0.48
CD244	0.66
CXCL6	0.32
FGF-21	0.56
EN-RAGE	0.69
CCL20 + CD244 + CXCL6 + FGF-21 + EN-RAGE	0.14

Supplementary Table 5. Linear regression associations of infant serum biomarker levels with continuous HMF duration among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use continuous HMF duration (months) to predict biomarker levels (standardized NPX).

Olink Biomarkers	Univariable			Multivariable		
	P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0.90	0.96	-0.002 (-0.029 - 0.025)	0.68	0.97	0.006 (-0.022 - 0.033)
ADA	0.22	0.96	0.017 (-0.010 - 0.044)	0.12	0.78	0.021 (-0.005 - 0.048)
AXIN1	0.30	0.96	0.014 (-0.013 - 0.041)	0.07	0.71	0.024 (-0.002 - 0.050)
CASP-8	0.78	0.96	-0.004 (-0.031 - 0.023)	0.48	0.97	-0.007 (-0.025 - 0.012)
CCL11	0.20	0.96	0.018 (-0.010 - 0.045)	0.30	0.97	0.015 (-0.013 - 0.042)
CCL19	0.84	0.96	-0.003 (-0.030 - 0.024)	0.74	0.97	-0.005 (-0.031 - 0.022)
CCL20	0.70	0.96	-0.005 (-0.032 - 0.022)	0.30	0.97	-0.015 (-0.042 - 0.013)
CCL23	0.78	0.96	0.004 (-0.023 - 0.031)	0.59	0.97	0.008 (-0.020 - 0.035)
CCL25	0.13	0.92	-0.021 (-0.048 - 0.006)	0.25	0.97	-0.016 (-0.044 - 0.012)
CCL28	0.47	0.96	0.010 (-0.017 - 0.037)	0.84	0.97	0.003 (-0.025 - 0.030)
CCL3	0.62	0.96	0.007 (-0.020 - 0.034)	0.85	0.97	-0.002 (-0.027 - 0.022)
CCL4	0.80	0.96	0.004 (-0.024 - 0.031)	0.81	0.97	-0.003 (-0.029 - 0.023)
CD244	0.02	0.48	0.032 (0.005 - 0.059)	0.01	0.37	0.031 (0.007 - 0.056)
CD40	0.60	0.96	0.007 (-0.020 - 0.034)	0.64	0.97	0.005 (-0.015 - 0.025)
CD5	0.83	0.96	-0.003 (-0.030 - 0.024)	0.88	0.97	-0.002 (-0.029 - 0.025)
CD6	0.25	0.96	0.016 (-0.011 - 0.043)	0.18	0.94	0.018 (-0.008 - 0.045)
CD8A	0.59	0.96	0.007 (-0.020 - 0.035)	0.68	0.97	0.006 (-0.022 - 0.033)
CDCP1	0.29	0.96	0.015 (-0.013 - 0.042)	0.19	0.94	0.019 (-0.009 - 0.047)
CSF-1	0.69	0.96	0.006 (-0.022 - 0.033)	0.76	0.97	0.004 (-0.023 - 0.031)
CST5	0.07	0.77	-0.025 (-0.052 - 0.002)	0.27	0.97	-0.016 (-0.043 - 0.012)
CX3CL1	0.03	0.48	-0.031 (-0.058 - -0.004)	0.06	0.71	-0.027 (-0.054 - 0.001)
CXCL1	0.21	0.96	0.017 (-0.010 - 0.044)	0.39	0.97	0.012 (-0.015 - 0.039)
CXCL10	0.71	0.96	0.005 (-0.022 - 0.032)	0.83	0.97	0.003 (-0.025 - 0.031)
CXCL11	0.58	0.96	0.008 (-0.020 - 0.035)	0.86	0.97	0.002 (-0.025 - 0.030)
CXCL5	0.90	0.96	0.002 (-0.025 - 0.029)	0.88	0.97	0.002 (-0.025 - 0.029)
CXCL6	0.37	0.96	0.012 (-0.015 - 0.040)	0.56	0.97	0.008 (-0.019 - 0.036)
CXCL9	0.01	0.33	0.035 (0.008 - 0.062)	0.02	0.37	0.034 (0.006 - 0.062)
DNER	0.80	0.96	-0.003 (-0.031 - 0.024)	0.63	0.97	-0.007 (-0.035 - 0.021)
EN-RAGE	0.28	0.96	-0.015 (-0.042 - 0.012)	0.17	0.94	-0.015 (-0.037 - 0.007)
FGF-19	0.08	0.77	-0.024 (-0.051 - 0.003)	0.06	0.71	-0.027 (-0.055 - 0.001)
FGF-21	0.96	0.97	0.001 (-0.026 - 0.028)	0.76	0.97	0.004 (-0.024 - 0.032)
FGF-23	0.61	0.96	-0.007 (-0.034 - 0.020)	0.88	0.97	-0.002 (-0.03 - 0.026)
FGF-5**	0.77	0.96	0.004 (-0.024 - 0.033)	0.79	0.97	0.004 (-0.025 - 0.033)
Flt3L	0.10	0.83	0.022 (-0.005 - 0.049)	0.07	0.71	0.026 (-0.002 - 0.054)
HGF	0.70	0.96	-0.005 (-0.033 - 0.022)	0.49	0.97	-0.009 (-0.034 - 0.016)
IFN-γ	0.68	0.96	0.006 (-0.021 - 0.033)	0.90	0.97	0.002 (-0.026 - 0.030)
IL-10RA	0.26	0.96	-0.016 (-0.043 - 0.012)	0.30	0.97	-0.015 (-0.043 - 0.013)
IL-10RB	0.34	0.96	0.013 (-0.014 - 0.040)	0.24	0.97	0.017 (-0.011 - 0.044)
IL-12B	0.57	0.96	-0.008 (-0.035 - 0.019)	0.42	0.97	-0.012 (-0.040 - 0.016)
IL-15RA	0.22	0.96	0.017 (-0.010 - 0.044)	0.22	0.97	0.018 (-0.010 - 0.046)
IL-17A	0.48	0.96	0.010 (-0.017 - 0.037)	0.47	0.97	0.01 (-0.018 - 0.039)
IL-17C	0.40	0.96	-0.012 (-0.039 - 0.015)	0.40	0.97	-0.012 (-0.040 - 0.016)
IL-18	0.65	0.96	0.006 (-0.021 - 0.033)	0.65	0.97	0.006 (-0.021 - 0.034)
IL-18R1	0.45	0.96	0.010 (-0.017 - 0.038)	0.45	0.97	0.011 (-0.017 - 0.038)
IL-4	0.95	0.97	0.001 (-0.026 - 0.028)	0.88	0.97	0.002 (-0.026 - 0.030)
IL-6	0.69	0.96	0.006 (-0.022 - 0.033)	0.81	0.97	-0.003 (-0.028 - 0.022)
IL-7	**<0.01**	**0.08**	**0.045 (0.018 - 0.072)**	**<0.01**	**0.07**	**0.049 (0.022 - 0.076)**
IL-8	0.57	0.96	0.008 (-0.019 - 0.035)	0.61	0.97	-0.005 (-0.024 - 0.014)
IL-10	0.03	0.54	0.030 (0.003 - 0.057)	0.06	0.71	0.027 (-0.001 - 0.055)
LAP TGF-β-1	0.93	0.97	-0.001 (-0.028 - 0.026)	0.81	0.97	-0.003 (-0.030 - 0.024)
LIF-R	0.08	0.77	0.024 (-0.003 - 0.051)	0.09	0.75	0.025 (-0.003 - 0.053)

MCP-1	0.87	0.96	-0.002 (-0.030 - 0.025)	0.52	0.97	-0.008 (-0.034 - 0.017)
MCP-2	0.27	0.958	-0.015 (-0.042 - 0.012)	0.27	0.97	-0.016 (-0.044 - 0.012)
MCP-3	0.28	0.96	0.015 (-0.012 - 0.042)	0.97	0.97	0.000 (-0.019 - 0.020)
MCP-4	0.75	0.96	0.004 (-0.023 - 0.032)	0.92	0.97	0.001 (-0.027 - 0.029)
MMP-1	0.73	0.96	-0.005 (-0.032 - 0.022)	0.85	0.97	-0.003 (-0.031 - 0.025)
MMP-10	0.56	0.96	-0.008 (-0.035 - 0.019)	0.42	0.97	-0.012 (-0.039 - 0.016)
NT-3	0.76	0.96	0.004 (-0.023 - 0.031)	0.80	0.97	0.004 (-0.024 - 0.032)
OPG	0.62	0.96	0.007 (-0.020 - 0.034)	0.46	0.97	0.011 (-0.017 - 0.039)
OSM	0.78	0.96	0.004 (-0.023 - 0.031)	0.67	0.97	-0.004 (-0.025 - 0.016)
PD-L1	0.51	0.96	0.009 (-0.018 - 0.036)	0.52	0.97	0.009 (-0.018 - 0.037)
SCF	0.01	0.25	-0.037 (-0.064 - -0.010)	0.01	0.27	-0.039 (-0.067 - -0.012)
SIRT2	0.70	0.96	0.005 (-0.022 - 0.032)	0.50	0.97	0.009 (-0.018 - 0.037)
SLAMF1	0.06	0.77	0.026 (-0.001 - 0.053)	0.02	0.37	0.034 (0.006 - 0.062)
ST1A1	0.96	0.97	0.001 (-0.027 - 0.028)	0.88	0.97	0.002 (-0.024 - 0.029)
STAMBP	0.65	0.96	0.006 (-0.021 - 0.033)	0.37	0.97	0.013 (-0.015 - 0.041)
TGF-α	0.76	0.96	0.004 (-0.023 - 0.031)	0.93	0.97	-0.001 (-0.027 - 0.025)
TNF	0.41	0.96	0.011 (-0.016 - 0.038)	0.69	0.97	0.006 (-0.022 - 0.034)
TNFB	0.12	0.90	0.021 (-0.006 - 0.048)	0.05	0.71	0.028 (0.000 - 0.056)
TNFRSF9	0.52	0.96	-0.009 (-0.036 - 0.018)	0.57	0.97	-0.008 (-0.036 - 0.020)
TNFSF14	0.66	0.96	-0.006 (-0.033 - 0.021)	0.37	0.97	-0.010 (-0.032 - 0.012)
TRAIL	0.95	0.97	0.001 (-0.026 - 0.028)	0.90	0.97	0.002 (-0.026 - 0.030)
TRANCE	0.90	0.96	0.002 (-0.025 - 0.029)	0.92	0.97	-0.001 (-0.030 - 0.027)
TWEAK	0.41	0.96	-0.011 (-0.039 - 0.016)	0.51	0.97	-0.009 (-0.038 - 0.019)
uPA	0.63	0.96	-0.007 (-0.034 - 0.020)	0.83	0.97	0.003 (-0.024 - 0.029)
VEGFA	0.47	0.96	0.010 (-0.017 - 0.037)	0.72	0.97	0.005 (-0.023 - 0.032)

**46 infants had an NA value for FGF-5.

Supplementary Table 6. Linear regression associations of infant serum biomarker levels with continuous exclusive HMF duration among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use continuous exclusive HMF duration (months) to predict biomarker levels (standardized NPX).

Olink Biomarkers	Univariable			Multivariable		
	P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0.42	0.96	-0.019 (-0.067 - 0.028)	0.55	0.97	-0.015 (-0.062 - 0.033)
ADA	0.12	0.90	-0.037 (-0.084 - 0.010)	0.16	0.91	-0.033 (-0.078 - 0.013)
AXIN1	0.63	0.96	0.012 (-0.036 - 0.060)	0.57	0.97	0.013 (-0.032 - 0.058)
CASP-8	0.48	0.96	-0.017 (-0.065 - 0.030)	0.67	0.97	-0.007 (-0.039 - 0.025)
CCL11	0.24	0.96	0.029 (-0.019 - 0.076)	0.33	0.97	0.023 (-0.024 - 0.071)
CCL19	0.64	0.96	0.011 (-0.036 - 0.059)	0.92	0.97	0.002 (-0.043 - 0.048)
CCL20	0.71	0.96	0.009 (-0.039 - 0.057)	0.88	0.97	-0.004 (-0.052 - 0.044)
CCL23	0.40	0.96	0.020 (-0.027 - 0.068)	0.48	0.97	0.017 (-0.031 - 0.065)
CCL25	0.08	0.77	-0.042 (-0.089 - 0.005)	0.10	0.75	-0.040 (-0.088 - 0.008)
CCL28	0.84	0.96	0.005 (-0.043 - 0.053)	0.93	0.97	-0.002 (-0.050 - 0.045)
CCL3	0.63	0.96	0.012 (-0.036 - 0.059)	0.45	0.97	0.017 (-0.027 - 0.060)
CCL4	0.90	0.96	-0.003 (-0.051 - 0.045)	0.89	0.97	0.003 (-0.042 - 0.048)
CD244	0.64	0.96	0.012 (-0.036 - 0.059)	0.44	0.97	0.017 (-0.026 - 0.060)
CD40	0.54	0.96	-0.015 (-0.062 - 0.033)	0.75	0.97	-0.006 (-0.040 - 0.029)
CD5	0.58	0.96	-0.013 (-0.061 - 0.034)	0.72	0.97	-0.008 (-0.055 - 0.038)
CD6	0.23	0.96	0.029 (-0.018 - 0.076)	0.11	0.75	0.038 (-0.008 - 0.084)
CD8A	0.09	0.83	0.041 (-0.007 - 0.088)	0.15	0.91	0.035 (-0.013 - 0.083)
CDCP1	0.58	0.96	0.013 (-0.034 - 0.061)	0.51	0.97	0.016 (-0.032 - 0.065)
CSF-1	0.91	0.96	-0.003 (-0.050 - 0.045)	0.92	0.97	0.002 (-0.044 - 0.049)
CST5	0.63	0.96	-0.012 (-0.059 - 0.036)	0.95	0.97	-0.002 (-0.050 - 0.047)
CX3CL1	0.35	0.96	-0.023 (-0.070 - 0.025)	0.38	0.97	-0.021 (-0.069 - 0.026)
CXCL1	0.50	0.96	0.016 (-0.031 - 0.064)	0.69	0.97	0.010 (-0.038 - 0.057)
CXCL10	0.89	0.96	-0.003 (-0.051 - 0.044)	0.73	0.97	-0.009 (-0.058 - 0.040)
CXCL11	0.48	0.96	-0.017 (-0.065 - 0.031)	0.31	0.97	-0.024 (-0.071 - 0.023)
CXCL5	0.47	0.96	0.018 (-0.030 - 0.065)	0.75	0.97	0.008 (-0.039 - 0.054)
CXCL6	0.07	0.77	0.043 (-0.004 - 0.091)	0.10	0.75	0.040 (-0.008 - 0.088)
CXCL9	0.98	0.98	0.001 (-0.047 - 0.048)	0.75	0.97	-0.008 (-0.056 - 0.041)
DNER	0.84	0.96	0.005 (-0.043 - 0.053)	0.74	0.97	0.008 (-0.040 - 0.056)
EN-RAGE	0.73	0.96	-0.008 (-0.056 - 0.039)	0.61	0.97	-0.010 (-0.049 - 0.029)
FGF-19	0.10	0.83	-0.038 (-0.084 - 0.007)	0.11	0.75	-0.039 (-0.086 - 0.008)
FGF-21	0.24	0.96	0.028 (-0.019 - 0.075)	0.21	0.96	0.031 (-0.017 - 0.079)
FGF-23	0.91	0.96	-0.003 (-0.050 - 0.045)	1.00	1.00	0.000 (-0.048 - 0.048)
FGF-5**	0.26	0.96	0.028 (-0.021 - 0.078)	0.30	0.97	0.027 (-0.024 - 0.077)
Flt3L	0.18	0.96	0.033 (-0.015 - 0.080)	0.10	0.75	0.041 (-0.007 - 0.089)
HGF	0.36	0.96	-0.022 (-0.070 - 0.025)	0.33	0.97	-0.022 (-0.066 - 0.022)
IFN-γ	0.67	0.96	-0.010 (-0.058 - 0.037)	0.46	0.97	-0.018 (-0.067 - 0.031)
IL-10RA	0.51	0.96	-0.016 (-0.062 - 0.031)	0.55	0.97	-0.014 (-0.062 - 0.033)
IL-10RB	0.64	0.96	-0.011 (-0.059 - 0.036)	0.78	0.97	-0.007 (-0.055 - 0.042)
IL-12B	0.73	0.96	0.008 (-0.040 - 0.056)	0.96	0.97	0.001 (-0.048 - 0.050)
IL-15RA	0.38	0.96	0.021 (-0.026 - 0.069)	0.43	0.97	0.020 (-0.029 - 0.069)
IL-17A	0.66	0.96	-0.011 (-0.058 - 0.037)	0.56	0.97	-0.014 (-0.063 - 0.034)
IL-17C	0.54	0.96	-0.015 (-0.062 - 0.033)	0.47	0.97	-0.018 (-0.067 - 0.031)
IL-18	0.76	0.96	0.007 (-0.040 - 0.055)	0.82	0.97	0.005 (-0.042 - 0.053)
IL-18R1	0.94	0.96	-0.002 (-0.049 - 0.046)	0.96	0.97	-0.001 (-0.049 - 0.047)
IL-4	0.72	0.97	-0.009 (-0.056 - 0.039)	0.85	0.97	-0.005 (-0.054 - 0.044)
IL-6	0.60	0.96	0.013 (-0.035 - 0.060)	0.50	0.97	0.015 (-0.029 - 0.059)
IL-7	**<0.01**	**0.08**	**0.079 (0.032 - 0.126)**	**<0.01**	**0.11**	**0.077 (0.030 - 0.124)**
IL-8	0.61	0.96	0.013 (-0.035 - 0.060)	0.32	0.97	0.016 (-0.016 - 0.048)
IL-10	0.86	0.54	0.004 (-0.043 - 0.052)	0.78	0.97	-0.007 (-0.055 - 0.042)
LAP TGF-β-1	0.27	0.97	0.027 (-0.021 - 0.075)	0.18	0.94	0.032 (-0.015 - 0.080)
LIF-R	0.02	0.77	0.055 (0.008 - 0.102)	0.03	0.51	0.055 (0.006 - 0.103)

MCP-1	0.88	0.96	0.004 (-0.044 - 0.051)	0.84	0.97	0.005 (-0.040 - 0.049)
MCP-2	0.88	0.96	0.004 (-0.044 - 0.052)	0.94	0.97	0.002 (-0.047 - 0.051)
MCP-3	0.28	0.96	0.026 (-0.022 - 0.073)	0.11	0.75	0.027 (-0.006 - 0.060)
MCP-4	0.80	0.96	-0.006 (-0.054 - 0.042)	0.55	0.97	-0.015 (-0.064 - 0.034)
MMP-1	0.49	0.96	-0.017 (-0.065 - 0.031)	0.55	0.97	-0.015 (-0.064 - 0.034)
MMP-10	0.74	0.96	-0.008 (-0.055 - 0.040)	0.42	0.97	-0.020 (-0.068 - 0.029)
NT-3	0.32	0.96	0.024 (-0.023 - 0.072)	0.26	0.97	0.028 (-0.020 - 0.076)
OPG	0.31	0.96	0.025 (-0.023 - 0.072)	0.19	0.94	0.032 (-0.016 - 0.081)
OSM	0.79	0.96	-0.006 (-0.054 - 0.041)	0.80	0.97	-0.004 (-0.039 - 0.030)
PD-L1	0.83	0.96	-0.005 (-0.053 - 0.043)	0.72	0.97	-0.009 (-0.057 - 0.039)
SCF	<0.01	0.25	-0.07 (-0.117 - -0.023)	0.01	0.32	-0.064 (-0.112 - -0.017)
SIRT2	0.62	0.96	-0.012 (-0.060 - 0.036)	0.80	0.97	-0.006 (-0.053 - 0.041)
SLAMF1	0.07	0.77	0.044 (-0.003 - 0.091)	0.04	0.59	0.052 (0.004 - 0.100)
ST1A1	0.72	0.97	-0.009 (-0.056 - 0.039)	0.82	0.97	-0.005 (-0.051 - 0.041)
STAMBP	0.46	0.96	-0.018 (-0.065 - 0.030)	0.56	0.97	-0.014 (-0.063 - 0.034)
TGF-α	0.95	0.96	-0.001 (-0.049 - 0.046)	0.65	0.97	-0.010 (-0.056 - 0.035)
TNF	0.59	0.96	0.013 (-0.035 - 0.061)	0.73	0.97	0.009 (-0.040 - 0.058)
TNFB	0.24	0.90	0.028 (-0.019 - 0.076)	0.20	0.96	0.031 (-0.017 - 0.080)
TNFRSF9	0.39	0.96	-0.021 (-0.068 - 0.027)	0.35	0.97	-0.023 (-0.071 - 0.025)
TNFSF14	0.38	0.96	-0.021 (-0.069 - 0.026)	0.39	0.97	-0.017 (-0.055 - 0.021)
TRAIL	0.28	0.97	-0.026 (-0.074 - 0.021)	0.16	0.91	-0.035 (-0.083 - 0.013)
TRANCE	0.67	0.96	-0.010 (-0.058 - 0.037)	0.56	0.97	-0.014 (-0.064 - 0.035)
TWEAK	0.81	0.96	0.006 (-0.042 - 0.054)	0.63	0.97	0.012 (-0.037 - 0.061)
uPA	0.23	0.96	-0.029 (-0.077 - 0.019)	0.64	0.97	-0.011 (-0.057 - 0.035)
VEGFA	0.35	0.96	0.023 (-0.025 - 0.070)	0.44	0.97	0.019 (-0.029 - 0.066)

**46 infants had an NA value for FGF-5.

Supplementary Table 7. Linear regression associations of infant serum biomarker levels with categorical HMF duration (infants grouped in two-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use categorical HMF duration (infants grouped in two-month intervals) to predict biomarker levels (standardized NPX). The >10m HMF group was used as reference.

Olink Biomarkers	Variable Groups	Univariable			Multivariable		
		P-value	FDR P-value	β -coefficient (95% CI)	P-value	FDR P-value	β -coefficient (95% CI)
4E-BP1	0m	0.60	0.90	0.139 (-0.378 - 0.656)	0.89	0.97	0.036 (-0.485 - 0.558)
	0 - ≤2m	0.80	0.95	-0.049 (-0.437 - 0.339)	0.41	0.78	-0.163 (-0.554 - 0.228)
	2 - ≤4m	0.71	0.93	-0.079 (-0.494 - 0.336)	0.64	0.87	-0.097 (-0.507 - 0.313)
	4 - ≤6m	0.82	0.95	-0.042 (-0.402 - 0.319)	0.82	0.93	-0.041 (-0.397 - 0.315)
	6 - ≤8m	0.22	0.71	-0.203 (-0.531 - 0.125)	0.23	0.71	-0.199 (-0.525 - 0.127)
	8 - ≤10m	0.86	0.96	-0.029 (-0.364 - 0.306)	0.87	0.96	-0.027 (-0.358 - 0.304)
ADA	0m	0.65	0.91	-0.120 (-0.638 - 0.398)	0.31	0.75	-0.258 (-0.763 - 0.246)
	0 - ≤2m	0.23	0.71	-0.235 (-0.623 - 0.153)	0.22	0.71	-0.238 (-0.616 - 0.141)
	2 - ≤4m	0.57	0.89	-0.120 (-0.535 - 0.296)	0.32	0.75	-0.202 (-0.599 - 0.195)
	4 - ≤6m	0.73	0.93	-0.064 (-0.425 - 0.297)	0.47	0.79	-0.126 (-0.471 - 0.218)
	6 - ≤8m	0.82	0.95	-0.038 (-0.366 - 0.290)	0.33	0.75	-0.156 (-0.471 - 0.159)
	8 - ≤10m	0.84	0.95	-0.034 (-0.369 - 0.301)	0.57	0.84	-0.093 (-0.414 - 0.228)
AXIN1	0m	0.94	0.98	-0.021 (-0.538 - 0.496)	0.21	0.71	-0.308 (-0.794 - 0.179)
	0 - ≤2m	0.19	0.71	-0.258 (-0.646 - 0.130)	0.06	0.55	-0.354 (-0.718 - 0.011)
	2 - ≤4m	0.53	0.87	-0.133 (-0.548 - 0.283)	0.21	0.71	-0.246 (-0.628 - 0.137)
	4 - ≤6m	0.45	0.84	-0.139 (-0.499 - 0.222)	0.23	0.71	-0.203 (-0.536 - 0.129)
	6 - ≤8m	0.49	0.85	-0.116 (-0.444 - 0.212)	0.06	0.55	-0.290 (-0.594 - 0.014)
	8 - ≤10m	0.89	0.97	-0.023 (-0.358 - 0.312)	0.39	0.77	-0.135 (-0.444 - 0.173)
CASP-8	0m	0.50	0.85	0.178 (-0.336 - 0.693)	0.47	0.79	0.130 (-0.221 - 0.480)
	0 - ≤2m	0.43	0.84	-0.154 (-0.540 - 0.232)	0.95	0.98	-0.009 (-0.272 - 0.253)
	2 - ≤4m	0.32	0.80	0.207 (-0.206 - 0.620)	0.45	0.79	0.107 (-0.169 - 0.382)
	4 - ≤6m	0.85	0.95	-0.034 (-0.392 - 0.325)	0.28	0.72	-0.132 (-0.371 - 0.108)
	6 - ≤8m	0.15	0.66	0.240 (-0.086 - 0.567)	0.45	0.79	0.085 (-0.134 - 0.303)
	8 - ≤10m	0.90	0.97	-0.022 (-0.355 - 0.312)	0.49	0.80	-0.078 (-0.300 - 0.145)
CCL11	0m	0.42	0.84	0.210 (-0.303 - 0.723)	0.45	0.79	0.199 (-0.319 - 0.716)
	0 - ≤2m	0.05	0.52	-0.390 (-0.775 - -0.006)	0.10	0.58	-0.326 (-0.713 - 0.062)
	2 - ≤4m	0.47	0.85	-0.152 (-0.564 - 0.260)	0.41	0.78	-0.170 (-0.576 - 0.237)
	4 - ≤6m	0.92	0.98	0.018 (-0.340 - 0.375)	0.86	0.95	0.033 (-0.321 - 0.386)
	6 - ≤8m	0.45	0.84	-0.124 (-0.450 - 0.201)	0.28	0.72	-0.179 (-0.502 - 0.144)
	8 - ≤10m	0.75	0.93	0.053 (-0.279 - 0.386)	0.82	0.93	0.039 (-0.290 - 0.367)
CCL19	0m	0.07	0.56	0.478 (-0.032 - 0.988)	0.03	0.55	0.553 (0.057 - 1.049)
	0 - ≤2m	0.99	0.99	-0.003 (-0.386 - 0.379)	0.94	0.98	-0.015 (-0.387 - 0.356)
	2 - ≤4m	0.07	0.56	-0.382 (-0.792 - 0.028)	0.11	0.58	-0.319 (-0.709 - 0.071)
	4 - ≤6m	0.30	0.78	-0.190 (-0.545 - 0.166)	0.52	0.82	-0.112 (-0.451 - 0.227)
	6 - ≤8m	0.17	0.68	-0.226 (-0.550 - 0.097)	0.33	0.75	-0.155 (-0.464 - 0.155)
	8 - ≤10m	0.46	0.84	-0.125 (-0.456 - 0.205)	0.59	0.86	-0.085 (-0.400 - 0.230)
CCL20	0m	0.38	0.82	0.229 (-0.285 - 0.743)	0.18	0.69	0.357 (-0.162 - 0.875)
	0 - ≤2m	0.26	0.74	-0.220 (-0.606 - 0.165)	0.58	0.85	-0.109 (-0.498 - 0.279)
	2 - ≤4m	0.17	0.68	0.286 (-0.127 - 0.698)	0.10	0.58	0.338 (-0.069 - 0.746)
	4 - ≤6m	0.70	0.93	-0.071 (-0.429 - 0.288)	0.98	1.00	-0.004 (-0.358 - 0.350)
	6 - ≤8m	0.55	0.88	-0.100 (-0.426 - 0.226)	0.66	0.88	-0.073 (-0.397 - 0.251)
	8 - ≤10m	0.54	0.88	-0.103 (-0.436 - 0.230)	0.64	0.87	-0.079 (-0.408 - 0.250)
CCL23	0m	0.84	0.95	0.052 (-0.465 - 0.568)	0.83	0.94	-0.055 (-0.577 - 0.466)
	0 - ≤2m	0.22	0.71	-0.244 (-0.631 - 0.144)	0.12	0.60	-0.311 (-0.702 - 0.079)
	2 - ≤4m	0.31	0.78	-0.215 (-0.63 - 0.200)	0.26	0.72	-0.235 (-0.645 - 0.175)
	4 - ≤6m	0.33	0.80	-0.178 (-0.538 - 0.182)	0.37	0.76	-0.163 (-0.519 - 0.193)
	6 - ≤8m	0.48	0.85	-0.118 (-0.446 - 0.210)	0.36	0.75	-0.152 (-0.478 - 0.173)
	8 - ≤10m	0.25	0.72	-0.196 (-0.531 - 0.139)	0.19	0.71	-0.221 (-0.552 - 0.110)
CCL25	0m	0.03	0.49	0.563 (0.049 - 1.078)	0.08	0.58	0.472 (-0.053 - 0.997)

	0 - ≤2m	0.75	0.93	0.062 (-0.324 - 0.448)	0.98	0.99	0.006 (-0.387 - 0.400)
	2 - ≤4m	0.22	0.71	0.260 (-0.153 - 0.674)	0.27	0.72	0.234 (-0.179 - 0.646)
	4 - ≤6m	0.44	0.84	0.140 (-0.219 - 0.498)	0.39	0.77	0.156 (-0.203 - 0.514)
	6 - ≤8m	0.36	0.82	0.152 (-0.174 - 0.478)	0.46	0.79	0.124 (-0.204 - 0.452)
	8 - ≤10m	0.71	0.93	0.064 (-0.270 - 0.397)	0.70	0.90	0.066 (-0.267 - 0.399)
	0m	0.77	0.95	-0.077 (-0.593 - 0.439)	0.86	0.95	0.046 (-0.470 - 0.562)
CCL28	0 - ≤2m	0.48	0.85	-0.139 (-0.526 - 0.248)	0.81	0.93	-0.048 (-0.435 - 0.339)
	2 - ≤4m	0.35	0.81	-0.197 (-0.611 - 0.217)	0.47	0.79	-0.149 (-0.554 - 0.257)
	4 - ≤6m	0.89	0.97	-0.024 (-0.384 - 0.336)	0.81	0.93	0.044 (-0.309 - 0.396)
	6 - ≤8m	0.11	0.61	-0.270 (-0.597 - 0.058)	0.17	0.69	-0.225 (-0.547 - 0.098)
	8 - ≤10m	0.87	0.96	-0.027 (-0.361 - 0.308)	0.89	0.97	0.022 (-0.306 - 0.350)
	0m	0.55	0.88	0.158 (-0.355 - 0.671)	0.16	0.69	0.333 (-0.132 - 0.798)
	0 - ≤2m	0.05	0.52	-0.386 (-0.771 - -0.001)	0.24	0.71	-0.210 (-0.558 - 0.139)
	2 - ≤4m	0.57	0.89	-0.121 (-0.533 - 0.291)	0.55	0.83	-0.110 (-0.476 - 0.256)
CCL3	4 - ≤6m	0.16	0.66	-0.258 (-0.616 - 0.100)	0.10	0.58	-0.270 (-0.588 - 0.048)
	6 - ≤8m	0.35	0.82	-0.154 (-0.479 - 0.172)	0.30	0.75	-0.152 (-0.442 - 0.139)
	8 - ≤10m	0.09	0.59	-0.290 (-0.623 - 0.042)	0.10	0.58	-0.250 (-0.545 - 0.046)
	0m	0.34	0.80	0.251 (-0.262 - 0.763)	0.11	0.59	0.388 (-0.094 - 0.869)
	0 - ≤2m	0.04	0.52	-0.394 (-0.778 - -0.009)	0.16	0.69	-0.260 (-0.620 - 0.101)
	2 - ≤4m	0.77	0.95	0.060 (-0.351 - 0.472)	0.74	0.90	0.065 (-0.314 - 0.444)
CCL4	4 - ≤6m	0.25	0.71	-0.211 (-0.568 - 0.146)	0.18	0.69	-0.227 (-0.556 - 0.102)
	6 - ≤8m	0.48	0.85	-0.118 (-0.443 - 0.208)	0.47	0.79	-0.110 (-0.411 - 0.191)
	8 - ≤10m	0.23	0.71	-0.203 (-0.535 - 0.129)	0.29	0.74	-0.165 (-0.471 - 0.141)
	0m	0.22	0.71	-0.321 (-0.832 - 0.190)	0.10	0.58	-0.387 (-0.847 - 0.073)
	0 - ≤2m	0.03	0.49	-0.425 (-0.808 - -0.041)	0.05	0.55	-0.348 (-0.693 - -0.003)
	2 - ≤4m	0.17	0.68	-0.285 (-0.696 - 0.125)	0.05	0.55	-0.364 (-0.725 - -0.002)
CD244	4 - ≤6m	0.63	0.91	0.089 (-0.268 - 0.445)	0.82	0.93	0.037 (-0.278 - 0.351)
	6 - ≤8m	0.98	0.99	-0.005 (-0.329 - 0.320)	0.39	0.77	-0.126 (-0.413 - 0.161)
	8 - ≤10m	0.84	0.95	0.035 (-0.297 - 0.366)	0.99	1.00	0.002 (-0.290 - 0.294)
	0m	0.67	0.93	-0.110 (-0.625 - 0.404)	0.39	0.77	-0.168 (-0.551 - 0.216)
	0 - ≤2m	0.23	0.71	-0.236 (-0.622 - 0.150)	0.45	0.79	-0.111 (-0.399 - 0.176)
	2 - ≤4m	0.37	0.82	0.189 (-0.224 - 0.602)	0.55	0.83	0.092 (-0.209 - 0.394)
CD40	4 - ≤6m	0.80	0.95	0.047 (-0.312 - 0.405)	0.80	0.93	-0.033 (-0.295 - 0.229)
	6 - ≤8m	0.20	0.71	0.214 (-0.112 - 0.540)	0.57	0.84	0.069 (-0.170 - 0.309)
	8 - ≤10m	0.73	0.93	0.058 (-0.275 - 0.391)	0.89	0.97	0.017 (-0.226 - 0.261)
	0m	0.03	0.49	0.569 (0.057 - 1.081)	0.04	0.55	0.517 (0.014 - 1.019)
	0 - ≤2m	0.21	0.71	-0.248 (-0.632 - 0.136)	0.28	0.72	-0.208 (-0.584 - 0.169)
	2 - ≤4m	0.57	0.89	-0.118 (-0.529 - 0.293)	0.39	0.77	-0.171 (-0.566 - 0.224)
CD5	4 - ≤6m	0.85	0.95	-0.035 (-0.392 - 0.322)	0.73	0.90	-0.061 (-0.404 - 0.282)
	6 - ≤8m	0.82	0.95	-0.037 (-0.362 - 0.288)	0.45	0.79	-0.122 (-0.435 - 0.192)
	8 - ≤10m	0.47	0.85	-0.121 (-0.453 - 0.211)	0.39	0.77	-0.140 (-0.459 - 0.179)
	0m	0.17	0.68	0.355 (-0.156 - 0.866)	0.23	0.71	0.303 (-0.197 - 0.802)
	0 - ≤2m	0.03	0.49	-0.417 (-0.800 - -0.033)	0.04	0.55	-0.388 (-0.763 - -0.014)
	2 - ≤4m	0.18	0.69	-0.278 (-0.688 - 0.132)	0.10	0.58	-0.334 (-0.727 - 0.059)
CD6	4 - ≤6m	0.46	0.84	-0.134 (-0.490 - 0.223)	0.30	0.75	-0.181 (-0.523 - 0.160)
	6 - ≤8m	0.53	0.87	-0.103 (-0.427 - 0.221)	0.26	0.72	-0.179 (-0.491 - 0.133)
	8 - ≤10m	0.14	0.66	-0.248 (-0.579 - 0.083)	0.10	0.58	-0.268 (-0.586 - 0.049)
	0m	0.15	0.66	0.372 (-0.139 - 0.882)	0.11	0.58	0.419 (-0.095 - 0.932)
	0 - ≤2m	0.30	0.78	-0.200 (-0.583 - 0.183)	0.32	0.75	-0.193 (-0.578 - 0.192)
	2 - ≤4m	0.04	0.49	-0.436 (-0.846 - -0.026)	0.05	0.55	-0.400 (-0.804 - 0.004)
CD8A	4 - ≤6m	0.51	0.86	-0.120 (-0.476 - 0.236)	0.73	0.90	-0.063 (-0.414 - 0.288)
	6 - ≤8m	0.14	0.66	-0.246 (-0.570 - 0.078)	0.18	0.69	-0.221 (-0.541 - 0.100)
	8 - ≤10m	0.16	0.66	-0.240 (-0.571 - 0.091)	0.19	0.71	-0.218 (-0.545 - 0.108)
	0m	0.53	0.87	-0.165 (-0.680 - 0.351)	0.31	0.75	-0.272 (-0.800 - 0.255)
	0 - ≤2m	0.40	0.84	-0.164 (-0.551 - 0.222)	0.34	0.75	-0.193 (-0.588 - 0.202)
	2 - ≤4m	0.16	0.66	-0.299 (-0.713 - 0.115)	0.10	0.58	-0.345 (-0.760 - 0.069)
CDCP1	4 - ≤6m	0.07	0.56	-0.335 (-0.695 - 0.024)	0.05	0.55	-0.366 (-0.726 - -0.005)
	6 - ≤8m	0.21	0.71	-0.209 (-0.536 - 0.118)	0.11	0.58	-0.271 (-0.600 - 0.058)
	8 - ≤10m	0.16	0.66	-0.239 (-0.573 - 0.095)	0.10	0.58	-0.277 (-0.612 - 0.058)
	0m	0.76	0.94	0.082 (-0.435 - 0.599)	0.76	0.91	0.079 (-0.431 - 0.589)
CSF-1	0 - ≤2m	0.29	0.77	-0.210 (-0.598 - 0.178)	0.45	0.79	-0.148 (-0.530 - 0.234)
	2 - ≤4m	0.70	0.93	0.082 (-0.333 - 0.497)	0.82	0.93	0.046 (-0.355 - 0.446)

	4 - ≤6m	0.81	0.95	-0.044 (-0.405 - 0.317)	0.64	0.87	-0.083 (-0.431 - 0.265)
	6 - ≤8m	0.99	0.99	-0.002 (-0.331 - 0.326)	0.72	0.90	-0.058 (-0.377 - 0.260)
	8 - ≤10m	0.80	0.95	-0.042 (-0.378 - 0.293)	0.73	0.90	-0.057 (-0.381 - 0.266)
	0m	0.16	0.66	0.366 (-0.147 - 0.879)	0.41	0.77	0.220 (-0.300 - 0.740)
	0 - ≤2m	0.48	0.85	0.140 (-0.245 - 0.525)	0.92	0.98	0.021 (-0.369 - 0.411)
CST5	2 - ≤4m	0.23	0.71	0.253 (-0.159 - 0.665)	0.32	0.75	0.206 (-0.202 - 0.615)
	4 - ≤6m	0.30	0.78	0.189 (-0.169 - 0.547)	0.40	0.77	0.152 (-0.204 - 0.507)
	6 - ≤8m	0.36	0.82	0.150 (-0.175 - 0.476)	0.48	0.79	0.116 (-0.209 - 0.440)
	8 - ≤10m	0.36	0.82	-0.156 (-0.488 - 0.176)	0.28	0.72	-0.182 (-0.512 - 0.148)
	0m	0.72	0.93	0.091 (-0.415 - 0.597)	0.88	0.96	0.039 (-0.469 - 0.547)
	0 - ≤2m	0.02	0.49	0.471 (0.091 - 0.851)	0.05	0.55	0.386 (0.006 - 0.767)
CX3CL1	2 - ≤4m	0.63	0.91	0.098 (-0.308 - 0.505)	0.60	0.86	0.106 (-0.293 - 0.505)
	4 - ≤6m	0.00	0.37	0.537 (0.184 - 0.890)	0.00	0.28	0.553 (0.206 - 0.900)
	6 - ≤8m	0.82	0.95	-0.037 (-0.358 - 0.284)	0.94	0.98	-0.012 (-0.329 - 0.305)
	8 - ≤10m	0.94	0.98	0.012 (-0.316 - 0.34)	0.93	0.98	0.014 (-0.308 - 0.336)
	0m	0.94	0.98	-0.019 (-0.531 - 0.492)	0.97	0.99	-0.010 (-0.518 - 0.499)
	0 - ≤2m	0.03	0.49	-0.421 (-0.805 - -0.038)	0.09	0.58	-0.328 (-0.709 - 0.053)
CXCL1	2 - ≤4m	0.60	0.90	0.110 (-0.300 - 0.521)	0.65	0.87	0.093 (-0.307 - 0.493)
	4 - ≤6m	0.49	0.85	0.125 (-0.231 - 0.482)	0.44	0.79	0.137 (-0.210 - 0.485)
	6 - ≤8m	0.43	0.84	0.130 (-0.194 - 0.455)	0.66	0.88	0.070 (-0.247 - 0.388)
	8 - ≤10m	0.45	0.84	0.126 (-0.205 - 0.457)	0.49	0.80	0.112 (-0.211 - 0.435)
	0m	0.20	0.71	0.333 (-0.182 - 0.848)	0.20	0.71	0.347 (-0.183 - 0.878)
	0 - ≤2m	0.22	0.71	-0.242 (-0.628 - 0.144)	0.31	0.75	-0.206 (-0.604 - 0.191)
CXCL10	2 - ≤4m	0.61	0.90	-0.106 (-0.519 - 0.307)	0.63	0.87	-0.101 (-0.518 - 0.316)
	4 - ≤6m	0.38	0.82	-0.161 (-0.520 - 0.198)	0.39	0.77	-0.159 (-0.521 - 0.204)
	6 - ≤8m	0.39	0.82	-0.142 (-0.469 - 0.184)	0.36	0.75	-0.155 (-0.486 - 0.176)
	8 - ≤10m	0.40	0.84	-0.142 (-0.476 - 0.191)	0.35	0.75	-0.160 (-0.497 - 0.177)
	0m	0.37	0.82	0.234 (-0.280 - 0.749)	0.32	0.75	0.256 (-0.254 - 0.766)
	0 - ≤2m	0.10	0.60	-0.319 (-0.705 - 0.067)	0.27	0.72	-0.217 (-0.599 - 0.165)
CXCL11	2 - ≤4m	0.94	0.98	0.015 (-0.398 - 0.429)	0.99	1.00	0.003 (-0.398 - 0.403)
	4 - ≤6m	0.42	0.84	-0.148 (-0.506 - 0.211)	0.40	0.77	-0.151 (-0.499 - 0.198)
	6 - ≤8m	0.98	0.99	0.005 (-0.321 - 0.332)	0.76	0.91	-0.050 (-0.368 - 0.269)
	8 - ≤10m	0.46	0.84	-0.126 (-0.459 - 0.207)	0.35	0.75	-0.153 (-0.476 - 0.171)
	0m	0.82	0.95	0.060 (-0.453 - 0.574)	0.89	0.97	-0.035 (-0.543 - 0.472)
	0 - ≤2m	0.80	0.95	-0.049 (-0.434 - 0.336)	0.71	0.90	-0.071 (-0.451 - 0.309)
CXCL5	2 - ≤4m	0.38	0.82	0.185 (-0.228 - 0.597)	0.40	0.77	0.173 (-0.226 - 0.571)
	4 - ≤6m	0.05	0.52	0.363 (0.005 - 0.721)	0.03	0.55	0.376 (0.029 - 0.722)
	6 - ≤8m	0.11	0.61	0.267 (-0.059 - 0.593)	0.16	0.69	0.225 (-0.092 - 0.542)
	8 - ≤10m	0.15	0.66	0.243 (-0.090 - 0.576)	0.24	0.71	0.192 (-0.131 - 0.514)
	0m	0.24	0.71	0.299 (-0.206 - 0.805)	0.22	0.71	0.318 (-0.194 - 0.83)
	0 - ≤2m	0.01	0.49	-0.507 (-0.886 - -0.128)	0.02	0.55	-0.444 (-0.827 - -0.061)
CXCL6	2 - ≤4m	0.32	0.80	0.203 (-0.202 - 0.609)	0.33	0.75	0.199 (-0.204 - 0.601)
	4 - ≤6m	0.52	0.87	0.116 (-0.236 - 0.468)	0.46	0.79	0.132 (-0.218 - 0.481)
	6 - ≤8m	0.10	0.59	0.272 (-0.049 - 0.592)	0.13	0.62	0.247 (-0.073 - 0.566)
	8 - ≤10m	0.52	0.87	0.107 (-0.220 - 0.434)	0.51	0.81	0.109 (-0.216 - 0.434)
	0m	0.92	0.98	-0.026 (-0.537 - 0.486)	0.81	0.93	-0.063 (-0.585 - 0.459)
	0 - ≤2m	0.01	0.49	-0.532 (-0.916 - -0.148)	0.01	0.45	-0.501 (-0.892 - -0.110)
CXCL9	2 - ≤4m	0.31	0.78	-0.213 (-0.624 - 0.198)	0.27	0.72	-0.229 (-0.639 - 0.181)
	4 - ≤6m	0.05	0.52	-0.357 (-0.713 – 0.000)	0.06	0.55	-0.341 (-0.698 - 0.015)
	6 - ≤8m	0.25	0.72	-0.189 (-0.514 - 0.136)	0.15	0.65	-0.241 (-0.566 - 0.085)
	8 - ≤10m	0.38	0.82	-0.148 (-0.480 - 0.183)	0.31	0.75	-0.172 (-0.504 - 0.159)
	0m	0.60	0.90	-0.137 (-0.651 - 0.378)	0.76	0.91	-0.082 (-0.604 - 0.440)
	0 - ≤2m	0.71	0.93	0.072 (-0.313 - 0.458)	0.50	0.81	0.133 (-0.258 - 0.524)
DNER	2 - ≤4m	0.65	0.91	-0.096 (-0.509 - 0.317)	0.64	0.87	-0.099 (-0.509 - 0.311)
	4 - ≤6m	0.08	0.59	0.320 (-0.039 - 0.679)	0.07	0.55	0.326 (-0.030 - 0.683)
	6 - ≤8m	0.73	0.93	-0.057 (-0.384 - 0.269)	0.69	0.90	-0.065 (-0.391 - 0.260)
	8 - ≤10m	0.83	0.95	0.037 (-0.296 - 0.370)	0.71	0.90	0.062 (-0.270 - 0.393)
	0m	0.02	0.49	0.587 (0.077 - 1.097)	0.05	0.55	0.419 (0.005 - 0.834)
	0 - ≤2m	0.41	0.84	-0.161 (-0.543 - 0.222)	0.61	0.87	-0.081 (-0.391 - 0.230)
EN-RAGE	2 - ≤4m	0.29	0.78	0.220 (-0.190 - 0.629)	0.52	0.82	0.105 (-0.220 - 0.431)
	4 - ≤6m	0.14	0.66	0.268 (-0.087 - 0.624)	0.24	0.71	0.169 (-0.114 - 0.453)
	6 - ≤8m	0.08	0.59	0.292 (-0.032 - 0.615)	0.56	0.84	0.077 (-0.182 - 0.336)

	8 - ≤10m	0.74	0.93	0.057 (-0.274 - 0.387)	0.56	0.84	-0.078 (-0.341 - 0.185)
	0m	0.10	0.60	0.430 (-0.086 - 0.945)	0.07	0.55	0.496 (-0.035 - 1.027)
	0 - ≤2m	0.18	0.69	0.265 (-0.122 - 0.652)	0.14	0.65	0.298 (-0.100 - 0.696)
FGF-19	2 - ≤4m	0.19	0.71	0.274 (-0.140 - 0.688)	0.17	0.69	0.291 (-0.126 - 0.709)
	4 - ≤6m	0.58	0.89	0.100 (-0.259 - 0.459)	0.60	0.86	0.097 (-0.265 - 0.460)
	6 - ≤8m	0.23	0.71	0.198 (-0.129 - 0.525)	0.19	0.71	0.221 (-0.110 - 0.552)
	8 - ≤10m	0.30	0.78	0.177 (-0.156 - 0.511)	0.27	0.72	0.19 (-0.147 - 0.527)
	0m	0.68	0.93	-0.110 (-0.627 - 0.407)	0.55	0.83	-0.159 (-0.686 - 0.368)
	0 - ≤2m	0.94	0.98	-0.015 (-0.403 - 0.372)	0.66	0.88	-0.087 (-0.482 - 0.308)
FGF-21	2 - ≤4m	0.79	0.95	0.056 (-0.359 - 0.471)	0.78	0.92	0.058 (-0.356 - 0.472)
	4 - ≤6m	0.24	0.71	0.217 (-0.144 - 0.577)	0.22	0.71	0.226 (-0.133 - 0.586)
	6 - ≤8m	0.56	0.88	0.098 (-0.230 - 0.426)	0.47	0.79	0.120 (-0.209 - 0.449)
	8 - ≤10m	0.92	0.98	-0.018 (-0.353 - 0.317)	0.94	0.98	-0.012 (-0.347 - 0.322)
	0m	0.43	0.84	0.209 (-0.306 - 0.724)	0.63	0.87	0.129 (-0.396 - 0.653)
	0 - ≤2m	0.63	0.91	0.095 (-0.291 - 0.482)	0.84	0.94	0.041 (-0.352 - 0.434)
FGF-23	2 - ≤4m	0.39	0.82	-0.182 (-0.596 - 0.231)	0.35	0.75	-0.197 (-0.609 - 0.216)
	4 - ≤6m	0.44	0.84	-0.141 (-0.500 - 0.218)	0.43	0.79	-0.143 (-0.502 - 0.215)
	6 - ≤8m	0.16	0.66	-0.235 (-0.562 - 0.092)	0.15	0.65	-0.242 (-0.569 - 0.086)
	8 - ≤10m	0.58	0.89	-0.095 (-0.428 - 0.239)	0.51	0.82	-0.111 (-0.444 - 0.222)
	0m	0.48	0.85	-0.198 (-0.755 - 0.359)	0.51	0.81	-0.192 (-0.758 - 0.375)
	0 - ≤2m	0.96	0.99	0.010 (-0.392 - 0.411)	0.98	1.00	-0.006 (-0.417 - 0.405)
FGF-5**	2 - ≤4m	0.35	0.81	-0.202 (-0.624 - 0.22)	0.39	0.77	-0.185 (-0.608 - 0.238)
	4 - ≤6m	0.15	0.66	0.277 (-0.097 - 0.651)	0.10	0.58	0.317 (-0.058 - 0.692)
	6 - ≤8m	0.13	0.64	-0.266 (-0.607 - 0.076)	0.15	0.65	-0.253 (-0.595 - 0.089)
	8 - ≤10m	0.56	0.88	-0.104 (-0.452 - 0.243)	0.61	0.87	-0.090 (-0.438 - 0.258)
	0m	0.88	0.96	0.039 (-0.474 - 0.551)	0.99	1.00	0.003 (-0.521 - 0.527)
	0 - ≤2m	0.04	0.52	-0.397 (-0.781 - -0.012)	0.04	0.55	-0.416 (-0.808 - -0.023)
Flt3L	2 - ≤4m	0.31	0.78	-0.211 (-0.623 - 0.200)	0.26	0.72	-0.235 (-0.647 - 0.177)
	4 - ≤6m	0.27	0.74	-0.202 (-0.560 - 0.155)	0.18	0.69	-0.245 (-0.603 - 0.112)
	6 - ≤8m	0.03	0.49	-0.361 (-0.686 - -0.036)	0.03	0.55	-0.370 (-0.697 - -0.043)
	8 - ≤10m	0.69	0.93	-0.067 (-0.399 - 0.266)	0.64	0.87	-0.078 (-0.411 - 0.255)
	0m	0.20	0.71	0.337 (-0.175 - 0.849)	0.20	0.71	0.311 (-0.168 - 0.789)
	0 - ≤2m	0.39	0.82	-0.168 (-0.552 - 0.216)	0.71	0.90	-0.068 (-0.427 - 0.290)
HGF	2 - ≤4m	0.19	0.71	0.272 (-0.139 - 0.683)	0.25	0.72	0.218 (-0.158 - 0.595)
	4 - ≤6m	0.75	0.93	0.057 (-0.300 - 0.414)	0.95	0.98	0.011 (-0.316 - 0.338)
	6 - ≤8m	0.08	0.59	0.287 (-0.038 - 0.612)	0.22	0.71	0.188 (-0.111 - 0.487)
	8 - ≤10m	0.19	0.71	0.219 (-0.113 - 0.551)	0.25	0.72	0.177 (-0.127 - 0.481)
	0m	0.62	0.90	0.131 (-0.387 - 0.648)	0.48	0.79	0.192 (-0.342 - 0.726)
	0 - ≤2m	0.87	0.96	-0.032 (-0.421 - 0.356)	0.96	0.99	0.011 (-0.389 - 0.411)
IFN-γ	2 - ≤4m	0.88	0.96	0.032 (-0.384 - 0.447)	0.79	0.92	0.057 (-0.363 - 0.477)
	4 - ≤6m	0.86	0.96	-0.032 (-0.393 - 0.329)	0.93	0.98	-0.016 (-0.381 - 0.349)
	6 - ≤8m	0.58	0.89	0.092 (-0.237 - 0.420)	0.54	0.83	0.104 (-0.229 - 0.438)
	8 - ≤10m	0.41	0.84	0.141 (-0.194 - 0.477)	0.42	0.78	0.140 (-0.199 - 0.479)
	0m	0.42	0.84	0.214 (-0.303 - 0.731)	0.46	0.79	0.202 (-0.332 - 0.736)
	0 - ≤2m	0.65	0.91	0.090 (-0.298 - 0.477)	0.74	0.90	0.068 (-0.332 - 0.468)
IL-10RA	2 - ≤4m	0.18	0.69	0.282 (-0.133 - 0.697)	0.19	0.71	0.283 (-0.136 - 0.703)
	4 - ≤6m	0.43	0.84	0.145 (-0.216 - 0.505)	0.40	0.77	0.155 (-0.209 - 0.520)
	6 - ≤8m	0.61	0.90	0.085 (-0.243 - 0.414)	0.58	0.84	0.095 (-0.238 - 0.428)
	8 - ≤10m	0.34	0.81	0.163 (-0.172 - 0.498)	0.31	0.75	0.174 (-0.165 - 0.513)
	0m	0.45	0.84	-0.198 (-0.711 - 0.316)	0.36	0.75	-0.244 (-0.767 - 0.279)
	0 - ≤2m	0.06	0.55	-0.370 (-0.755 - 0.015)	0.04	0.55	-0.420 (-0.812 - -0.027)
IL-10RB	2 - ≤4m	0.71	0.93	-0.079 (-0.491 - 0.334)	0.64	0.87	-0.099 (-0.510 - 0.313)
	4 - ≤6m	0.49	0.85	0.125 (-0.233 - 0.483)	0.47	0.79	0.130 (-0.227 - 0.488)
	6 - ≤8m	0.44	0.84	-0.127 (-0.453 - 0.199)	0.42	0.78	-0.135 (-0.461 - 0.192)
	8 - ≤10m	0.25	0.71	-0.197 (-0.530 - 0.136)	0.30	0.75	-0.176 (-0.508 - 0.157)
	0m	0.06	0.55	0.491 (-0.022 - 1.005)	0.06	0.55	0.512 (-0.013 - 1.037)
	0 - ≤2m	0.99	0.99	0.001 (-0.384 - 0.387)	0.75	0.90	0.065 (-0.328 - 0.458)
IL-12B	2 - ≤4m	0.22	0.71	-0.258 (-0.671 - 0.154)	0.22	0.71	-0.258 (-0.671 - 0.155)
	4 - ≤6m	0.90	0.97	0.024 (-0.334 - 0.382)	0.90	0.98	0.022 (-0.337 - 0.381)
	6 - ≤8m	0.87	0.96	0.027 (-0.299 - 0.353)	0.93	0.98	-0.016 (-0.343 - 0.312)
	8 - ≤10m	0.71	0.93	-0.062 (-0.395 - 0.270)	0.56	0.84	-0.098 (-0.431 - 0.235)
IL-15RA	0m	0.83	0.95	-0.057 (-0.567 - 0.454)	0.73	0.90	-0.093 (-0.618 - 0.432)

	0 - ≤2m	0.08	0.59	-0.340 (-0.723 - 0.043)	0.09	0.58	-0.336 (-0.729 - 0.058)
	2 - ≤4m	0.02	0.49	-0.497 (-0.907 - -0.087)	0.02	0.45	-0.512 (-0.925 - -0.100)
	4 - ≤6m	0.24	0.71	-0.211 (-0.567 - 0.145)	0.26	0.72	-0.204 (-0.562 - 0.155)
	6 - ≤8m	0.01	0.49	-0.418 (-0.742 - -0.094)	0.01	0.43	-0.455 (-0.783 - -0.128)
	8 - ≤10m	0.02	0.49	-0.393 (-0.724 - -0.062)	0.02	0.45	-0.407 (-0.741 - -0.074)
	0m	0.41	0.84	0.214 (-0.301 - 0.728)	0.47	0.79	0.193 (-0.337 - 0.723)
IL-17A	0 - ≤2m	0.21	0.71	-0.247 (-0.633 - 0.138)	0.20	0.71	-0.257 (-0.654 - 0.140)
	2 - ≤4m	0.33	0.80	-0.205 (-0.618 - 0.208)	0.33	0.75	-0.205 (-0.621 - 0.212)
	4 - ≤6m	0.93	0.98	0.017 (-0.342 - 0.375)	0.87	0.96	0.029 (-0.332 - 0.391)
	6 - ≤8m	0.16	0.66	-0.236 (-0.562 - 0.091)	0.14	0.65	-0.248 (-0.579 - 0.082)
	8 - ≤10m	0.80	0.95	-0.043 (-0.377 - 0.290)	0.75	0.91	-0.054 (-0.390 - 0.283)
	0m	0.28	0.76	0.287 (-0.230 - 0.805)	0.34	0.75	0.259 (-0.274 - 0.793)
	0 - ≤2m	0.91	0.97	-0.022 (-0.410 - 0.366)	0.93	0.98	-0.018 (-0.417 - 0.382)
	2 - ≤4m	0.36	0.82	0.194 (-0.221 - 0.610)	0.38	0.77	0.188 (-0.231 - 0.608)
IL-17C	4 - ≤6m	0.70	0.93	0.070 (-0.291 - 0.431)	0.68	0.89	0.076 (-0.288 - 0.440)
	6 - ≤8m	0.75	0.93	0.053 (-0.275 - 0.382)	0.85	0.95	0.032 (-0.301 - 0.365)
	8 - ≤10m	0.70	0.93	0.066 (-0.270 - 0.401)	0.78	0.92	0.049 (-0.290 - 0.387)
	0m	0.12	0.62	0.411 (-0.102 - 0.924)	0.20	0.71	0.340 (-0.176 - 0.857)
	0 - ≤2m	0.10	0.59	-0.326 (-0.711 - 0.059)	0.14	0.65	-0.292 (-0.679 - 0.094)
	2 - ≤4m	0.48	0.85	-0.147 (-0.559 - 0.265)	0.36	0.75	-0.190 (-0.596 - 0.216)
IL-18	4 - ≤6m	0.42	0.84	-0.148 (-0.505 - 0.210)	0.36	0.75	-0.164 (-0.517 - 0.188)
	6 - ≤8m	0.78	0.95	-0.046 (-0.371 - 0.280)	0.42	0.78	-0.132 (-0.454 - 0.190)
	8 - ≤10m	0.46	0.84	-0.125 (-0.457 - 0.207)	0.31	0.75	-0.168 (-0.496 - 0.159)
	0m	0.74	0.93	0.088 (-0.428 - 0.605)	0.88	0.96	0.041 (-0.479 - 0.562)
	0 - ≤2m	0.13	0.64	-0.302 (-0.690 - 0.085)	0.17	0.69	-0.271 (-0.661 - 0.118)
	2 - ≤4m	0.67	0.93	-0.090 (-0.505 - 0.324)	0.54	0.83	-0.128 (-0.537 - 0.281)
IL-18R1	4 - ≤6m	0.80	0.95	-0.046 (-0.406 - 0.314)	0.62	0.87	-0.090 (-0.445 - 0.266)
	6 - ≤8m	0.36	0.82	-0.151 (-0.479 - 0.176)	0.20	0.71	-0.213 (-0.538 - 0.112)
	8 - ≤10m	0.62	0.90	-0.085 (-0.420 - 0.249)	0.45	0.79	-0.128 (-0.458 - 0.202)
	0m	0.38	0.82	-0.227 (-0.739 - 0.284)	0.42	0.78	-0.218 (-0.744 - 0.308)
	0 - ≤2m	0.11	0.62	0.309 (-0.074 - 0.693)	0.13	0.62	0.307 (-0.088 - 0.701)
	2 - ≤4m	0.35	0.81	-0.197 (-0.607 - 0.214)	0.35	0.75	-0.198 (-0.611 - 0.216)
IL-4	4 - ≤6m	0.23	0.71	-0.217 (-0.574 - 0.139)	0.27	0.72	-0.202 (-0.561 - 0.158)
	6 - ≤8m	0.18	0.69	-0.221 (-0.545 - 0.104)	0.20	0.71	-0.212 (-0.541 - 0.116)
	8 - ≤10m	0.99	0.99	0.002 (-0.329 - 0.333)	0.86	0.95	0.030 (-0.305 - 0.364)
	0m	0.54	0.88	0.159 (-0.356 - 0.673)	0.24	0.71	0.281 (-0.191 - 0.753)
	0 - ≤2m	0.06	0.55	-0.368 (-0.753 - 0.018)	0.27	0.72	-0.200 (-0.554 - 0.154)
	2 - ≤4m	0.81	0.95	0.051 (-0.362 - 0.464)	0.81	0.93	0.046 (-0.325 - 0.417)
IL-6	4 - ≤6m	0.30	0.78	-0.188 (-0.546 - 0.171)	0.23	0.71	-0.197 (-0.520 - 0.125)
	6 - ≤8m	0.62	0.90	-0.082 (-0.409 - 0.244)	0.46	0.79	-0.111 (-0.406 - 0.184)
	8 - ≤10m	0.31	0.78	-0.172 (-0.505 - 0.161)	0.32	0.75	-0.152 (-0.452 - 0.147)
	0m	0.28	0.76	-0.279 (-0.785 - 0.227)	0.20	0.71	-0.327 (-0.834 - 0.179)
	0 - ≤2m	0.00	0.37	-0.575 (-0.954 - -0.195)	0.00	0.28	-0.645 (-1.025 - -0.266)
	2 - ≤4m	0.00	0.44	-0.586 (-0.992 - -0.18)	0.00	0.43	-0.575 (-0.974 - -0.177)
IL-7	4 - ≤6m	0.13	0.64	-0.274 (-0.626 - 0.079)	0.17	0.69	-0.240 (-0.586 - 0.107)
	6 - ≤8m	0.01	0.49	-0.421 (-0.742 - -0.100)	0.01	0.45	-0.396 (-0.712 - -0.080)
	8 - ≤10m	0.74	0.93	-0.056 (-0.384 - 0.272)	0.78	0.92	-0.045 (-0.367 - 0.277)
	0m	0.78	0.95	0.073 (-0.438 - 0.585)	0.17	0.69	0.241 (-0.107 - 0.589)
	0 - ≤2m	0.05	0.52	-0.383 (-0.767 – 0.000)	0.35	0.75	-0.123 (-0.384 - 0.137)
	2 - ≤4m	0.69	0.93	0.083 (-0.328 - 0.494)	0.66	0.88	0.062 (-0.212 - 0.335)
IL-8	4 - ≤6m	0.23	0.71	-0.218 (-0.575 - 0.138)	0.04	0.55	-0.253 (-0.491 - -0.015)
	6 - ≤8m	0.50	0.86	0.111 (-0.214 - 0.435)	0.69	0.90	0.044 (-0.174 - 0.261)
	8 - ≤10m	0.22	0.71	-0.209 (-0.540 - 0.122)	0.08	0.58	-0.197 (-0.418 - 0.024)
	0m	0.28	0.76	-0.279 (-0.790 - 0.231)	0.27	0.72	-0.294 (-0.815 - 0.228)
	0 - ≤2m	0.03	0.49	-0.435 (-0.818 - -0.052)	0.04	0.55	-0.404 (-0.795 - -0.014)
	2 - ≤4m	0.04	0.49	-0.435 (-0.845 - -0.025)	0.04	0.55	-0.434 (-0.844 - -0.024)
IL-10	4 - ≤6m	0.07	0.57	-0.328 (-0.684 - 0.028)	0.10	0.58	-0.299 (-0.655 - 0.057)
	6 - ≤8m	0.59	0.89	-0.089 (-0.413 - 0.235)	0.46	0.79	-0.122 (-0.448 - 0.203)
	8 - ≤10m	0.02	0.49	-0.404 (-0.735 - -0.073)	0.01	0.45	-0.423 (-0.754 - -0.092)
	0m	0.68	0.93	-0.107 (-0.625 - 0.411)	0.83	0.94	-0.056 (-0.569 - 0.457)
LAP TGF-β-1	0 - ≤2m	0.82	0.95	0.046 (-0.343 - 0.434)	0.67	0.88	0.082 (-0.302 - 0.466)
	2 - ≤4m	0.99	0.99	0.002 (-0.414 - 0.418)	0.95	0.98	0.014 (-0.389 - 0.417)

	4 - ≤6m	0.88	0.96	-0.028 (-0.389 - 0.334)	0.93	0.98	0.015 (-0.336 - 0.365)
	6 - ≤8m	0.68	0.93	0.069 (-0.260 - 0.398)	0.53	0.83	0.102 (-0.218 - 0.422)
	8 - ≤10m	0.71	0.93	0.065 (-0.271 - 0.400)	0.45	0.79	0.125 (-0.201 - 0.450)
	0m	0.43	0.84	-0.204 (-0.717 - 0.309)	0.40	0.77	-0.225 (-0.753 - 0.303)
	0 - ≤2m	0.05	0.52	-0.391 (-0.776 - -0.007)	0.06	0.55	-0.382 (-0.778 - 0.014)
LIF-R	2 - ≤4m	0.08	0.59	-0.363 (-0.775 - 0.049)	0.08	0.58	-0.371 (-0.786 - 0.044)
	4 - ≤6m	0.55	0.88	-0.110 (-0.467 - 0.248)	0.54	0.83	-0.114 (-0.475 - 0.247)
	6 - ≤8m	0.03	0.49	-0.361 (-0.687 - -0.036)	0.02	0.55	-0.378 (-0.708 - -0.048)
	8 - ≤10m	0.15	0.66	-0.245 (-0.577 - 0.088)	0.13	0.62	-0.259 (-0.595 - 0.076)
	0m	0.65	0.91	0.121 (-0.397 - 0.639)	0.47	0.79	0.179 (-0.310 - 0.667)
	0 - ≤2m	0.88	0.96	-0.029 (-0.418 - 0.360)	0.56	0.84	0.108 (-0.258 - 0.474)
MCP-1	2 - ≤4m	0.72	0.93	0.075 (-0.341 - 0.491)	0.77	0.92	0.056 (-0.328 - 0.440)
	4 - ≤6m	0.82	0.95	-0.041 (-0.403 - 0.32)	0.72	0.90	-0.061 (-0.395 - 0.273)
	6 - ≤8m	0.91	0.97	0.020 (-0.309 - 0.349)	0.83	0.94	-0.033 (-0.338 - 0.272)
	8 - ≤10m	0.72	0.93	-0.06 (-0.396 - 0.275)	0.65	0.87	-0.071 (-0.382 - 0.239)
	0m	0.59	0.89	0.142 (-0.374 - 0.657)	0.62	0.87	0.133 (-0.399 - 0.664)
	0 - ≤2m	0.68	0.93	0.081 (-0.306 - 0.468)	0.66	0.88	0.088 (-0.311 - 0.486)
MCP-2	2 - ≤4m	0.98	0.99	-0.005 (-0.419 - 0.409)	0.99	1.00	-0.002 (-0.420 - 0.416)
	4 - ≤6m	0.95	0.98	-0.011 (-0.371 - 0.348)	1.00	1.00	-0.001 (-0.364 - 0.362)
	6 - ≤8m	0.67	0.93	-0.071 (-0.398 - 0.256)	0.64	0.87	-0.078 (-0.410 - 0.254)
	8 - ≤10m	0.15	0.66	-0.244 (-0.578 - 0.09)	0.14	0.65	-0.254 (-0.591 - 0.084)
	0m	0.24	0.71	-0.309 (-0.823 - 0.204)	0.55	0.83	-0.111 (-0.477 - 0.255)
	0 - ≤2m	0.24	0.71	-0.231 (-0.616 - 0.154)	0.79	0.92	0.038 (-0.237 - 0.312)
MCP-3	2 - ≤4m	0.38	0.82	0.184 (-0.228 - 0.596)	0.21	0.71	0.183 (-0.105 - 0.471)
	4 - ≤6m	0.27	0.75	-0.200 (-0.558 - 0.158)	0.11	0.58	-0.206 (-0.456 - 0.045)
	6 - ≤8m	0.56	0.88	0.098 (-0.228 - 0.424)	0.61	0.87	0.059 (-0.170 - 0.288)
	8 - ≤10m	0.88	0.96	-0.025 (-0.358 - 0.307)	0.95	0.98	0.008 (-0.225 - 0.241)
	0m	0.17	0.68	0.360 (-0.152 - 0.871)	0.17	0.69	0.366 (-0.157 - 0.889)
	0 - ≤2m	0.48	0.85	-0.138 (-0.521 - 0.246)	0.62	0.87	-0.098 (-0.490 - 0.294)
MCP-4	2 - ≤4m	0.43	0.84	-0.166 (-0.576 - 0.245)	0.45	0.79	-0.160 (-0.571 - 0.252)
	4 - ≤6m	0.09	0.59	0.304 (-0.053 - 0.660)	0.09	0.58	0.311 (-0.046 - 0.669)
	6 - ≤8m	0.23	0.71	0.199 (-0.126 - 0.523)	0.28	0.72	0.181 (-0.145 - 0.508)
	8 - ≤10m	0.20	0.71	0.215 (-0.116 - 0.546)	0.26	0.72	0.191 (-0.141 - 0.523)
	0m	0.89	0.97	-0.034 (-0.545 - 0.476)	0.70	0.90	-0.102 (-0.624 - 0.420)
	0 - ≤2m	0.83	0.95	0.041 (-0.342 - 0.424)	0.96	0.99	0.010 (-0.382 - 0.401)
MMP-1	2 - ≤4m	0.05	0.52	0.406 (-0.004 - 0.816)	0.07	0.55	0.382 (-0.029 - 0.793)
	4 - ≤6m	0.09	0.59	0.312 (-0.044 - 0.668)	0.10	0.58	0.299 (-0.058 - 0.656)
	6 - ≤8m	0.06	0.54	0.315 (-0.009 - 0.639)	0.07	0.55	0.299 (-0.028 - 0.625)
	8 - ≤10m	0.01	0.49	0.414 (0.083 - 0.745)	0.02	0.45	0.405 (0.073 - 0.737)
	0m	0.99	0.99	-0.002 (-0.517 - 0.512)	0.94	0.98	-0.020 (-0.542 - 0.502)
	0 - ≤2m	0.39	0.82	-0.169 (-0.555 - 0.217)	0.47	0.79	-0.144 (-0.536 - 0.247)
MMP-10	2 - ≤4m	0.09	0.59	0.357 (-0.056 - 0.770)	0.08	0.58	0.365 (-0.046 - 0.775)
	4 - ≤6m	0.95	0.98	0.012 (-0.347 - 0.371)	0.84	0.94	0.036 (-0.321 - 0.393)
	6 - ≤8m	0.84	0.95	-0.034 (-0.361 - 0.292)	0.71	0.90	-0.062 (-0.388 - 0.264)
	8 - ≤10m	0.57	0.89	-0.097 (-0.430 - 0.236)	0.44	0.79	-0.130 (-0.461 - 0.202)
	0m	0.81	0.95	-0.062 (-0.579 - 0.455)	0.91	0.98	-0.031 (-0.559 - 0.497)
	0 - ≤2m	0.75	0.93	-0.062 (-0.450 - 0.325)	0.79	0.92	-0.055 (-0.450 - 0.341)
NT-3	2 - ≤4m	0.99	0.99	0.004 (-0.411 - 0.419)	0.96	0.99	0.010 (-0.405 - 0.424)
	4 - ≤6m	0.32	0.79	0.182 (-0.178 - 0.543)	0.24	0.71	0.215 (-0.146 - 0.575)
	6 - ≤8m	0.70	0.93	-0.064 (-0.392 - 0.265)	0.77	0.92	-0.048 (-0.377 - 0.281)
	8 - ≤10m	0.69	0.93	0.067 (-0.268 - 0.402)	0.51	0.81	0.112 (-0.223 - 0.447)
	0m	0.60	0.90	0.137 (-0.380 - 0.654)	0.74	0.90	0.088 (-0.442 - 0.619)
	0 - ≤2m	0.70	0.93	-0.075 (-0.463 - 0.313)	0.60	0.86	-0.107 (-0.504 - 0.291)
OPG	2 - ≤4m	0.51	0.86	-0.141 (-0.556 - 0.274)	0.43	0.79	-0.167 (-0.584 - 0.250)
	4 - ≤6m	0.61	0.90	0.094 (-0.266 - 0.454)	0.77	0.92	0.054 (-0.309 - 0.416)
	6 - ≤8m	0.62	0.90	0.082 (-0.245 - 0.41)	0.68	0.89	0.070 (-0.261 - 0.401)
	8 - ≤10m	0.46	0.84	0.126 (-0.209 - 0.461)	0.50	0.81	0.114 (-0.223 - 0.451)
	0m	0.84	0.95	0.051 (-0.461 - 0.564)	0.64	0.87	0.088 (-0.288 - 0.465)
	0 - ≤2m	0.15	0.66	-0.283 (-0.668 - 0.101)	0.56	0.84	-0.083 (-0.365 - 0.199)
OSM	2 - ≤4m	0.34	0.81	0.199 (-0.212 - 0.611)	0.37	0.75	0.136 (-0.160 - 0.432)
	4 - ≤6m	0.41	0.84	-0.150 (-0.507 - 0.207)	0.11	0.58	-0.211 (-0.469 - 0.046)
	6 - ≤8m	0.28	0.76	0.180 (-0.146 - 0.505)	0.68	0.89	0.049 (-0.186 - 0.284)

	8 - ≤10m	0.59	0.89	-0.091 (-0.424 - 0.241)	0.28	0.72	-0.133 (-0.372 - 0.106)
	0m	0.78	0.95	0.075 (-0.440 - 0.590)	1.00	1.00	0.000 (-0.517 - 0.517)
	0 - ≤2m	0.10	0.60	-0.320 (-0.706 - 0.067)	0.15	0.65	-0.288 (-0.675 - 0.100)
PD-L1	2 - ≤4m	0.28	0.76	-0.227 (-0.640 - 0.186)	0.19	0.71	-0.270 (-0.676 - 0.137)
	4 - ≤6m	0.53	0.87	-0.115 (-0.473 - 0.244)	0.49	0.80	-0.124 (-0.477 - 0.229)
	6 - ≤8m	0.20	0.71	-0.212 (-0.538 - 0.115)	0.07	0.55	-0.302 (-0.625 - 0.021)
	8 - ≤10m	0.09	0.59	-0.289 (-0.622 - 0.044)	0.05	0.55	-0.331 (-0.659 - -0.002)
	0m	0.31	0.78	0.264 (-0.246 - 0.774)	0.17	0.69	0.360 (-0.157 - 0.877)
	0 - ≤2m	0.00	0.37	0.596 (0.213 - 0.979)	0.00	0.28	0.618 (0.231 - 1.006)
SCF	2 - ≤4m	0.09	0.59	0.353 (-0.057 - 0.762)	0.07	0.55	0.376 (-0.031 - 0.783)
	4 - ≤6m	0.04	0.49	0.377 (0.021 - 0.733)	0.03	0.55	0.386 (0.032 - 0.739)
	6 - ≤8m	0.02	0.49	0.402 (0.078 - 0.725)	0.01	0.43	0.457 (0.134 - 0.78)0
	8 - ≤10m	0.13	0.65	0.255 (-0.076 - 0.585)	0.06	0.55	0.312 (-0.017 - 0.64)
	0m	0.64	0.91	-0.123 (-0.641 - 0.395)	0.35	0.75	-0.245 (-0.762 - 0.272)
	0 - ≤2m	0.39	0.83	-0.168 (-0.557 - 0.220)	0.34	0.75	-0.187 (-0.575 - 0.200)
SIRT2	2 - ≤4m	0.85	0.95	-0.040 (-0.456 - 0.376)	0.60	0.86	-0.109 (-0.515 - 0.298)
	4 - ≤6m	0.82	0.95	-0.041 (-0.402 - 0.320)	0.55	0.83	-0.107 (-0.460 - 0.246)
	6 - ≤8m	0.95	0.98	-0.010 (-0.338 - 0.319)	0.55	0.83	-0.099 (-0.421 - 0.224)
	8 - ≤10m	0.52	0.87	-0.110 (-0.445 - 0.226)	0.33	0.75	-0.164 (-0.492 - 0.165)
	0m	0.75	0.93	0.083 (-0.427 - 0.592)	0.81	0.93	-0.063 (-0.583 - 0.457)
	0 - ≤2m	0.14	0.66	-0.286 (-0.668 - 0.096)	0.07	0.55	-0.364 (-0.754 - 0.026)
SLAMF1	2 - ≤4m	0.03	0.49	-0.46 (-0.869 - -0.051)	0.01	0.45	-0.513 (-0.922 - -0.104)
	4 - ≤6m	0.03	0.49	-0.406 (-0.761 - -0.051)	0.01	0.45	-0.457 (-0.812 - -0.101)
	6 - ≤8m	0.03	0.49	-0.367 (-0.69 - -0.044)	0.01	0.45	-0.419 (-0.744 - -0.094)
	8 - ≤10m	0.81	0.95	-0.040 (-0.370 - 0.290)	0.60	0.86	-0.088 (-0.418 - 0.243)
	0m	0.38	0.82	-0.227 (-0.740 - 0.285)	0.24	0.71	-0.295 (-0.789 - 0.199)
	0 - ≤2m	0.93	0.98	-0.016 (-0.401 - 0.368)	0.95	0.98	-0.012 (-0.383 - 0.358)
ST1A1	2 - ≤4m	0.33	0.80	0.203 (-0.208 - 0.615)	0.45	0.79	0.151 (-0.238 - 0.540)
	4 - ≤6m	0.83	0.95	0.038 (-0.319 - 0.395)	0.72	0.90	-0.062 (-0.400 - 0.275)
	6 - ≤8m	0.03	0.49	0.359 (0.033 - 0.684)	0.07	0.55	0.288 (-0.020 - 0.597)
	8 - ≤10m	0.70	0.93	0.065 (-0.267 - 0.397)	0.96	0.99	-0.009 (-0.323 - 0.305)
	0m	0.95	0.98	0.017 (-0.501 - 0.534)	0.64	0.87	-0.127 (-0.653 - 0.400)
	0 - ≤2m	0.30	0.78	-0.204 (-0.593 - 0.184)	0.17	0.69	-0.278 (-0.672 - 0.116)
STAMBP	2 - ≤4m	0.57	0.89	-0.122 (-0.537 - 0.294)	0.40	0.77	-0.177 (-0.590 - 0.237)
	4 - ≤6m	0.92	0.98	-0.018 (-0.379 - 0.343)	0.77	0.92	-0.053 (-0.413 - 0.306)
	6 - ≤8m	0.64	0.91	-0.077 (-0.406 - 0.251)	0.39	0.77	-0.145 (-0.473 - 0.184)
	8 - ≤10m	0.47	0.85	-0.124 (-0.459 - 0.212)	0.33	0.75	-0.164 (-0.499 - 0.170)
	0m	0.46	0.84	0.193 (-0.323 - 0.709)	0.48	0.79	0.178 (-0.317 - 0.673)
	0 - ≤2m	0.25	0.71	-0.228 (-0.615 - 0.159)	0.52	0.82	-0.121 (-0.492 - 0.250)
TGF-α	2 - ≤4m	0.97	0.99	0.008 (-0.407 - 0.422)	0.88	0.96	-0.029 (-0.419 - 0.360)
	4 - ≤6m	0.57	0.89	-0.103 (-0.463 - 0.257)	0.37	0.76	-0.154 (-0.492 - 0.185)
	6 - ≤8m	0.74	0.93	0.056 (-0.271 - 0.383)	0.74	0.90	-0.052 (-0.361 - 0.257)
	8 - ≤10m	0.63	0.91	0.082 (-0.252 - 0.416)	1.00	1.00	0.001 (-0.314 - 0.315)
	0m	0.45	0.84	0.197 (-0.314 - 0.709)	0.27	0.72	0.292 (-0.232 - 0.817)
	0 - ≤2m	0.08	0.59	-0.348 (-0.732 - 0.036)	0.20	0.71	-0.258 (-0.651 - 0.135)
TNF	2 - ≤4m	0.09	0.59	-0.360 (-0.771 - 0.051)	0.11	0.58	-0.338 (-0.75 - 0.074)
	4 - ≤6m	0.09	0.59	-0.304 (-0.660 - 0.053)	0.13	0.62	-0.280 (-0.638 - 0.079)
	6 - ≤8m	0.05	0.52	-0.320 (-0.645 - 0.004)	0.06	0.55	-0.317 (-0.644 - 0.011)
	8 - ≤10m	0.10	0.59	-0.279 (-0.611 - 0.052)	0.12	0.61	-0.263 (-0.596 - 0.070)
	0m	0.71	0.93	0.097 (-0.416 - 0.611)	0.94	0.98	-0.021 (-0.543 - 0.502)
	0 - ≤2m	0.10	0.59	-0.328 (-0.713 - 0.057)	0.04	0.55	-0.405 (-0.797 - -0.014)
TNFB	2 - ≤4m	0.10	0.59	-0.348 (-0.760 - 0.064)	0.07	0.55	-0.384 (-0.795 - 0.026)
	4 - ≤6m	0.26	0.74	-0.206 (-0.564 - 0.152)	0.21	0.71	-0.227 (-0.584 - 0.130)
	6 - ≤8m	0.05	0.52	-0.323 (-0.649 - 0.003)	0.03	0.55	-0.366 (-0.693 - -0.04)
	8 - ≤10m	0.33	0.80	-0.164 (-0.496 - 0.169)	0.24	0.71	-0.197 (-0.529 - 0.134)
	0m	0.06	0.55	0.488 (-0.026 - 1.001)	0.11	0.59	0.418 (-0.100 - 0.935)
	0 - ≤2m	0.51	0.86	-0.130 (-0.515 - 0.255)	0.54	0.83	-0.121 (-0.508 - 0.267)
TNFRSF9	2 - ≤4m	0.76	0.94	-0.063 (-0.476 - 0.349)	0.64	0.87	-0.098 (-0.504 - 0.309)
	4 - ≤6m	0.66	0.93	-0.079 (-0.437 - 0.279)	0.71	0.90	-0.068 (-0.421 - 0.285)
	6 - ≤8m	0.54	0.88	-0.102 (-0.428 - 0.224)	0.28	0.73	-0.176 (-0.499 - 0.147)
	8 - ≤10m	0.26	0.74	-0.190 (-0.522 - 0.143)	0.21	0.71	-0.212 (-0.540 - 0.117)
TNFSF14	0m	0.37	0.82	0.236 (-0.278 - 0.751)	0.30	0.75	0.219 (-0.196 - 0.634)

	0 - ≤2m	0.45	0.84	-0.150 (-0.535 - 0.236)	0.92	0.98	-0.017 (-0.328 - 0.294)
	2 - ≤4m	0.48	0.85	0.148 (-0.265 - 0.561)	0.65	0.87	0.076 (-0.251 - 0.402)
	4 - ≤6m	0.80	0.95	0.047 (-0.312 - 0.405)	0.70	0.90	-0.056 (-0.340 - 0.228)
	6 - ≤8m	0.12	0.63	0.260 (-0.067 - 0.586)	0.30	0.75	0.136 (-0.123 - 0.395)
	8 - ≤10m	0.99	0.99	-0.003 (-0.336 - 0.331)	0.58	0.85	-0.074 (-0.337 - 0.190)
	0m	0.23	0.71	0.316 (-0.196 - 0.827)	0.31	0.75	0.266 (-0.254 - 0.787)
TRAIL	0 - ≤2m	0.71	0.93	-0.072 (-0.456 - 0.311)	0.67	0.88	-0.085 (-0.475 - 0.305)
	2 - ≤4m	0.04	0.52	-0.424 (-0.834 - -0.013)	0.04	0.55	-0.431 (-0.84 - -0.022)
	4 - ≤6m	0.91	0.97	0.020 (-0.336 - 0.377)	0.91	0.98	0.020 (-0.335 - 0.375)
	6 - ≤8m	0.11	0.62	-0.261 (-0.585 - 0.064)	0.07	0.55	-0.300 (-0.624 - 0.025)
	8 - ≤10m	0.58	0.89	-0.093 (-0.425 - 0.238)	0.42	0.78	-0.136 (-0.466 - 0.195)
	0m	0.42	0.84	0.212 (-0.300 - 0.724)	0.34	0.75	0.255 (-0.273 - 0.783)
	0 - ≤2m	0.96	0.99	0.009 (-0.375 - 0.394)	0.75	0.91	0.063 (-0.332 - 0.459)
	2 - ≤4m	0.24	0.71	-0.245 (-0.657 - 0.166)	0.26	0.72	-0.236 (-0.651 - 0.179)
TRANCE	4 - ≤6m	0.81	0.95	0.044 (-0.313 - 0.401)	0.73	0.90	0.062 (-0.299 - 0.423)
	6 - ≤8m	0.12	0.64	-0.254 (-0.579 - 0.071)	0.12	0.59	-0.265 (-0.594 - 0.065)
	8 - ≤10m	0.34	0.81	0.160 (-0.172 - 0.492)	0.34	0.75	0.163 (-0.172 - 0.498)
	0m	0.03	0.49	0.559 (0.053 - 1.066)	0.05	0.55	0.512 (-0.008 - 1.031)
	0 - ≤2m	0.82	0.95	-0.044 (-0.423 - 0.336)	0.77	0.91	-0.059 (-0.448 - 0.330)
	2 - ≤4m	0.18	0.69	0.277 (-0.13 - 0.683)	0.23	0.71	0.248 (-0.160 - 0.656)
TWEAK	4 - ≤6m	0.01	0.49	0.476 (0.123 - 0.829)	0.01	0.45	0.466 (0.111 - 0.820)
	6 - ≤8m	0.03	0.49	0.347 (0.026 - 0.668)	0.05	0.55	0.322 (-0.002 - 0.647)
	8 - ≤10m	0.00	0.37	0.494 (0.166 - 0.821)	0.00	0.35	0.500 (0.170 - 0.829)
	0m	0.14	0.66	0.384 (-0.127 - 0.895)	0.33	0.75	0.243 (-0.250 - 0.736)
	0 - ≤2m	0.49	0.85	0.134 (-0.249 - 0.518)	0.73	0.90	0.066 (-0.304 - 0.436)
	2 - ≤4m	0.61	0.90	-0.108 (-0.518 - 0.302)	0.34	0.75	-0.189 (-0.577 - 0.198)
uPA	4 - ≤6m	0.07	0.59	0.324 (-0.032 - 0.680)	0.22	0.71	0.211 (-0.126 - 0.548)
	6 - ≤8m	0.91	0.97	0.019 (-0.305 - 0.343)	0.80	0.92	-0.041 (-0.348 - 0.267)
	8 - ≤10m	0.03	0.49	0.364 (0.033 - 0.695)	0.05	0.55	0.320 (0.007 - 0.633)
	0m	0.58	0.89	0.144 (-0.369 - 0.656)	0.52	0.82	0.168 (-0.347 - 0.683)
	0 - ≤2m	0.11	0.62	-0.310 (-0.695 - 0.074)	0.24	0.71	-0.230 (-0.616 - 0.156)
	2 - ≤4m	0.50	0.85	0.142 (-0.269 - 0.553)	0.52	0.82	0.133 (-0.272 - 0.537)
VEGFA	4 - ≤6m	0.72	0.93	0.066 (-0.291 - 0.423)	0.62	0.87	0.089 (-0.263 - 0.441)
	6 - ≤8m	0.56	0.88	0.098 (-0.228 - 0.423)	0.72	0.90	0.058 (-0.264 - 0.379)
	8 - ≤10m	0.12	0.63	0.263 (-0.069 - 0.594)	0.11	0.58	0.268 (-0.059 - 0.595)

**46 infants had an NA value for FGF-5.

Supplementary Table 8. Linear regression associations of infant serum biomarker levels with categorical HMF duration (infants grouped in three-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use categorical HMF duration (infants grouped in three-month intervals) to predict biomarker levels (standardized NPX). The >9m HMF group was used as reference.

Olink Biomarkers	Variable Groups	Univariable			Multivariable		
		P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0m	0.51	0.93	0.169 (-0.335 - 0.672)	0.77	0.95	0.076 (-0.433 - 0.585)
	0 - ≤3m	0.98	0.99	0.004 (-0.314 - 0.321)	0.72	0.94	-0.059 (-0.378 - 0.260)
	3 - ≤6m	0.75	0.95	-0.053 (-0.374 - 0.268)	0.71	0.94	-0.061 (-0.378 - 0.257)
	6 - ≤9m	0.51	0.93	-0.091 (-0.365 - 0.182)	0.57	0.93	-0.079 (-0.353 - 0.194)
ADA	0m	0.82	0.96	-0.058 (-0.561 - 0.445)	0.44	0.93	-0.192 (-0.684 - 0.300)
	0 - ≤3m	0.49	0.93	-0.111 (-0.428 - 0.206)	0.30	0.88	-0.164 (-0.473 - 0.145)
	3 - ≤6m	0.84	0.96	-0.033 (-0.354 - 0.288)	0.64	0.94	-0.072 (-0.379 - 0.235)
	6 - ≤9m	0.57	0.93	0.080 (-0.193 - 0.353)	0.81	0.95	-0.031 (-0.296 - 0.233)
AXIN1	0m	0.95	0.98	-0.017 (-0.520 - 0.486)	0.21	0.76	-0.300 (-0.773 - 0.173)
	0 - ≤3m	0.22	0.84	-0.200 (-0.517 - 0.118)	0.03	0.56	-0.325 (-0.622 - -0.028)
	3 - ≤6m	0.38	0.90	-0.142 (-0.463 - 0.178)	0.24	0.79	-0.178 (-0.473 - 0.117)
	6 - ≤9m	0.56	0.93	-0.082 (-0.355 - 0.191)	0.05	0.56	-0.256 (-0.511 - -0.002)
CASP-8	0m	0.43	0.91	0.203 (-0.300 - 0.705)	0.40	0.93	0.148 (-0.195 - 0.490)
	0 - ≤3m	0.79	0.96	0.043 (-0.273 - 0.360)	0.65	0.94	0.049 (-0.166 - 0.264)
	3 - ≤6m	0.94	0.98	-0.013 (-0.333 - 0.307)	0.50	0.93	-0.073 (-0.287 - 0.141)
	6 - ≤9m	0.16	0.84	0.194 (-0.078 - 0.467)	0.65	0.94	0.043 (-0.141 - 0.227)
CCL11	0m	0.60	0.93	0.134 (-0.365 - 0.632)	0.69	0.94	0.102 (-0.400 - 0.604)
	0 - ≤3m	0.02	0.45	-0.380 (-0.694 - -0.065)	0.02	0.49	-0.379 (-0.693 - -0.064)
	3 - ≤6m	0.58	0.93	-0.089 (-0.407 - 0.229)	0.66	0.94	-0.070 (-0.383 - 0.243)
	6 - ≤9m	0.14	0.78	-0.205 (-0.475 - 0.066)	0.04	0.56	-0.282 (-0.551 - -0.012)
CCL19	0m	0.05	0.58	0.505 (0.007 - 1.003)	0.02	0.49	0.576 (0.091 - 1.060)
	0 - ≤3m	0.54	0.93	-0.098 (-0.412 - 0.216)	0.64	0.94	-0.072 (-0.375 - 0.232)
	3 - ≤6m	0.19	0.84	-0.212 (-0.529 - 0.106)	0.31	0.89	-0.156 (-0.458 - 0.145)
	6 - ≤9m	0.21	0.84	-0.172 (-0.442 - 0.098)	0.43	0.93	-0.105 (-0.365 - 0.156)
CCL20	0m	0.26	0.84	0.289 (-0.215 - 0.792)	0.11	0.67	0.415 (-0.092 - 0.923)
	0 - ≤3m	0.67	0.94	0.069 (-0.249 - 0.386)	0.37	0.93	0.147 (-0.172 - 0.465)
	3 - ≤6m	1.00	1.00	0.001 (-0.320 - 0.322)	0.70	0.94	0.063 (-0.254 - 0.379)
	6 - ≤9m	0.95	0.98	-0.008 (-0.281 - 0.265)	1.00	1.00	0.000 (-0.272 - 0.273)
CCL23	0m	0.55	0.93	0.152 (-0.351 - 0.655)	0.86	0.95	0.047 (-0.462 - 0.555)
	0 - ≤3m	0.33	0.89	-0.157 (-0.474 - 0.160)	0.19	0.76	-0.212 (-0.531 - 0.107)
	3 - ≤6m	0.72	0.95	-0.059 (-0.380 - 0.261)	0.77	0.95	-0.046 (-0.363 - 0.271)
	6 - ≤9m	0.97	0.99	0.005 (-0.268 - 0.278)	0.81	0.95	-0.034 (-0.307 - 0.239)
CCL25	0m	0.02	0.45	0.593 (0.094 - 1.093)	0.05	0.57	0.510 (-0.001 - 1.020)
	0 - ≤3m	0.11	0.76	0.254 (-0.061 - 0.569)	0.21	0.76	0.206 (-0.114 - 0.527)
	3 - ≤6m	0.55	0.93	0.097 (-0.221 - 0.415)	0.51	0.93	0.106 (-0.212 - 0.425)
	6 - ≤9m	0.15	0.80	0.201 (-0.070 - 0.472)	0.21	0.76	0.175 (-0.099 - 0.449)
CCL28	0m	0.96	0.98	-0.014 (-0.518 - 0.490)	0.70	0.94	0.099 (-0.406 - 0.604)
	0 - ≤3m	0.65	0.94	-0.074 (-0.391 - 0.244)	0.93	0.99	-0.014 (-0.330 - 0.303)
	3 - ≤6m	0.93	0.98	-0.014 (-0.335 - 0.307)	0.82	0.95	0.037 (-0.278 - 0.352)
	6 - ≤9m	0.63	0.93	-0.066 (-0.340 - 0.207)	0.79	0.95	-0.036 (-0.307 - 0.235)
CCL3	0m	0.40	0.90	0.214 (-0.287 - 0.715)	0.10	0.66	0.383 (-0.071 - 0.837)
	0 - ≤3m	0.20	0.84	-0.207 (-0.523 - 0.109)	0.46	0.93	-0.107 (-0.392 - 0.178)
	3 - ≤6m	0.20	0.84	-0.206 (-0.525 - 0.113)	0.14	0.73	-0.211 (-0.494 - 0.072)
	6 - ≤9m	0.23	0.84	-0.165 (-0.437 - 0.107)	0.21	0.76	-0.154 (-0.398 - 0.090)
CCL4	0m	0.25	0.84	0.294 (-0.208 - 0.795)	0.07	0.61	0.430 (-0.041 - 0.900)
	0 - ≤3m	0.34	0.89	-0.154 (-0.470 - 0.162)	0.61	0.93	-0.076 (-0.372 - 0.219)
	3 - ≤6m	0.34	0.89	-0.156 (-0.476 - 0.163)	0.27	0.86	-0.166 (-0.460 - 0.127)
	6 - ≤9m	0.41	0.90	-0.115 (-0.387 - 0.157)	0.44	0.93	-0.100 (-0.353 - 0.153)
CD244	0m	0.22	0.84	-0.313 (-0.812 - 0.185)	0.09	0.64	-0.389 (-0.837 - 0.060)

	0 - ≤3m	0.02	0.46	-0.362 (-0.676 - -0.048)	0.01	0.43	-0.379 (-0.66 - -0.098)
	3 - ≤6m	0.87	0.97	0.027 (-0.290 - 0.345)	0.98	0.99	-0.004 (-0.284 - 0.275)
	6 - ≤9m	0.81	0.96	0.033 (-0.237 - 0.303)	0.50	0.93	-0.083 (-0.324 - 0.158)
	0m	0.62	0.93	-0.128 (-0.630 - 0.375)	0.31	0.89	-0.195 (-0.569 - 0.179)
CD40	0 - ≤3m	0.73	0.95	-0.056 (-0.373 - 0.206)	0.60	0.93	-0.062 (-0.297 - 0.173)
	3 - ≤6m	0.96	0.98	0.009 (-0.311 - 0.329)	0.73	0.94	-0.042 (-0.275 - 0.192)
	6 - ≤9m	0.31	0.89	0.142 (-0.131 - 0.415)	0.98	0.99	-0.002 (-0.203 - 0.199)
	0m	0.02	0.45	0.585 (0.086 - 1.083)	0.03	0.56	0.530 (0.041 - 1.020)
CD5	0 - ≤3m	0.47	0.93	-0.115 (-0.429 - 0.200)	0.41	0.93	-0.129 (-0.436 - 0.178)
	3 - ≤6m	0.51	0.93	-0.107 (-0.424 - 0.211)	0.44	0.93	-0.120 (-0.425 - 0.185)
	6 - ≤9m	0.63	0.93	-0.067 (-0.338 - 0.203)	0.28	0.87	-0.143 (-0.406 - 0.120)
	0m	0.12	0.76	0.400 (-0.098 - 0.899)	0.16	0.74	0.347 (-0.140 - 0.835)
CD6	0 - ≤3m	0.08	0.72	-0.283 (-0.597 - 0.032)	0.05	0.60	-0.299 (-0.605 - 0.006)
	3 - ≤6m	0.34	0.89	-0.154 (-0.471 - 0.164)	0.23	0.79	-0.186 (-0.490 - 0.118)
	6 - ≤9m	0.35	0.90	-0.129 (-0.399 - 0.142)	0.15	0.73	-0.193 (-0.455 - 0.069)
	0m	0.06	0.68	0.475 (-0.024 - 0.975)	0.04	0.56	0.525 (0.022 - 1.028)
CD8A	0 - ≤3m	0.32	0.89	-0.160 (-0.475 - 0.155)	0.40	0.93	-0.136 (-0.452 - 0.179)
	3 - ≤6m	0.57	0.93	-0.092 (-0.410 - 0.227)	0.77	0.95	-0.046 (-0.360 - 0.268)
	6 - ≤9m	0.47	0.93	-0.099 (-0.370 - 0.173)	0.62	0.93	-0.068 (-0.339 - 0.202)
	0m	0.89	0.97	-0.035 (-0.538 - 0.468)	0.59	0.93	-0.141 (-0.657 - 0.375)
CDCP1	0 - ≤3m	0.60	0.93	-0.085 (-0.403 - 0.232)	0.41	0.93	-0.135 (-0.459 - 0.189)
	3 - ≤6m	0.23	0.84	-0.198 (-0.518 - 0.123)	0.18	0.75	-0.218 (-0.540 - 0.104)
	6 - ≤9m	0.88	0.97	-0.021 (-0.294 - 0.252)	0.55	0.93	-0.084 (-0.362 - 0.193)
	0m	0.58	0.93	0.141 (-0.362 - 0.644)	0.58	0.93	0.139 (-0.357 - 0.636)
CSF-1	0 - ≤3m	0.56	0.93	-0.095 (-0.412 - 0.222)	0.60	0.93	-0.084 (-0.395 - 0.228)
	3 - ≤6m	0.59	0.93	0.088 (-0.232 - 0.409)	0.68	0.94	0.065 (-0.245 - 0.374)
	6 - ≤9m	0.50	0.93	0.093 (-0.180 - 0.366)	0.74	0.95	0.045 (-0.222 - 0.312)
	0m	0.08	0.72	0.443 (-0.056 - 0.942)	0.24	0.80	0.303 (-0.202 - 0.809)
CST5	0 - ≤3m	0.38	0.90	0.141 (-0.173 - 0.456)	0.72	0.94	0.059 (-0.259 - 0.376)
	3 - ≤6m	0.01	0.45	0.397 (0.080 - 0.715)	0.02	0.49	0.364 (0.048 - 0.679)
	6 - ≤9m	0.25	0.84	0.160 (-0.111 - 0.431)	0.32	0.89	0.139 (-0.133 - 0.411)
	0m	0.72	0.95	0.092 (-0.403 - 0.586)	0.88	0.96	0.039 (-0.458 - 0.535)
CX3CL1	0 - ≤3m	0.05	0.58	0.315 (0.004 - 0.627)	0.08	0.63	0.276 (-0.036 - 0.587)
	3 - ≤6m	0.00	0.27	0.485 (0.170 - 0.800)	0.00	0.30	0.490 (0.181 - 0.799)
	6 - ≤9m	0.90	0.97	-0.016 (-0.285 - 0.252)	0.96	0.99	0.008 (-0.259 - 0.274)
	0m	0.87	0.97	-0.041 (-0.541 - 0.459)	0.87	0.96	-0.040 (-0.537 - 0.457)
CXCL1	0 - ≤3m	0.13	0.77	-0.243 (-0.559 - 0.072)	0.16	0.74	-0.222 (-0.533 - 0.090)
	3 - ≤6m	0.57	0.93	0.093 (-0.225 - 0.412)	0.47	0.93	0.114 (-0.196 - 0.423)
	6 - ≤9m	0.39	0.90	0.120 (-0.152 - 0.391)	0.75	0.95	0.043 (-0.224 - 0.310)
	0m	0.13	0.77	0.388 (-0.113 - 0.890)	0.12	0.69	0.405 (-0.112 - 0.922)
CXCL10	0 - ≤3m	0.45	0.93	-0.121 (-0.437 - 0.195)	0.54	0.93	-0.102 (-0.427 - 0.222)
	3 - ≤6m	0.48	0.93	-0.114 (-0.433 - 0.206)	0.53	0.93	-0.104 (-0.426 - 0.218)
	6 - ≤9m	0.62	0.93	-0.068 (-0.340 - 0.204)	0.52	0.93	-0.090 (-0.368 - 0.188)
	0m	0.24	0.84	0.299 (-0.203 - 0.800)	0.22	0.76	0.313 (-0.185 - 0.810)
CXCL11	0 - ≤3m	0.36	0.90	-0.146 (-0.462 - 0.170)	0.46	0.93	-0.116 (-0.428 - 0.196)
	3 - ≤6m	0.79	0.96	-0.044 (-0.364 - 0.276)	0.83	0.95	-0.033 (-0.343 - 0.277)
	6 - ≤9m	0.68	0.95	0.057 (-0.216 - 0.329)	0.91	0.98	-0.015 (-0.283 - 0.252)
	0m	0.97	0.99	-0.009 (-0.510 - 0.492)	0.65	0.94	-0.113 (-0.609 - 0.382)
CXCL5	0 - ≤3m	0.86	0.97	-0.027 (-0.343 - 0.289)	0.67	0.94	-0.068 (-0.379 - 0.243)
	3 - ≤6m	0.11	0.76	0.257 (-0.062 - 0.577)	0.08	0.63	0.275 (-0.034 - 0.584)
	6 - ≤9m	0.18	0.84	0.185 (-0.087 - 0.457)	0.44	0.93	0.106 (-0.160 - 0.372)
	0m	0.20	0.84	0.32 (-0.175 - 0.816)	0.18	0.75	0.339 (-0.162 - 0.840)
CXCL6	0 - ≤3m	0.15	0.83	-0.226 (-0.539 - 0.086)	0.20	0.76	-0.205 (-0.520 - 0.109)
	3 - ≤6m	0.35	0.90	0.149 (-0.167 - 0.464)	0.29	0.88	0.167 (-0.145 - 0.480)
	6 - ≤9m	0.04	0.58	0.288 (0.019 - 0.556)	0.07	0.61	0.249 (-0.020 - 0.519)
	0m	0.99	0.99	-0.005 (-0.503 - 0.494)	0.84	0.95	-0.051 (-0.559 - 0.457)
CXCL9	0 - ≤3m	0.01	0.45	-0.408 (-0.722 - -0.094)	0.01	0.43	-0.417 (-0.736 - -0.099)
	3 - ≤6m	0.06	0.68	-0.299 (-0.617 - 0.019)	0.08	0.63	-0.278 (-0.595 - 0.039)
	6 - ≤9m	0.21	0.84	-0.173 (-0.443 - 0.098)	0.08	0.63	-0.241 (-0.514 - 0.032)
	0m	0.65	0.94	-0.115 (-0.617 - 0.387)	0.80	0.95	-0.064 (-0.575 - 0.446)
DNER	0 - ≤3m	0.77	0.96	0.047 (-0.270 - 0.363)	0.64	0.94	0.076 (-0.244 - 0.396)
	3 - ≤6m	0.11	0.76	0.257 (-0.062 - 0.577)	0.11	0.67	0.262 (-0.057 - 0.580)

	6 - ≤9m	0.83	0.96	0.029 (-0.243 - 0.302)	0.82	0.95	0.031 (-0.243 - 0.305)
EN-RAGE	0m	0.01	0.45	0.630 (0.133 - 1.126)	0.02	0.49	0.469 (0.065 - 0.873)
	0 - ≤3m	0.79	0.96	0.042 (-0.271 - 0.355)	0.95	0.99	0.008 (-0.246 - 0.261)
	3 - ≤6m	0.08	0.72	0.280 (-0.037 - 0.596)	0.07	0.61	0.235 (-0.017 - 0.486)
	6 - ≤9m	0.02	0.45	0.314 (0.045 - 0.584)	0.37	0.93	0.098 (-0.119 - 0.315)
FGF-19	0m	0.11	0.76	0.406 (-0.096 - 0.907)	0.07	0.61	0.479 (-0.038 - 0.995)
	0 - ≤3m	0.13	0.77	0.242 (-0.074 - 0.558)	0.09	0.64	0.279 (-0.045 - 0.603)
	3 - ≤6m	0.51	0.93	0.107 (-0.212 - 0.427)	0.52	0.93	0.106 (-0.216 - 0.428)
	6 - ≤9m	0.17	0.84	0.190 (-0.082 - 0.462)	0.11	0.68	0.224 (-0.054 - 0.501)
FGF-21	0m	0.73	0.95	-0.089 (-0.592 - 0.414)	0.61	0.93	-0.132 (-0.646 - 0.381)
	0 - ≤3m	0.79	0.96	0.042 (-0.275 - 0.359)	0.96	0.99	0.008 (-0.314 - 0.331)
	3 - ≤6m	0.22	0.84	0.200 (-0.120 - 0.520)	0.22	0.76	0.202 (-0.119 - 0.522)
	6 - ≤9m	0.49	0.93	0.096 (-0.176 - 0.369)	0.41	0.93	0.115 (-0.160 - 0.391)
FGF-23	0m	0.30	0.88	0.265 (-0.237 - 0.768)	0.49	0.93	0.180 (-0.332 - 0.693)
	0 - ≤3m	0.72	0.95	0.057 (-0.259 - 0.374)	0.96	0.99	0.009 (-0.312 - 0.330)
	3 - ≤6m	0.55	0.93	-0.098 (-0.418 - 0.222)	0.52	0.93	-0.104 (-0.424 - 0.215)
	6 - ≤9m	0.48	0.93	-0.099 (-0.371 - 0.174)	0.39	0.93	-0.120 (-0.395 - 0.155)
FGF-5**	0m	0.59	0.93	-0.151 (-0.697 - 0.395)	0.62	0.93	-0.142 (-0.699 - 0.414)
	0 - ≤3m	0.94	0.98	0.013 (-0.316 - 0.343)	0.93	0.99	0.015 (-0.322 - 0.351)
	3 - ≤6m	0.24	0.84	0.201 (-0.132 - 0.534)	0.17	0.75	0.233 (-0.102 - 0.567)
	6 - ≤9m	0.33	0.89	-0.143 (-0.428 - 0.142)	0.39	0.93	-0.126 (-0.414 - 0.162)
Flt3L	0m	0.77	0.96	0.074 (-0.427 - 0.575)	0.86	0.95	0.047 (-0.465 - 0.560)
	0 - ≤3m	0.12	0.76	-0.252 (-0.568 - 0.064)	0.10	0.67	-0.267 (-0.589 - 0.055)
	3 - ≤6m	0.19	0.84	-0.213 (-0.533 - 0.106)	0.13	0.70	-0.248 (-0.567 - 0.072)
	6 - ≤9m	0.13	0.77	-0.208 (-0.480 - 0.064)	0.12	0.69	-0.217 (-0.492 - 0.059)
HGF	0m	0.21	0.84	0.320 (-0.180 - 0.820)	0.22	0.76	0.293 (-0.173 - 0.760)
	0 - ≤3m	0.99	0.99	-0.003 (-0.318 - 0.312)	0.95	0.99	0.009 (-0.284 - 0.302)
	3 - ≤6m	0.75	0.95	0.053 (-0.266 - 0.371)	0.84	0.95	0.031 (-0.261 - 0.322)
	6 - ≤9m	0.04	0.58	0.289 (0.018 - 0.561)	0.14	0.73	0.187 (-0.064 - 0.437)
IFN-γ	0m	0.74	0.95	0.085 (-0.418 - 0.589)	0.58	0.93	0.146 (-0.374 - 0.666)
	0 - ≤3m	0.63	0.93	-0.077 (-0.395 - 0.240)	0.81	0.95	-0.039 (-0.365 - 0.288)
	3 - ≤6m	0.79	0.96	-0.043 (-0.364 - 0.277)	0.88	0.96	-0.025 (-0.350 - 0.299)
	6 - ≤9m	0.69	0.95	0.055 (-0.218 - 0.328)	0.65	0.94	0.065 (-0.215 - 0.344)
IL-10RA	0m	0.56	0.93	0.148 (-0.355 - 0.652)	0.60	0.93	0.138 (-0.383 - 0.659)
	0 - ≤3m	0.37	0.90	0.144 (-0.174 - 0.461)	0.42	0.93	0.134 (-0.193 - 0.461)
	3 - ≤6m	0.76	0.96	0.050 (-0.271 - 0.371)	0.74	0.95	0.055 (-0.270 - 0.380)
	6 - ≤9m	0.87	0.97	0.023 (-0.251 - 0.296)	0.83	0.95	0.030 (-0.250 - 0.310)
IL-10RB	0m	0.54	0.93	-0.155 (-0.654 - 0.344)	0.44	0.93	-0.202 (-0.711 - 0.307)
	0 - ≤3m	0.09	0.75	-0.268 (-0.583 - 0.047)	0.06	0.61	-0.301 (-0.621 - 0.018)
	3 - ≤6m	0.27	0.84	0.181 (-0.138 - 0.499)	0.27	0.86	0.179 (-0.139 - 0.496)
	6 - ≤9m	0.39	0.90	-0.118 (-0.389 - 0.153)	0.41	0.93	-0.115 (-0.388 - 0.159)
IL-12B	0m	0.02	0.45	0.592 (0.093 - 1.092)	0.02	0.49	0.623 (0.111 - 1.135)
	0 - ≤3m	0.77	0.96	0.046 (-0.269 - 0.361)	0.62	0.93	0.080 (-0.241 - 0.401)
	3 - ≤6m	0.82	0.96	0.038 (-0.281 - 0.356)	0.75	0.95	0.051 (-0.268 - 0.37)
	6 - ≤9m	0.18	0.84	0.184 (-0.087 - 0.455)	0.29	0.88	0.147 (-0.128 - 0.422)
IL-15RA	0m	0.82	0.96	0.058 (-0.442 - 0.558)	0.94	0.99	0.020 (-0.495 - 0.535)
	0 - ≤3m	0.13	0.77	-0.244 (-0.559 - 0.071)	0.12	0.68	-0.257 (-0.580 - 0.066)
	3 - ≤6m	0.26	0.84	-0.184 (-0.503 - 0.135)	0.29	0.87	-0.174 (-0.495 - 0.147)
	6 - ≤9m	0.04	0.58	-0.284 (-0.555 - -0.012)	0.02	0.49	-0.322 (-0.598 - -0.045)
IL-17A	0m	0.29	0.87	0.269 (-0.233 - 0.771)	0.34	0.91	0.254 (-0.264 - 0.772)
	0 - ≤3m	0.31	0.89	-0.162 (-0.478 - 0.155)	0.32	0.89	-0.166 (-0.491 - 0.159)
	3 - ≤6m	0.91	0.97	0.019 (-0.301 - 0.339)	0.84	0.95	0.033 (-0.290 - 0.355)
	6 - ≤9m	0.61	0.93	-0.070 (-0.343 - 0.202)	0.56	0.93	-0.083 (-0.361 - 0.195)
IL-17C	0m	0.22	0.84	0.312 (-0.191 - 0.815)	0.28	0.86	0.288 (-0.231 - 0.807)
	0 - ≤3m	0.54	0.93	0.099 (-0.218 - 0.416)	0.58	0.93	0.093 (-0.233 - 0.418)
	3 - ≤6m	0.55	0.93	0.098 (-0.223 - 0.418)	0.51	0.93	0.107 (-0.216 - 0.431)
	6 - ≤9m	0.36	0.90	0.126 (-0.147 - 0.399)	0.50	0.93	0.097 (-0.182 - 0.376)
IL-18	0m	0.08	0.72	0.450 (-0.049 - 0.950)	0.14	0.73	0.378 (-0.125 - 0.881)
	0 - ≤3m	0.27	0.85	-0.176 (-0.491 - 0.139)	0.23	0.78	-0.194 (-0.510 - 0.121)
	3 - ≤6m	0.34	0.89	-0.156 (-0.474 - 0.162)	0.32	0.90	-0.157 (-0.471 - 0.156)
	6 - ≤9m	0.85	0.96	-0.026 (-0.298 - 0.245)	0.39	0.93	-0.119 (-0.390 - 0.151)
IL-18R1	0m	0.46	0.93	0.188 (-0.315 - 0.691)	0.57	0.93	0.148 (-0.359 - 0.656)

	0 - ≤3m	0.40	0.90	-0.137 (-0.454 - 0.18)	0.38	0.93	-0.143 (-0.461 - 0.176)
	3 - ≤6m	0.73	0.95	0.057 (-0.263 - 0.377)	0.84	0.95	0.033 (-0.283 - 0.350)
	6 - ≤9m	0.72	0.95	0.050 (-0.223 - 0.323)	0.93	0.99	-0.013 (-0.286 - 0.260)
	0m	0.41	0.90	-0.209 (-0.710 - 0.292)	0.43	0.93	-0.206 (-0.722 - 0.309)
IL-4	0 - ≤3m	0.33	0.89	0.158 (-0.158 - 0.473)	0.36	0.93	0.151 (-0.173 - 0.475)
	3 - ≤6m	0.20	0.84	-0.209 (-0.528 - 0.110)	0.21	0.76	-0.205 (-0.526 - 0.117)
	6 - ≤9m	0.44	0.92	-0.108 (-0.379 - 0.164)	0.53	0.93	-0.089 (-0.366 - 0.188)
	0m	0.43	0.91	0.202 (-0.300 - 0.705)	0.18	0.75	0.314 (-0.146 - 0.775)
IL-6	0 - ≤3m	0.28	0.86	-0.174 (-0.491 - 0.143)	0.51	0.93	-0.098 (-0.387 - 0.191)
	3 - ≤6m	0.53	0.93	-0.103 (-0.423 - 0.218)	0.49	0.93	-0.102 (-0.389 - 0.186)
	6 - ≤9m	0.61	0.93	-0.071 (-0.344 - 0.201)	0.42	0.93	-0.102 (-0.350 - 0.145)
	0m	0.37	0.90	-0.227 (-0.724 - 0.270)	0.29	0.87	-0.271 (-0.770 - 0.227)
IL-7	0 - ≤3m	0.00	0.27	-0.482 (-0.795 - -0.169)	0.00	0.30	-0.515 (-0.828 - -0.202)
	3 - ≤6m	0.05	0.58	-0.321 (-0.637 - -0.004)	0.06	0.61	-0.300 (-0.611 - 0.011)
	6 - ≤9m	0.13	0.77	-0.206 (-0.476 - 0.064)	0.16	0.74	-0.192 (-0.460 - 0.077)
	0m	0.64	0.93	0.120 (-0.382 - 0.623)	0.12	0.68	0.275 (-0.068 - 0.618)
IL-8	0 - ≤3m	0.35	0.89	-0.152 (-0.469 - 0.165)	0.71	0.94	-0.040 (-0.255 - 0.175)
	3 - ≤6m	0.40	0.90	-0.136 (-0.457 - 0.184)	0.17	0.75	-0.148 (-0.362 - 0.066)
	6 - ≤9m	0.77	0.96	0.041 (-0.232 - 0.314)	0.80	0.95	-0.024 (-0.208 - 0.160)
	0m	0.66	0.94	-0.112 (-0.613 - 0.389)	0.62	0.93	-0.128 (-0.640 - 0.385)
IL-10	0 - ≤3m	0.10	0.75	-0.266 (-0.581 - 0.050)	0.11	0.67	-0.262 (-0.584 - 0.059)
	3 - ≤6m	0.26	0.84	-0.182 (-0.501 - 0.137)	0.36	0.93	-0.150 (-0.470 - 0.169)
	6 - ≤9m	0.81	0.96	0.033 (-0.239 - 0.305)	0.95	0.99	-0.010 (-0.285 - 0.266)
	0m	0.79	0.96	-0.068 (-0.571 - 0.435)	0.91	0.98	-0.027 (-0.525 - 0.47)
LAP TGF-β-1	0 - ≤3m	0.50	0.93	0.108 (-0.209 - 0.425)	0.46	0.93	0.119 (-0.194 - 0.431)
	3 - ≤6m	0.88	0.97	-0.024 (-0.344 - 0.296)	0.98	0.99	-0.003 (-0.314 - 0.307)
	6 - ≤9m	0.24	0.84	0.164 (-0.109 - 0.437)	0.16	0.74	0.190 (-0.077 - 0.458)
	0m	0.61	0.93	-0.130 (-0.632 - 0.371)	0.56	0.93	-0.152 (-0.668 - 0.365)
LIF-R	0 - ≤3m	0.10	0.75	-0.267 (-0.583 - 0.049)	0.10	0.66	-0.272 (-0.596 - 0.052)
	3 - ≤6m	0.46	0.93	-0.120 (-0.440 - 0.199)	0.46	0.93	-0.120 (-0.442 - 0.202)
	6 - ≤9m	0.09	0.73	-0.238 (-0.510 - 0.035)	0.06	0.61	-0.266 (-0.544 - 0.012)
	0m	0.62	0.93	0.126 (-0.378 - 0.630)	0.49	0.93	0.169 (-0.307 - 0.645)
MCP-1	0 - ≤3m	0.86	0.97	0.029 (-0.289 - 0.347)	0.63	0.94	0.073 (-0.226 - 0.371)
	3 - ≤6m	0.84	0.96	-0.033 (-0.354 - 0.288)	0.80	0.95	-0.039 (-0.335 - 0.258)
	6 - ≤9m	0.92	0.98	-0.014 (-0.288 - 0.259)	0.55	0.93	-0.078 (-0.334 - 0.177)
	0m	0.41	0.90	0.211 (-0.292 - 0.714)	0.45	0.93	0.198 (-0.321 - 0.717)
MCP-2	0 - ≤3m	0.46	0.93	0.12 (-0.197 - 0.437)	0.48	0.93	0.116 (-0.209 - 0.442)
	3 - ≤6m	0.72	0.95	0.058 (-0.262 - 0.379)	0.68	0.94	0.069 (-0.255 - 0.393)
	6 - ≤9m	0.69	0.95	-0.056 (-0.329 - 0.217)	0.61	0.93	-0.072 (-0.351 - 0.207)
	0m	0.25	0.84	-0.292 (-0.795 - 0.210)	0.53	0.93	-0.116 (-0.475 - 0.244)
MCP-3	0 - ≤3m	0.65	0.94	-0.074 (-0.391 - 0.242)	0.69	0.94	0.045 (-0.180 - 0.271)
	3 - ≤6m	0.51	0.93	-0.108 (-0.428 - 0.212)	0.37	0.93	-0.102 (-0.326 - 0.122)
	6 - ≤9m	0.55	0.93	0.083 (-0.190 - 0.355)	0.71	0.94	0.036 (-0.157 - 0.229)
	0m	0.29	0.87	0.269 (-0.233 - 0.771)	0.30	0.88	0.270 (-0.244 - 0.783)
MCP-4	0 - ≤3m	0.32	0.89	-0.160 (-0.477 - 0.156)	0.37	0.93	-0.146 (-0.469 - 0.176)
	3 - ≤6m	0.74	0.95	0.053 (-0.267 - 0.373)	0.69	0.94	0.066 (-0.254 - 0.386)
	6 - ≤9m	0.57	0.93	0.079 (-0.193 - 0.351)	0.78	0.95	0.040 (-0.236 - 0.316)
	0m	0.80	0.96	-0.065 (-0.562 - 0.431)	0.62	0.93	-0.128 (-0.638 - 0.381)
MMP-1	0 - ≤3m	0.40	0.90	0.135 (-0.178 - 0.448)	0.54	0.93	0.100 (-0.219 - 0.420)
	3 - ≤6m	0.06	0.67	0.304 (-0.013 - 0.620)	0.07	0.61	0.291 (-0.027 - 0.608)
	6 - ≤9m	0.00	0.30	0.398 (0.128 - 0.667)	0.01	0.43	0.372 (0.098 - 0.645)
	0m	0.70	0.95	0.097 (-0.406 - 0.601)	0.75	0.95	0.084 (-0.427 - 0.596)
MMP-10	0 - ≤3m	0.60	0.93	0.085 (-0.232 - 0.402)	0.57	0.93	0.093 (-0.228 - 0.414)
	3 - ≤6m	0.21	0.84	0.207 (-0.114 - 0.527)	0.14	0.73	0.238 (-0.008 - 0.557)
	6 - ≤9m	0.39	0.90	0.120 (-0.153 - 0.393)	0.60	0.93	0.074 (-0.200 - 0.349)
	0m	0.78	0.96	-0.072 (-0.576 - 0.431)	0.87	0.96	-0.044 (-0.559 - 0.471)
NT-3	0 - ≤3m	0.82	0.96	-0.037 (-0.355 - 0.280)	0.85	0.95	-0.030 (-0.353 - 0.293)
	3 - ≤6m	0.42	0.91	0.131 (-0.190 - 0.452)	0.36	0.93	0.149 (-0.172 - 0.470)
	6 - ≤9m	0.88	0.97	-0.020 (-0.294 - 0.253)	0.98	0.99	0.004 (-0.272 - 0.281)
	0m	0.58	0.93	0.141 (-0.362 - 0.644)	0.70	0.94	0.101 (-0.416 - 0.618)
OPG	0 - ≤3m	0.66	0.94	-0.070 (-0.387 - 0.247)	0.57	0.93	-0.094 (-0.419 - 0.230)
	3 - ≤6m	0.84	0.96	0.034 (-0.286 - 0.354)	1.00	1.00	0.000 (-0.323 - 0.322)

	6 - ≤9m	0.31	0.89	0.141 (-0.132 - 0.414)	0.34	0.92	0.134 (-0.143 - 0.412)
OSM	0m	0.71	0.95	0.095 (-0.408 - 0.597)	0.51	0.93	0.123 (-0.247 - 0.493)
	0 - ≤3m	0.74	0.95	-0.054 (-0.370 - 0.263)	1.00	1.00	0.000 (-0.232 - 0.232)
	3 - ≤6m	0.71	0.95	-0.060 (-0.380 - 0.260)	0.46	0.93	-0.087 (-0.317 - 0.144)
	6 - ≤9m	0.28	0.86	0.151 (-0.122 - 0.423)	0.85	0.95	0.02 (-0.179 - 0.218)
PD-L1	0m	0.48	0.93	0.179 (-0.324 - 0.681)	0.70	0.94	0.099 (-0.406 - 0.605)
	0 - ≤3m	0.26	0.84	-0.180 (-0.497 - 0.136)	0.21	0.76	-0.203 (-0.52 - 0.114)
	3 - ≤6m	0.85	0.96	-0.031 (-0.351 - 0.289)	0.87	0.96	-0.027 (-0.342 - 0.288)
	6 - ≤9m	0.45	0.93	-0.105 (-0.378 - 0.167)	0.15	0.73	-0.201 (-0.472 - 0.071)
SCF	0m	0.46	0.93	0.188 (-0.311 - 0.686)	0.27	0.86	0.282 (-0.224 - 0.788)
	0 - ≤3m	0.01	0.45	0.406 (0.092 - 0.721)	0.01	0.43	0.441 (0.124 - 0.758)
	3 - ≤6m	0.05	0.58	0.324 (0.006 - 0.641)	0.05	0.56	0.319 (0.004 - 0.634)
	6 - ≤9m	0.05	0.62	0.267 (-0.004 - 0.537)	0.01	0.46	0.343 (0.071 - 0.614)
SIRT2	0m	0.81	0.96	-0.060 (-0.564 - 0.444)	0.50	0.93	-0.174 (-0.678 - 0.33)
	0 - ≤3m	0.89	0.97	-0.023 (-0.340 - 0.295)	0.66	0.94	-0.07 (-0.386 - 0.246)
	3 - ≤6m	0.92	0.98	-0.016 (-0.337 - 0.305)	0.71	0.94	-0.06 (-0.374 - 0.254)
	6 - ≤9m	0.70	0.95	0.054 (-0.220 - 0.327)	0.83	0.95	-0.029 (-0.300 - 0.242)
SLAMF1	0m	0.56	0.93	0.149 (-0.350 - 0.648)	0.97	0.99	0.011 (-0.500 - 0.521)
	0 - ≤3m	0.11	0.76	-0.260 (-0.574 - 0.055)	0.04	0.56	-0.331 (-0.652 - -0.011)
	3 - ≤6m	0.02	0.45	-0.372 (-0.69 - -0.054)	0.01	0.43	-0.412 (-0.730 - -0.094)
	6 - ≤9m	0.34	0.89	-0.132 (-0.402 - 0.139)	0.18	0.75	-0.186 (-0.460 - 0.088)
ST1A1	0m	0.25	0.84	-0.291 (-0.793 - 0.211)	0.16	0.74	-0.347 (-0.832 - 0.137)
	0 - ≤3m	0.98	0.99	-0.004 (-0.320 - 0.312)	0.91	0.98	-0.017 (-0.321 - 0.287)
	3 - ≤6m	0.97	0.99	0.005 (-0.314 - 0.325)	0.70	0.94	-0.060 (-0.362 - 0.242)
	6 - ≤9m	0.29	0.87	0.147 (-0.126 - 0.419)	0.52	0.93	0.085 (-0.176 - 0.345)
STAMBP	0m	0.79	0.96	0.068 (-0.436 - 0.572)	0.80	0.95	-0.066 (-0.579 - 0.447)
	0 - ≤3m	0.56	0.93	-0.093 (-0.411 - 0.224)	0.33	0.90	-0.160 (-0.482 - 0.162)
	3 - ≤6m	0.93	0.98	-0.015 (-0.336 - 0.306)	0.81	0.95	-0.040 (-0.360 - 0.28)
	6 - ≤9m	0.87	0.97	-0.023 (-0.296 - 0.251)	0.56	0.93	-0.082 (-0.358 - 0.193)
TGF-α	0m	0.36	0.90	0.234 (-0.267 - 0.735)	0.35	0.93	0.23 (-0.252 - 0.712)
	0 - ≤3m	0.67	0.94	-0.069 (-0.385 - 0.247)	0.82	0.95	-0.035 (-0.337 - 0.267)
	3 - ≤6m	0.64	0.93	-0.077 (-0.396 - 0.243)	0.56	0.93	-0.09 (-0.39 - 0.211)
	6 - ≤9m	0.22	0.84	0.171 (-0.101 - 0.443)	0.64	0.94	0.062 (-0.197 - 0.321)
TNF	0m	0.19	0.84	0.336 (-0.164 - 0.837)	0.10	0.66	0.434 (-0.079 - 0.947)
	0 - ≤3m	0.21	0.84	-0.200 (-0.515 - 0.116)	0.39	0.93	-0.141 (-0.463 - 0.181)
	3 - ≤6m	0.25	0.84	-0.188 (-0.507 - 0.131)	0.32	0.89	-0.162 (-0.482 - 0.158)
	6 - ≤9m	0.47	0.93	-0.100 (-0.371 - 0.172)	0.51	0.93	-0.092 (-0.368 - 0.184)
TNFB	0m	0.61	0.93	0.131 (-0.369 - 0.631)	0.94	0.99	0.018 (-0.491 - 0.528)
	0 - ≤3m	0.07	0.72	-0.290 (-0.605 - 0.025)	0.03	0.56	-0.348 (-0.668 - -0.028)
	3 - ≤6m	0.20	0.84	-0.207 (-0.526 - 0.111)	0.17	0.75	-0.222 (-0.540 - 0.095)
	6 - ≤9m	0.08	0.72	-0.244 (-0.515 - 0.027)	0.04	0.56	-0.284 (-0.558 - -0.010)
TNFRSF9	0m	0.02	0.45	0.603 (0.103 - 1.103)	0.04	0.56	0.535 (0.031 - 1.040)
	0 - ≤3m	0.84	0.96	0.032 (-0.283 - 0.347)	0.96	0.99	0.008 (-0.309 - 0.325)
	3 - ≤6m	0.92	0.98	0.016 (-0.303 - 0.335)	0.84	0.95	0.033 (-0.282 - 0.347)
	6 - ≤9m	0.71	0.95	0.051 (-0.220 - 0.322)	0.90	0.98	-0.017 (-0.288 - 0.255)
TNFSF14	0m	0.34	0.89	0.246 (-0.257 - 0.748)	0.26	0.85	0.233 (-0.173 - 0.639)
	0 - ≤3m	0.91	0.97	0.019 (-0.298 - 0.336)	0.72	0.94	0.047 (-0.208 - 0.301)
	3 - ≤6m	0.90	0.97	0.020 (-0.300 - 0.340)	0.76	0.95	-0.039 (-0.292 - 0.214)
	6 - ≤9m	0.17	0.84	0.189 (-0.083 - 0.462)	0.53	0.93	0.069 (-0.149 - 0.287)
TRAIL	0m	0.15	0.80	0.370 (-0.131 - 0.872)	0.21	0.76	0.326 (-0.185 - 0.837)
	0 - ≤3m	0.49	0.93	-0.112 (-0.428 - 0.204)	0.45	0.93	-0.124 (-0.445 - 0.196)
	3 - ≤6m	0.83	0.96	-0.034 (-0.354 - 0.285)	0.88	0.96	-0.025 (-0.343 - 0.294)
	6 - ≤9m	0.39	0.90	-0.118 (-0.391 - 0.154)	0.26	0.85	-0.158 (-0.432 - 0.116)
TRANCE	0m	0.46	0.93	0.189 (-0.314 - 0.692)	0.39	0.93	0.228 (-0.291 - 0.748)
	0 - ≤3m	0.61	0.93	-0.082 (-0.399 - 0.235)	0.75	0.95	-0.054 (-0.379 - 0.272)
	3 - ≤6m	0.75	0.96	-0.051 (-0.372 - 0.269)	0.84	0.95	-0.034 (-0.357 - 0.290)
	6 - ≤9m	0.41	0.90	-0.116 (-0.389 - 0.157)	0.37	0.93	-0.127 (-0.406 - 0.153)
TWEAK	0m	0.05	0.58	0.505 (0.010 – 1.000)	0.07	0.61	0.467 (-0.042 - 0.975)
	0 - ≤3m	0.67	0.94	0.067 (-0.244 - 0.379)	0.78	0.95	0.046 (-0.273 - 0.365)
	3 - ≤6m	0.04	0.58	0.336 (0.021 - 0.652)	0.04	0.56	0.325 (0.008 - 0.643)
	6 - ≤9m	0.00	0.27	0.421 (0.152 - 0.689)	0.00	0.42	0.401 (0.128 - 0.675)
uPA	0m	0.25	0.84	0.297 (-0.205 - 0.800)	0.51	0.93	0.163 (-0.324 - 0.649)

	0 - ≤3m	0.95	0.98	-0.011 (-0.328 - 0.306)	0.59	0.93	-0.083 (-0.388 - 0.222)
	3 - ≤6m	0.41	0.90	0.133 (-0.187 - 0.454)	0.79	0.95	0.040 (-0.263 - 0.344)
	6 - ≤9m	0.67	0.94	0.059 (-0.214 - 0.332)	0.95	0.99	0.009 (-0.252 - 0.270)
VEGFA	0m	0.57	0.93	0.146 (-0.354 - 0.647)	0.50	0.93	0.172 (-0.332 - 0.676)
	0 - ≤3m	0.58	0.93	-0.089 (-0.404 - 0.227)	0.70	0.94	-0.061 (-0.378 - 0.255)
	3 - ≤6m	0.88	0.97	0.024 (-0.295 - 0.343)	0.76	0.95	0.049 (-0.265 - 0.363)
	6 - ≤9m	0.10	0.75	0.230 (-0.041 - 0.502)	0.18	0.75	0.185 (-0.086 - 0.455)

**46 infants had an NA value for FGF-5.

Supplementary Table 9. Linear regression associations of infant serum biomarker levels with categorical exclusive HMF duration (infants grouped in four-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use categorical exclusive HMF duration (infants grouped in four-month intervals) to predict biomarker levels (standardized NPX). The >8m HMF group was used as reference.

Olink Biomarkers	Variable Groups	Univariable			Multivariable		
		P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0m	0.55	0.92	0.152 (-0.342 - 0.645)	0.84	0.95	0.05 (-0.447 - 0.547)
	0 - ≤4m	0.73	0.94	-0.050 (-0.336 - 0.237)	0.41	0.79	-0.121 (-0.409 - 0.167)
	4 - ≤8m	0.33	0.80	-0.123 (-0.369 - 0.124)	0.33	0.79	-0.120 (-0.364 - 0.123)
ADA	0m	0.68	0.94	-0.105 (-0.598 - 0.389)	0.38	0.79	-0.215 (-0.695 - 0.266)
	0 - ≤4m	0.25	0.78	-0.168 (-0.455 - 0.119)	0.21	0.71	-0.18 (-0.458 - 0.099)
	4 - ≤8m	0.79	0.94	-0.034 (-0.2800 - 0.213)	0.40	0.79	-0.101 (-0.337 - 0.134)
AXIN1	0m	0.97	0.99	-0.011 (-0.504 - 0.482)	0.30	0.79	-0.243 (-0.706 - 0.221)
	0 - ≤4m	0.19	0.77	-0.191 (-0.478 - 0.095)	0.08	0.62	-0.243 (-0.512 - 0.026)
	4 - ≤8m	0.36	0.81	-0.115 (-0.361 - 0.131)	0.10	0.62	-0.192 (-0.42 - 0.035)
CASP-8	0m	0.45	0.88	0.188 (-0.305 - 0.681)	0.33	0.79	0.168 (-0.167 - 0.503)
	0 - ≤4m	0.90	0.97	0.018 (-0.268 - 0.305)	0.41	0.79	0.081 (-0.114 - 0.275)
	4 - ≤8m	0.28	0.80	0.135 (-0.111 - 0.382)	0.73	0.93	0.029 (-0.135 - 0.193)
CCL11	0m	0.46	0.88	0.186 (-0.304 - 0.676)	0.46	0.84	0.184 (-0.309 - 0.678)
	0 - ≤4m	0.03	0.52	-0.307 (-0.592 - -0.022)	0.06	0.62	-0.272 (-0.558 - 0.015)
	4 - ≤8m	0.48	0.90	-0.089 (-0.334 - 0.156)	0.38	0.79	-0.107 (-0.349 - 0.134)
CCL19	0m	0.03	0.52	0.534 (0.045 - 1.023)	0.02	0.49	0.587 (0.113 - 1.060)
	0 - ≤4m	0.41	0.85	-0.118 (-0.402 - 0.166)	0.40	0.79	-0.119 (-0.393 - 0.156)
	4 - ≤8m	0.21	0.77	-0.155 (-0.399 - 0.089)	0.40	0.79	-0.099 (-0.331 - 0.134)
CCL20	0m	0.27	0.80	0.275 (-0.218 - 0.768)	0.11	0.62	0.402 (-0.094 - 0.898)
	0 - ≤4m	0.71	0.94	0.054 (-0.233 - 0.341)	0.36	0.79	0.134 (-0.154 - 0.422)
	4 - ≤8m	0.74	0.94	-0.041 (-0.288 - 0.205)	0.95	0.97	-0.008 (-0.251 - 0.236)
CCL23	0m	0.58	0.92	0.139 (-0.354 - 0.632)	0.85	0.95	0.048 (-0.449 - 0.546)
	0 - ≤4m	0.33	0.80	-0.143 (-0.430 - 0.144)	0.23	0.71	-0.177 (-0.465 - 0.112)
	4 - ≤8m	0.66	0.94	-0.056 (-0.302 - 0.191)	0.65	0.91	-0.057 (-0.301 - 0.187)
CCL25	0m	0.03	0.52	0.535 (0.044 - 1.026)	0.08	0.62	0.446 (-0.054 - 0.946)
	0 - ≤4m	0.40	0.85	0.123 (-0.162 - 0.408)	0.58	0.90	0.082 (-0.208 - 0.372)
	4 - ≤8m	0.34	0.80	0.118 (-0.127 - 0.364)	0.39	0.79	0.108 (-0.137 - 0.353)
CCL28	0m	0.79	0.94	-0.065 (-0.559 - 0.428)	0.89	0.96	0.034 (-0.459 - 0.527)
	0 - ≤4m	0.29	0.80	-0.153 (-0.440 - 0.134)	0.46	0.84	-0.106 (-0.392 - 0.180)
	4 - ≤8m	0.22	0.77	-0.155 (-0.401 - 0.091)	0.32	0.79	-0.122 (-0.364 - 0.120)
CCL3	0m	0.25	0.78	0.288 (-0.205 - 0.780)	0.05	0.57	0.451 (0.005 - 0.896)
	0 - ≤4m	0.35	0.80	-0.137 (-0.423 - 0.150)	0.70	0.93	-0.051 (-0.309 - 0.207)
	4 - ≤8m	0.59	0.92	-0.067 (-0.313 - 0.179)	0.42	0.80	-0.089 (-0.307 - 0.129)
CCL4	0m	0.17	0.76	0.342 (-0.151 - 0.834)	0.05	0.57	0.470 (0.010 - 0.931)
	0 - ≤4m	0.50	0.91	-0.098 (-0.384 - 0.188)	0.80	0.95	-0.034 (-0.301 - 0.233)
	4 - ≤8m	0.60	0.92	-0.066 (-0.312 - 0.180)	0.46	0.84	-0.084 (-0.310 - 0.141)
CD244	0m	0.18	0.76	-0.336 (-0.824 - 0.151)	0.08	0.62	-0.388 (-0.826 - 0.051)
	0 - ≤4m	0.01	0.47	-0.377 (-0.661 - -0.094)	0.01	0.42	-0.357 (-0.612 - -0.103)
	4 - ≤8m	0.88	0.97	0.019 (-0.225 - 0.263)	0.59	0.90	-0.059 (-0.273 - 0.156)
CD40	0m	0.59	0.92	-0.136 (-0.629 - 0.356)	0.36	0.79	-0.172 (-0.538 - 0.194)
	0 - ≤4m	0.63	0.94	-0.070 (-0.357 - 0.216)	0.83	0.95	-0.024 (-0.236 - 0.188)
	4 - ≤8m	0.35	0.80	0.118 (-0.128 - 0.364)	0.84	0.95	0.019 (-0.161 - 0.198)
CD5	0m	0.01	0.48	0.623 (0.135 - 1.112)	0.02	0.49	0.582 (0.104 - 1.061)
	0 - ≤4m	0.35	0.80	-0.135 (-0.419 - 0.149)	0.36	0.79	-0.128 (-0.406 - 0.150)
	4 - ≤8m	0.88	0.97	0.018 (-0.226 - 0.262)	0.78	0.95	-0.033 (-0.267 - 0.202)
CD6	0m	0.06	0.61	0.466 (-0.023 - 0.955)	0.08	0.62	0.428 (-0.050 - 0.905)
	0 - ≤4m	0.09	0.65	-0.243 (-0.528 - 0.041)	0.09	0.62	-0.243 (-0.520 - 0.034)
	4 - ≤8m	0.97	0.99	-0.005 (-0.249 - 0.239)	0.62	0.91	-0.058 (-0.292 - 0.176)

	0m	0.06	0.61	0.479 (-0.011 - 0.968)	0.04	0.57	0.516 (0.025 - 1.007)
CD8A	0 - ≤4m	0.17	0.76	-0.199 (-0.484 - 0.085)	0.19	0.71	-0.192 (-0.477 - 0.093)
	4 - ≤8m	0.49	0.90	-0.086 (-0.331 - 0.158)	0.65	0.91	-0.056 (-0.297 - 0.185)
	0m	0.82	0.95	-0.058 (-0.551 - 0.435)	0.57	0.90	-0.147 (-0.651 - 0.357)
CDCP1	0 - ≤4m	0.42	0.85	-0.118 (-0.405 - 0.168)	0.35	0.79	-0.139 (-0.432 - 0.153)
	4 - ≤8m	0.22	0.77	-0.155 (-0.401 - 0.091)	0.14	0.69	-0.186 (-0.433 - 0.061)
	0m	0.69	0.94	0.101 (-0.393 - 0.595)	0.66	0.91	0.110 (-0.376 - 0.595)
CSF-1	0 - ≤4m	0.69	0.94	-0.059 (-0.347 - 0.228)	0.82	0.95	-0.032 (-0.314 - 0.250)
	4 - ≤8m	0.99	1.00	-0.001 (-0.248 - 0.246)	0.73	0.93	-0.042 (-0.281 - 0.196)
	0m	0.08	0.64	0.436 (-0.054 - 0.926)	0.22	0.71	0.308 (-0.188 - 0.804)
CST5	0 - ≤4m	0.07	0.64	0.261 (-0.024 - 0.545)	0.20	0.71	0.188 (-0.099 - 0.476)
	4 - ≤8m	0.06	0.61	0.236 (-0.009 - 0.481)	0.09	0.62	0.213 (-0.030 - 0.456)
	0m	0.73	0.94	0.086 (-0.405 - 0.577)	0.91	0.96	0.027 (-0.463 - 0.518)
CX3CL1	0 - ≤4m	0.04	0.52	0.298 (0.012 - 0.583)	0.09	0.62	0.246 (-0.039 - 0.531)
	4 - ≤8m	0.11	0.65	0.198 (-0.047 - 0.443)	0.07	0.62	0.219 (-0.022 - 0.459)
	0m	0.76	0.94	-0.076 (-0.567 - 0.416)	0.83	0.95	-0.053 (-0.540 - 0.434)
CXCL1	0 - ≤4m	0.10	0.65	-0.238 (-0.524 - 0.048)	0.20	0.71	-0.183 (-0.465 - 0.099)
	4 - ≤8m	0.57	0.92	0.072 (-0.174 - 0.317)	0.69	0.93	0.048 (-0.190 - 0.287)
	0m	0.11	0.65	0.396 (-0.095 - 0.888)	0.10	0.62	0.423 (-0.082 - 0.929)
CXCL10	0 - ≤4m	0.42	0.85	-0.117 (-0.403 - 0.168)	0.57	0.90	-0.086 (-0.379 - 0.208)
	4 - ≤8m	0.49	0.90	-0.087 (-0.332 - 0.159)	0.50	0.87	-0.084 (-0.332 - 0.163)
	0m	0.25	0.78	0.291 (-0.202 - 0.783)	0.18	0.71	0.331 (-0.156 - 0.818)
CXCL11	0 - ≤4m	0.44	0.88	-0.112 (-0.399 - 0.174)	0.75	0.94	-0.046 (-0.328 - 0.237)
	4 - ≤8m	0.98	0.99	-0.003 (-0.249 - 0.244)	0.85	0.95	-0.023 (-0.261 - 0.216)
	0m	0.85	0.97	-0.048 (-0.540 - 0.443)	0.63	0.91	-0.119 (-0.604 - 0.366)
CXCL5	0 - ≤4m	0.72	0.94	-0.052 (-0.338 - 0.234)	0.76	0.94	-0.045 (-0.326 - 0.237)
	4 - ≤8m	0.11	0.65	0.199 (-0.047 - 0.444)	0.10	0.62	0.202 (-0.035 - 0.440)
	0m	0.31	0.80	0.251 (-0.237 - 0.740)	0.26	0.76	0.280 (-0.213 - 0.773)
CXCL6	0 - ≤4m	0.11	0.65	-0.234 (-0.519 - 0.050)	0.18	0.71	-0.193 (-0.479 - 0.093)
	4 - ≤8m	0.20	0.77	0.159 (-0.086 - 0.403)	0.22	0.71	0.150 (-0.092 - 0.392)
	0m	0.87	0.97	0.041 (-0.450 - 0.531)	0.93	0.96	0.023 (-0.476 - 0.521)
CXCL9	0 - ≤4m	0.03	0.52	-0.322 (-0.607 - -0.037)	0.04	0.57	-0.297 (-0.586 - -0.008)
	4 - ≤8m	0.12	0.66	-0.193 (-0.438 - 0.052)	0.10	0.62	-0.205 (-0.449 - 0.040)
	0m	0.54	0.92	-0.153 (-0.647 - 0.340)	0.65	0.91	-0.115 (-0.616 - 0.385)
DNER	0 - ≤4m	0.89	0.97	-0.020 (-0.307 - 0.267)	0.97	0.98	-0.005 (-0.295 - 0.286)
	4 - ≤8m	0.50	0.91	0.084 (-0.162 - 0.331)	0.57	0.90	0.071 (-0.174 - 0.316)
	0m	0.02	0.52	0.561 (0.073 - 1.049)	0.02	0.50	0.459 (0.064 - 0.854)
EN-RAGE	0 - ≤4m	0.92	0.97	-0.015 (-0.298 - 0.269)	0.73	0.93	0.040 (-0.189 - 0.270)
	4 - ≤8m	0.04	0.52	0.257 (0.013 - 0.500)	0.13	0.64	0.151 (-0.043 - 0.345)
	0m	0.16	0.76	0.351 (-0.142 - 0.843)	0.11	0.62	0.408 (-0.099 - 0.914)
FGF-19	0 - ≤4m	0.19	0.77	0.190 (-0.097 - 0.476)	0.16	0.71	0.210 (-0.083 - 0.504)
	4 - ≤8m	0.53	0.92	0.078 (-0.168 - 0.324)	0.51	0.88	0.083 (-0.165 - 0.331)
	0m	0.68	0.94	-0.102 (-0.595 - 0.391)	0.56	0.90	-0.150 (-0.652 - 0.351)
FGF-21	0 - ≤4m	0.86	0.97	0.025 (-0.262 - 0.312)	0.92	0.96	-0.015 (-0.306 - 0.276)
	4 - ≤8m	0.21	0.77	0.156 (-0.091 - 0.402)	0.17	0.71	0.170 (-0.076 - 0.416)
	0m	0.32	0.80	0.251 (-0.241 - 0.743)	0.49	0.87	0.175 (-0.325 - 0.676)
FGF-23	0 - ≤4m	0.93	0.98	0.013 (-0.273 - 0.299)	0.89	0.96	-0.021 (-0.311 - 0.269)
	4 - ≤8m	0.22	0.77	-0.153 (-0.399 - 0.093)	0.23	0.71	-0.151 (-0.396 - 0.094)
	0m	0.58	0.92	-0.151 (-0.690 - 0.388)	0.59	0.90	-0.148 (-0.696 - 0.399)
FGF-5**	0 - ≤4m	0.79	0.94	-0.041 (-0.339 - 0.257)	0.73	0.93	-0.054 (-0.358 - 0.250)
	4 - ≤8m	0.94	0.98	0.010 (-0.249 - 0.268)	0.84	0.95	0.026 (-0.233 - 0.285)
	0m	0.78	0.94	0.068 (-0.421 - 0.558)	0.87	0.96	0.043 (-0.456 - 0.542)
Flt3L	0 - ≤4m	0.05	0.61	-0.284 (-0.568 - 0.001)	0.04	0.57	-0.298 (-0.587 - -0.008)
	4 - ≤8m	0.03	0.52	-0.265 (-0.509 - -0.020)	0.02	0.50	-0.282 (-0.527 - -0.038)
	0m	0.34	0.80	0.239 (-0.254 - 0.732)	0.32	0.79	0.234 (-0.224 - 0.692)
HGF	0 - ≤4m	0.64	0.94	-0.068 (-0.354 - 0.219)	0.92	0.96	-0.013 (-0.279 - 0.252)
	4 - ≤8m	0.46	0.88	0.093 (-0.153 - 0.339)	0.77	0.95	0.034 (-0.191 - 0.258)
	0m	0.79	0.94	0.067 (-0.427 - 0.562)	0.62	0.91	0.128 (-0.381 - 0.637)
IFN-γ	0 - ≤4m	0.65	0.94	-0.067 (-0.354 - 0.221)	0.84	0.95	-0.030 (-0.325 - 0.266)
	4 - ≤8m	0.85	0.97	-0.023 (-0.270 - 0.224)	0.94	0.97	-0.010 (-0.259 - 0.240)
	0m	0.57	0.92	0.141 (-0.353 - 0.635)	0.63	0.91	0.126 (-0.384 - 0.635)
IL-10RA	0 - ≤4m	0.48	0.90	0.104 (-0.184 - 0.391)	0.55	0.90	0.090 (-0.206 - 0.385)

	4 - ≤8m	0.77	0.94	0.037 (-0.209 - 0.284)	0.74	0.94	0.042 (-0.208 - 0.292)
	0m	0.66	0.94	-0.110 (-0.602 - 0.383)	0.54	0.90	-0.156 (-0.658 - 0.345)
IL-10RB	0 - ≤4m	0.30	0.80	-0.151 (-0.437 - 0.136)	0.19	0.71	-0.193 (-0.484 - 0.098)
	4 - ≤8m	0.59	0.92	0.067 (-0.180 - 0.313)	0.65	0.91	0.056 (-0.189 - 0.302)
	0m	0.04	0.52	0.519 (0.029 - 1.010)	0.03	0.57	0.551 (0.050 - 1.052)
IL-12B	0 - ≤4m	0.55	0.92	-0.088 (-0.373 - 0.197)	0.78	0.95	-0.041 (-0.332 - 0.249)
	4 - ≤8m	0.67	0.94	0.053 (-0.192 - 0.298)	0.72	0.93	0.044 (-0.201 - 0.290)
	0m	0.63	0.94	0.119 (-0.373 - 0.611)	0.72	0.93	0.093 (-0.413 - 0.598)
IL-15RA	0 - ≤4m	0.11	0.65	-0.235 (-0.521 - 0.051)	0.11	0.62	-0.237 (-0.530 - 0.056)
	4 - ≤8m	0.21	0.77	-0.155 (-0.401 - 0.090)	0.19	0.71	-0.166 (-0.413 - 0.082)
	0m	0.35	0.80	0.233 (-0.259 - 0.725)	0.39	0.79	0.219 (-0.286 - 0.725)
IL-17A	0 - ≤4m	0.15	0.74	-0.209 (-0.495 - 0.077)	0.16	0.71	-0.210 (-0.504 - 0.083)
	4 - ≤8m	0.38	0.83	-0.111 (-0.356 - 0.135)	0.40	0.79	-0.107 (-0.355 - 0.141)
	0m	0.30	0.80	0.258 (-0.236 - 0.752)	0.35	0.79	0.241 (-0.267 - 0.749)
IL-17C	0 - ≤4m	0.75	0.94	0.046 (-0.241 - 0.333)	0.71	0.93	0.056 (-0.239 - 0.351)
	4 - ≤8m	0.80	0.95	0.031 (-0.216 - 0.278)	0.82	0.95	0.029 (-0.220 - 0.278)
	0m	0.06	0.61	0.467 (-0.023 - 0.956)	0.09	0.62	0.420 (-0.072 - 0.913)
IL-18	0 - ≤4m	0.19	0.77	-0.190 (-0.475 - 0.095)	0.24	0.72	-0.169 (-0.455 - 0.116)
	4 - ≤8m	0.79	0.94	-0.033 (-0.277 - 0.212)	0.57	0.90	-0.069 (-0.311 - 0.172)
	0m	0.61	0.93	0.127 (-0.367 - 0.620)	0.68	0.93	0.104 (-0.392 - 0.600)
IL-18R1	0 - ≤4m	0.25	0.78	-0.169 (-0.455 - 0.118)	0.31	0.79	-0.148 (-0.436 - 0.140)
	4 - ≤8m	0.58	0.92	-0.069 (-0.315 - 0.177)	0.40	0.79	-0.103 (-0.346 - 0.140)
	0m	0.36	0.81	-0.228 (-0.719 - 0.262)	0.35	0.79	-0.242 (-0.746 - 0.262)
IL-4	0 - ≤4m	0.58	0.92	0.080 (-0.205 - 0.365)	0.69	0.93	0.059 (-0.234 - 0.351)
	4 - ≤8m	0.08	0.64	-0.220 (-0.465 - 0.025)	0.08	0.62	-0.222 (-0.469 - 0.025)
	0m	0.35	0.80	0.236 (-0.258 - 0.729)	0.12	0.64	0.357 (-0.094 - 0.807)
IL-6	0 - ≤4m	0.48	0.90	-0.102 (-0.389 - 0.185)	0.90	0.96	-0.017 (-0.278 - 0.245)
	4 - ≤8m	0.69	0.94	-0.049 (-0.296 - 0.197)	0.49	0.87	-0.078 (-0.299 - 0.143)
	0m	0.30	0.80	-0.254 (-0.737 - 0.229)	0.21	0.71	-0.305 (-0.787 - 0.178)
IL-7	**0 - ≤4m**	**<0.01**	**0.03**	**-0.555 (-0.835 - -0.274)**	**<0.01**	**0.01**	**-0.593 (-0.873 - -0.313)**
	4 - ≤8m	0.01	0.47	-0.334 (-0.575 - -0.093)	0.01	0.47	-0.310 (-0.546 - -0.073)
	0m	0.51	0.91	0.166 (-0.327 - 0.660)	0.05	0.57	0.336 (0.000 - 0.672)
IL-8	0 - ≤4m	0.58	0.92	-0.080 (-0.367 - 0.207)	0.60	0.90	0.052 (-0.143 - 0.247)
	4 - ≤8m	0.60	0.92	0.066 (-0.180 - 0.313)	0.92	0.96	0.008 (-0.157 - 0.173)
	0m	0.69	0.94	-0.099 (-0.591 - 0.393)	0.70	0.93	-0.098 (-0.600 - 0.403)
IL-10	0 - ≤4m	0.08	0.64	-0.255 (-0.541 - 0.031)	0.13	0.64	-0.227 (-0.518 - 0.063)
	4 - ≤8m	0.94	0.98	-0.009 (-0.255 - 0.237)	0.97	0.98	-0.005 (-0.251 - 0.240)
	0m	0.59	0.92	-0.136 (-0.630 - 0.358)	0.64	0.91	-0.115 (-0.604 - 0.373)
LAP TGF-β-1	0 - ≤4m	0.98	0.99	-0.003 (-0.290 - 0.284)	0.97	0.98	-0.005 (-0.288 - 0.278)
	4 - ≤8m	1.00	1.00	0.000 (-0.247 - 0.247)	0.94	0.97	0.009 (-0.231 - 0.248)
	0m	0.70	0.94	-0.095 (-0.587 - 0.397)	0.69	0.93	-0.104 (-0.610 - 0.402)
LIF-R	0 - ≤4m	0.06	0.62	-0.269 (-0.555 - 0.017)	0.08	0.62	-0.262 (-0.556 - 0.031)
	4 - ≤8m	0.24	0.78	-0.147 (-0.392 - 0.099)	0.24	0.71	-0.150 (-0.398 - 0.098)
	0m	0.56	0.92	0.148 (-0.346 - 0.642)	0.37	0.79	0.211 (-0.255 - 0.676)
MCP-1	0 - ≤4m	0.76	0.94	0.045 (-0.242 - 0.332)	0.40	0.79	0.116 (-0.154 - 0.386)
	4 - ≤8m	0.87	0.97	0.021 (-0.226 - 0.268)	0.91	0.96	-0.012 (-0.240 - 0.216)
	0m	0.32	0.80	0.251 (-0.243 - 0.744)	0.34	0.79	0.249 (-0.259 - 0.756)
MCP-2	0 - ≤4m	0.30	0.80	0.151 (-0.136 - 0.438)	0.29	0.79	0.159 (-0.135 - 0.454)
	4 - ≤8m	0.61	0.93	0.063 (-0.183 - 0.310)	0.59	0.90	0.069 (-0.180 - 0.318)
	0m	0.24	0.78	-0.298 (-0.791 - 0.196)	0.53	0.89	-0.112 (-0.463 - 0.239)
MCP-3	0 - ≤4m	0.82	0.95	-0.032 (-0.319 - 0.254)	0.32	0.79	0.103 (-0.101 - 0.307)
	4 - ≤8m	0.90	0.97	-0.016 (-0.262 - 0.231)	0.52	0.89	-0.056 (-0.228 - 0.116)
	0m	0.29	0.80	0.263 (-0.225 - 0.752)	0.28	0.78	0.276 (-0.223 - 0.775)
MCP-4	0 - ≤4m	0.09	0.65	-0.247 (-0.531 - 0.038)	0.15	0.71	-0.213 (-0.502 - 0.077)
	4 - ≤8m	0.24	0.78	0.147 (-0.098 - 0.391)	0.23	0.71	0.150 (-0.095 - 0.394)
	0m	0.38	0.83	-0.219 (-0.712 - 0.273)	0.27	0.77	-0.282 (-0.785 - 0.221)
MMP-1	0 - ≤4m	0.89	0.97	0.021 (-0.266 - 0.307)	0.99	1.00	0.001 (-0.290 - 0.293)
	4 - ≤8m	0.30	0.80	0.129 (-0.117 - 0.375)	0.35	0.79	0.116 (-0.130 - 0.363)
	0m	0.87	0.97	0.041 (-0.453 - 0.535)	0.84	0.95	0.050 (-0.450 - 0.551)
MMP-10	0 - ≤4m	0.45	0.88	0.112 (-0.176 - 0.399)	0.31	0.79	0.150 (-0.141 - 0.441)
	4 - ≤8m	0.82	0.95	0.028 (-0.219 - 0.275)	0.76	0.94	0.039 (-0.207 - 0.284)
NT-3	0m	0.71	0.94	-0.092 (-0.587 - 0.402)	0.75	0.94	-0.081 (-0.585 - 0.422)

	0 - ≤4m	0.67	0.94	-0.063 (-0.350 - 0.225)	0.61	0.90	-0.077 (-0.369 - 0.216)
	4 - ≤8m	0.94	0.98	0.009 (-0.238 - 0.256)	0.93	0.96	0.012 (-0.235 - 0.259)
	0m	0.75	0.94	0.080 (-0.413 - 0.573)	0.89	0.96	0.034 (-0.471 - 0.540)
OPG	0 - ≤4m	0.27	0.80	-0.161 (-0.448 - 0.126)	0.21	0.71	-0.186 (-0.479 - 0.107)
	4 - ≤8m	0.81	0.95	0.031 (-0.215 - 0.277)	0.93	0.96	0.011 (-0.236 - 0.259)
	0m	0.71	0.94	0.092 (-0.402 - 0.586)	0.40	0.79	0.154 (-0.208 - 0.516)
OSM	0 - ≤4m	0.86	0.97	-0.025 (-0.312 - 0.262)	0.45	0.84	0.080 (-0.130 - 0.290)
	4 - ≤8m	0.51	0.91	0.082 (-0.164 - 0.329)	1.00	1.00	0.000 (-0.177 - 0.177)
	0m	0.42	0.85	0.204 (-0.289 - 0.697)	0.54	0.90	0.154 (-0.342 - 0.649)
PD-L1	0 - ≤4m	0.31	0.80	-0.149 (-0.435 - 0.138)	0.37	0.79	-0.132 (-0.420 - 0.155)
	4 - ≤8m	0.74	0.94	-0.042 (-0.288 - 0.204)	0.53	0.89	-0.078 (-0.320 - 0.165)
	0m	0.55	0.92	0.150 (-0.339 - 0.638)	0.40	0.79	0.211 (-0.285 - 0.706)
SCF	0 - ≤4m	0.01	0.47	0.372 (0.088 - 0.656)	0.01	0.48	0.366 (0.079 - 0.654)
	4 - ≤8m	0.03	0.52	0.277 (0.033 - 0.522)	0.02	0.50	0.286 (0.043 - 0.529)
	0m	0.77	0.94	-0.074 (-0.568 - 0.420)	0.50	0.87	-0.168 (-0.660 - 0.325)
SIRT2	0 - ≤4m	0.67	0.94	-0.062 (-0.349 - 0.226)	0.59	0.90	-0.077 (-0.363 - 0.208)
	4 - ≤8m	0.83	0.96	0.026 (-0.221 - 0.273)	0.82	0.95	-0.028 (-0.27 - 0.213)
	0m	0.68	0.94	0.101 (-0.385 - 0.586)	0.92	0.96	-0.025 (-0.521 - 0.47)
SLAMF1	0 - ≤4m	0.02	0.52	-0.347 (-0.629 - -0.064)	0.01	0.42	-0.394 (-0.681 - -0.106)
	4 - ≤8m	0.00	0.37	-0.365 (-0.608 - -0.123)	0.00	0.17	-0.395 (-0.638 - -0.152)
	0m	0.31	0.80	-0.256 (-0.747 - 0.235)	0.23	0.71	-0.288 (-0.762 - 0.185)
ST1A1	0 - ≤4m	0.71	0.94	0.054 (-0.232 - 0.339)	0.62	0.91	0.070 (-0.205 - 0.344)
	4 - ≤8m	0.12	0.66	0.195 (-0.050 - 0.441)	0.22	0.71	0.145 (-0.087 - 0.377)
	0m	0.78	0.94	0.072 (-0.422 - 0.566)	0.85	0.95	-0.048 (-0.550 - 0.453)
STAMBP	0 - ≤4m	0.44	0.88	-0.112 (-0.399 - 0.175)	0.29	0.79	-0.158 (-0.449 - 0.133)
	4 - ≤8m	0.98	0.99	0.003 (-0.244 - 0.249)	0.80	0.95	-0.032 (-0.278 - 0.214)
	0m	0.53	0.92	0.156 (-0.337 - 0.649)	0.46	0.84	0.179 (-0.292 - 0.651)
TGF-α	0 - ≤4m	0.28	0.80	-0.159 (-0.445 - 0.128)	0.57	0.90	-0.078 (-0.351 - 0.195)
	4 - ≤8m	0.71	0.94	-0.047 (-0.294 - 0.199)	0.42	0.80	-0.095 (-0.326 - 0.136)
	0m	0.20	0.77	0.322 (-0.168 - 0.812)	0.11	0.62	0.412 (-0.088 - 0.913)
TNF	0 - ≤4m	0.11	0.65	-0.229 (-0.513 - 0.056)	0.23	0.71	-0.177 (-0.468 - 0.113)
	4 - ≤8m	0.13	0.68	-0.189 (-0.433 - 0.056)	0.14	0.70	-0.182 (-0.428 - 0.063)
	0m	0.49	0.91	0.170 (-0.320 - 0.661)	0.78	0.95	0.071 (-0.427 - 0.570)
TNFB	0 - ≤4m	0.07	0.63	-0.264 (-0.549 - 0.021)	0.04	0.57	-0.308 (-0.597 - -0.019)
	4 - ≤8m	0.11	0.65	-0.200 (-0.445 - 0.044)	0.08	0.62	-0.218 (-0.463 - 0.026)
	0m	0.02	0.52	0.573 (0.082 - 1.063)	0.04	0.57	0.516 (0.023 - 1.010)
TNFRSF9	0 - ≤4m	0.92	0.97	-0.015 (-0.300 - 0.270)	0.91	0.96	-0.016 (-0.302 - 0.270)
	4 - ≤8m	0.95	0.98	-0.008 (-0.253 - 0.237)	0.78	0.95	-0.035 (-0.277 - 0.207)
	0m	0.34	0.80	0.237 (-0.255 - 0.730)	0.21	0.71	0.255 (-0.141 - 0.651)
TNFSF14	0 - ≤4m	0.92	0.97	-0.014 (-0.301 - 0.272)	0.61	0.90	0.060 (-0.170 - 0.290)
	4 - ≤8m	0.17	0.76	0.172 (-0.074 - 0.418)	0.37	0.79	0.089 (-0.106 - 0.283)
	0m	0.15	0.74	0.357 (-0.133 - 0.848)	0.20	0.71	0.323 (-0.176 - 0.822)
TRAIL	0 - ≤4m	0.19	0.77	-0.189 (-0.474 - 0.096)	0.20	0.71	-0.187 (-0.477 - 0.102)
	4 - ≤8m	0.42	0.85	-0.101 (-0.347 - 0.144)	0.40	0.79	-0.104 (-0.349 - 0.140)
	0m	0.57	0.92	0.140 (-0.351 - 0.632)	0.50	0.87	0.174 (-0.332 - 0.680)
TRANCE	0 - ≤4m	0.22	0.77	-0.177 (-0.463 - 0.109)	0.31	0.79	-0.151 (-0.444 - 0.143)
	4 - ≤8m	0.11	0.65	-0.201 (-0.446 - 0.045)	0.11	0.62	-0.201 (-0.449 - 0.047)
	0m	0.17	0.76	0.339 (-0.151 - 0.829)	0.26	0.76	0.286 (-0.216 - 0.788)
TWEAK	0 - ≤4m	0.41	0.85	-0.120 (-0.405 - 0.165)	0.34	0.79	-0.141 (-0.432 - 0.150)
	4 - ≤8m	0.15	0.74	0.181 (-0.064 - 0.425)	0.21	0.71	0.157 (-0.089 - 0.403)
	0m	0.38	0.83	0.222 (-0.271 - 0.715)	0.71	0.93	0.090 (-0.384 - 0.564)
uPA	0 - ≤4m	0.35	0.80	-0.137 (-0.424 - 0.149)	0.16	0.71	-0.198 (-0.473 - 0.078)
	4 - ≤8m	0.90	0.97	-0.016 (-0.262 - 0.230)	0.50	0.87	-0.079 (-0.312 - 0.153)
	0m	0.92	0.97	0.026 (-0.466 - 0.519)	0.84	0.95	0.051 (-0.442 - 0.544)
VEGFA	0 - ≤4m	0.13	0.66	-0.224 (-0.510 - 0.062)	0.21	0.71	-0.182 (-0.468 - 0.105)
	4 - ≤8m	0.79	0.94	-0.033 (-0.279 - 0.213)	0.69	0.93	-0.050 (-0.291 - 0.192)

**46 infants had an NA value for FGF-5.

Supplementary Table 10. Linear regression associations of infant serum biomarker levels with categorical HMF duration (infants grouped in two-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use categorical exclusive HMF duration (infants grouped in two-month intervals) to predict biomarker levels (standardized NPX). The exclusive HMF >4 months group was used as reference.

Olink Biomarkers	Variable Groups	Univariable			Multivariable		
		P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0m	0.23	0.85	0.180 (-0.112 - 0.472)	0.35	0.88	0.142 (-0.155 - 0.44)
	0 - ≤2m	0.94	0.98	-0.011 (-0.281 - 0.260)	0.89	1.00	-0.018 (-0.287 - 0.250)
	2 - ≤4m	0.97	0.98	-0.007 (-0.335 - 0.320)	0.98	1.00	-0.005 (-0.328 - 0.319)
ADA	0m	0.07	0.85	0.273 (-0.017 - 0.562)	0.11	0.81	0.233 (-0.051 - 0.517)
	0 - ≤2m	0.50	0.96	0.092 (-0.177 - 0.361)	0.40	0.90	0.110 (-0.146 - 0.366)
	2 - ≤4m	0.36	0.92	0.152 (-0.173 - 0.477)	0.37	0.89	0.142 (-0.167 - 0.451)
AXIN1	0m	0.83	0.97	0.032 (-0.260 - 0.324)	0.87	1.00	-0.023 (-0.302 - 0.256)
	0 - ≤2m	0.44	0.95	-0.106 (-0.377 - 0.165)	0.66	0.95	-0.056 (-0.308 - 0.195)
	2 - ≤4m	0.07	0.85	0.299 (-0.029 - 0.627)	0.07	0.81	0.278 (-0.025 - 0.581)
CASP-8	0m	0.17	0.85	0.205 (-0.088 - 0.498)	0.18	0.81	0.135 (-0.062 - 0.332)
	0 - ≤2m	0.95	0.98	-0.008 (-0.280 - 0.263)	0.96	1.00	-0.005 (-0.183 - 0.173)
	2 - ≤4m	0.13	0.85	0.252 (-0.076 - 0.581)	0.03	0.81	0.233 (0.019 - 0.448)
CCL11	0m	0.80	0.97	-0.038 (-0.331 - 0.254)	0.94	1.00	-0.012 (-0.309 - 0.285)
	0 - ≤2m	0.28	0.90	-0.148 (-0.420 - 0.123)	0.43	0.90	-0.107 (-0.375 - 0.161)
	2 - ≤4m	0.12	0.85	0.259 (-0.070 - 0.587)	0.10	0.81	0.267 (-0.055 - 0.590)
CCL19	0m	0.83	0.97	-0.032 (-0.326 - 0.261)	0.83	1.00	0.031 (-0.256 - 0.318)
	0 - ≤2m	0.73	0.96	-0.048 (-0.320 - 0.224)	0.83	1.00	-0.028 (-0.287 - 0.231)
	2 - ≤4m	0.85	0.97	-0.032 (-0.361 - 0.297)	0.98	1.00	-0.005 (-0.316 - 0.307)
CCL20	0m	0.88	0.98	-0.022 (-0.317 - 0.273)	0.66	0.95	0.068 (-0.232 - 0.369)
	0 - ≤2m	0.95	0.98	0.009 (-0.265 - 0.282)	0.71	0.98	0.051 (-0.220 - 0.322)
	2 - ≤4m	0.39	0.95	0.146 (-0.185 - 0.476)	0.31	0.86	0.167 (-0.159 - 0.493)
CCL23	0m	0.36	0.92	-0.136 (-0.431 - 0.158)	0.34	0.87	-0.145 (-0.445 - 0.154)
	0 - ≤2m	0.84	0.97	-0.029 (-0.302 - 0.244)	1.00	1.00	0.001 (-0.269 - 0.271)
	2 - ≤4m	0.55	0.96	0.101 (-0.229 - 0.431)	0.54	0.90	0.103 (-0.223 - 0.428)
CCL25	0m	0.04	0.85	0.304 (0.012 - 0.596)	0.07	0.81	0.274 (-0.026 - 0.574)
	0 - ≤2m	0.22	0.85	0.170 (-0.101 - 0.441)	0.17	0.81	0.191 (-0.080 - 0.461)
	2 - ≤4m	0.44	0.95	0.129 (-0.199 - 0.456)	0.41	0.90	0.138 (-0.188 - 0.464)
CCL28	0m	0.78	0.97	-0.041 (-0.335 - 0.253)	0.92	1.00	0.014 (-0.282 - 0.311)
	0 - ≤2m	0.64	0.96	0.064 (-0.209 - 0.337)	0.54	0.90	0.084 (-0.184 - 0.351)
	2 - ≤4m	0.35	0.92	0.157 (-0.173 - 0.487)	0.27	0.81	0.182 (-0.141 - 0.504)
CCL3	0m	0.84	0.97	-0.030 (-0.325 - 0.265)	0.85	1.00	-0.027 (-0.297 - 0.243)
	0 - ≤2m	0.83	0.97	-0.029 (-0.303 - 0.244)	0.64	0.95	-0.057 (-0.301 - 0.186)
	2 - ≤4m	0.33	0.92	0.164 (-0.167 - 0.495)	0.20	0.81	0.191 (-0.103 - 0.484)
CCL4	0m	0.76	0.97	0.047 (-0.248 - 0.342)	0.80	1.00	0.035 (-0.245 - 0.315)
	0 - ≤2m	0.76	0.97	0.043 (-0.231 - 0.317)	0.93	1.00	0.012 (-0.240 - 0.264)
	2 - ≤4m	0.17	0.85	0.229 (-0.102 - 0.560)	0.11	0.81	0.247 (-0.057 - 0.551)
CD244	0m	0.68	0.96	-0.061 (-0.355 - 0.233)	0.45	0.90	-0.103 (-0.369 - 0.164)
	0 - ≤2m	0.57	0.96	-0.079 (-0.352 - 0.194)	0.58	0.93	-0.067 (-0.308 - 0.174)
	2 - ≤4m	0.26	0.85	0.190 (-0.140 - 0.520)	0.18	0.81	0.198 (-0.092 - 0.487)
CD40	0m	0.52	0.96	0.095 (-0.197 - 0.388)	0.81	1.00	0.026 (-0.191 - 0.242)
	0 - ≤2m	0.57	0.96	0.079 (-0.192 - 0.350)	0.38	0.90	0.086 (-0.109 - 0.281)
	2 - ≤4m	0.15	0.85	0.241 (-0.087 - 0.569)	0.05	0.81	0.230 (-0.005 - 0.465)
CD5	0m	0.18	0.85	0.199 (-0.094 - 0.492)	0.25	0.81	0.170 (-0.120 - 0.460)
	0 - ≤2m	0.67	0.96	-0.058 (-0.330 - 0.214)	0.75	0.98	-0.043 (-0.304 - 0.218)
	2 - ≤4m	0.49	0.96	-0.117 (-0.445 - 0.212)	0.52	0.90	-0.104 (-0.418 - 0.211)
CD6	0m	0.34	0.92	-0.140 (-0.432 - 0.151)	0.17	0.81	-0.201 (-0.489 - 0.086)
	0 - ≤2m	0.13	0.85	-0.206 (-0.477 - 0.064)	0.10	0.81	-0.215 (-0.474 - 0.044)
	2 - ≤4m	0.29	0.91	-0.175 (-0.502 - 0.152)	0.27	0.81	-0.174 (-0.486 - 0.137)

	0m	0.08	0.85	-0.266 (-0.559 - 0.028)	0.13	0.81	-0.231 (-0.530 - 0.067)
CD8A	0 - ≤2m	0.19	0.85	-0.180 (-0.452 - 0.092)	0.24	0.81	-0.163 (-0.432 - 0.107)
	2 - ≤4m	0.33	0.92	-0.164 (-0.493 - 0.165)	0.41	0.90	-0.136 (-0.460 - 0.188)
	0m	0.61	0.96	0.076 (-0.217 - 0.368)	0.74	0.98	0.051 (-0.251 - 0.353)
CDCP1	0 - ≤2m	0.11	0.85	-0.223 (-0.495 - 0.048)	0.14	0.81	-0.208 (-0.481 - 0.065)
	2 - ≤4m	0.13	0.85	-0.255 (-0.583 - 0.073)	0.10	0.81	-0.272 (-0.601 - 0.057)
	0m	0.46	0.96	0.111 (-0.183 - 0.404)	0.54	0.90	0.092 (-0.199 - 0.383)
CSF-1	0 - ≤2m	0.35	0.92	-0.130 (-0.402 - 0.142)	0.32	0.86	-0.133 (-0.396 - 0.130)
	2 - ≤4m	0.43	0.95	-0.131 (-0.460 - 0.198)	0.41	0.90	-0.132 (-0.448 - 0.185)
	0m	0.91	0.98	-0.017 (-0.312 - 0.278)	0.46	0.90	-0.112 (-0.413 - 0.188)
CST5	0 - ≤2m	0.57	0.96	0.080 (-0.194 - 0.354)	0.66	0.95	0.061 (-0.211 - 0.332)
	2 - ≤4m	0.98	0.99	0.004 (-0.327 - 0.335)	0.94	1.00	-0.013 (-0.340 - 0.313)
	0m	0.24	0.85	0.177 (-0.117 - 0.471)	0.28	0.81	0.162 (-0.134 - 0.459)
CX3CL1	0 - ≤2m	0.41	0.95	0.114 (-0.159 - 0.386)	0.42	0.90	0.110 (-0.158 - 0.378)
	2 - ≤4m	0.54	0.96	-0.102 (-0.432 - 0.227)	0.51	0.90	-0.109 (-0.432 - 0.213)
	0m	0.72	0.96	-0.054 (-0.349 - 0.241)	0.92	1.00	-0.015 (-0.309 - 0.280)
CXCL1	0 - ≤2m	0.61	0.96	-0.071 (-0.345 - 0.203)	0.85	1.00	-0.025 (-0.291 - 0.241)
	2 - ≤4m	0.48	0.96	0.118 (-0.213 - 0.449)	0.43	0.90	0.129 (-0.191 - 0.449)
	0m	0.47	0.96	0.107 (-0.186 - 0.401)	0.34	0.87	0.148 (-0.157 - 0.453)
CXCL10	0 - ≤2m	0.48	0.96	-0.097 (-0.370 - 0.175)	0.60	0.93	-0.074 (-0.349 - 0.201)
	2 - ≤4m	0.51	0.96	-0.111 (-0.440 - 0.218)	0.49	0.90	-0.118 (-0.449 - 0.214)
	0m	0.43	0.95	0.118 (-0.178 - 0.413)	0.28	0.81	0.161 (-0.133 - 0.455)
CXCL11	0 - ≤2m	0.96	0.98	0.006 (-0.267 - 0.280)	0.71	0.98	0.049 (-0.216 - 0.315)
	2 - ≤4m	0.96	0.98	-0.008 (-0.339 - 0.323)	0.93	1.00	-0.015 (-0.334 - 0.305)
	0m	0.79	0.97	-0.039 (-0.333 - 0.255)	0.94	1.00	-0.011 (-0.303 - 0.282)
CXCL5	0 - ≤2m	0.93	0.98	-0.013 (-0.285 - 0.259)	0.73	0.98	0.046 (-0.218 - 0.310)
	2 - ≤4m	0.17	0.85	0.230 (-0.099 - 0.560)	0.23	0.81	0.194 (-0.124 - 0.512)
	0m	0.16	0.85	-0.210 (-0.503 - 0.083)	0.20	0.81	-0.196 (-0.494 - 0.103)
CXCL6	0 - ≤2m	0.21	0.85	-0.174 (-0.446 - 0.098)	0.29	0.81	-0.146 (-0.416 - 0.123)
	2 - ≤4m	0.63	0.96	0.081 (-0.248 - 0.410)	0.61	0.94	0.084 (-0.241 - 0.408)
	0m	0.79	0.97	-0.039 (-0.335 - 0.256)	1.00	1.00	0.001 (-0.303 - 0.304)
CXCL9	0 - ≤2m	0.70	0.96	0.054 (-0.220 - 0.328)	0.46	0.90	0.104 (-0.170 - 0.377)
	2 - ≤4m	0.99	0.99	0.002 (-0.329 - 0.334)	0.96	1.00	0.008 (-0.321 - 0.337)
	0m	0.87	0.98	0.025 (-0.269 - 0.319)	0.89	1.00	0.021 (-0.281 - 0.322)
DNER	0 - ≤2m	0.71	0.96	0.052 (-0.220 - 0.325)	0.76	0.98	0.042 (-0.229 - 0.314)
	2 - ≤4m	0.25	0.85	0.192 (-0.138 - 0.521)	0.19	0.81	0.216 (-0.111 - 0.543)
	0m	0.43	0.95	0.117 (-0.177 - 0.411)	0.45	0.90	0.092 (-0.148 - 0.332)
EN-RAGE	0 - ≤2m	0.61	0.96	-0.07 (-0.342 - 0.203)	0.92	1.00	-0.011 (-0.228 - 0.206)
	2 - ≤4m	0.13	0.85	0.253 (-0.077 - 0.582)	0.10	0.81	0.216 (-0.045 - 0.476)
	0m	0.06	0.85	0.269 (-0.015 - 0.552)	0.05	0.81	0.290 (-0.005 - 0.584)
FGF-19	0 - ≤2m	0.37	0.93	0.119 (-0.144 - 0.382)	0.42	0.90	0.108 (-0.158 - 0.374)
	2 - ≤4m	0.26	0.85	0.183 (-0.135 - 0.501)	0.25	0.81	0.188 (-0.132 - 0.508)
	0m	0.63	0.96	-0.072 (-0.364 - 0.220)	0.55	0.90	-0.091 (-0.392 - 0.210)
FGF-21	0 - ≤2m	0.95	0.98	-0.009 (-0.280 - 0.262)	0.92	1.00	-0.014 (-0.285 - 0.258)
	2 - ≤4m	0.12	0.85	-0.261 (-0.589 - 0.066)	0.10	0.81	-0.270 (-0.597 - 0.057)
	0m	0.87	0.98	0.024 (-0.269 - 0.317)	0.94	1.00	-0.012 (-0.312 - 0.289)
FGF-23	0 - ≤2m	0.56	0.96	-0.081 (-0.353 - 0.191)	0.59	0.93	-0.075 (-0.346 - 0.196)
	2 - ≤4m	0.14	0.85	-0.249 (-0.578 - 0.079)	0.09	0.81	-0.279 (-0.605 - 0.048)
	0m	0.20	0.85	-0.204 (-0.514 - 0.106)	0.21	0.81	-0.203 (-0.522 - 0.116)
FGF-5**	0 - ≤2m	0.82	0.97	-0.032 (-0.317 - 0.252)	0.86	1.00	-0.026 (-0.311 - 0.259)
	2 - ≤4m	0.27	0.87	-0.194 (-0.537 - 0.149)	0.30	0.82	-0.183 (-0.526 - 0.160)
	0m	0.39	0.95	-0.129 (-0.424 - 0.166)	0.25	0.81	-0.178 (-0.482 - 0.125)
Flt3L	0 - ≤2m	0.20	0.85	-0.179 (-0.452 - 0.094)	0.14	0.81	-0.208 (-0.482 - 0.065)
	2 - ≤4m	0.25	0.85	-0.193 (-0.524 - 0.137)	0.20	0.81	-0.217 (-0.546 - 0.112)
	0m	0.36	0.92	0.137 (-0.156 - 0.431)	0.38	0.90	0.122 (-0.152 - 0.396)
HGF	0 - ≤2m	0.59	0.96	0.075 (-0.197 - 0.347)	0.43	0.90	0.100 (-0.147 - 0.347)
	2 - ≤4m	0.03	0.85	0.370 (0.040 - 0.699)	0.02	0.81	0.358 (0.060 - 0.656)
	0m	0.59	0.96	0.081 (-0.215 - 0.376)	0.35	0.89	0.145 (-0.162 - 0.451)
IFN-γ	0 - ≤2m	0.88	0.98	0.021 (-0.253 - 0.295)	0.77	0.99	0.041 (-0.235 - 0.318)
	2 - ≤4m	0.63	0.96	-0.081 (-0.412 - 0.250)	0.66	0.95	-0.075 (-0.408 - 0.258)
IL-10RA	0m	0.20	0.85	0.184 (-0.100 - 0.468)	0.24	0.81	0.177 (-0.119 - 0.473)
	0 - ≤2m	0.72	0.96	-0.048 (-0.312 - 0.215)	0.75	0.98	-0.044 (-0.311 - 0.223)

	2 - ≤4m	0.64	0.96	0.075 (-0.243 - 0.394)	0.64	0.95	0.076 (-0.246 - 0.398)
	0m	0.96	0.98	-0.008 (-0.303 - 0.287)	0.78	1.00	-0.042 (-0.345 - 0.261)
IL-10RB	0 - ≤2m	0.23	0.85	0.166 (-0.107 - 0.439)	0.26	0.81	0.155 (-0.118 - 0.429)
	2 - ≤4m	0.58	0.96	0.093 (-0.237 - 0.423)	0.48	0.90	0.119 (-0.211 - 0.448)
	0m	0.84	0.97	-0.030 (-0.325 - 0.266)	0.94	1.00	0.011 (-0.293 - 0.316)
IL-12B	0 - ≤2m	0.58	0.96	-0.076 (-0.350 - 0.197)	0.75	0.98	-0.045 (-0.320 - 0.230)
	2 - ≤4m	0.55	0.96	0.100 (-0.231 - 0.431)	0.56	0.92	0.097 (-0.234 - 0.428)
	0m	0.78	0.97	-0.042 (-0.336 - 0.253)	0.85	1.00	-0.029 (-0.335 - 0.278)
IL-15RA	0 - ≤2m	0.25	0.85	-0.160 (-0.433 - 0.113)	0.33	0.86	-0.138 (-0.414 - 0.138)
	2 - ≤4m	0.19	0.85	-0.222 (-0.553 - 0.108)	0.21	0.81	-0.212 (-0.544 - 0.121)
	0m	0.14	0.85	0.218 (-0.071 - 0.506)	0.11	0.81	0.248 (-0.052 - 0.547)
IL-17A	0 - ≤2m	0.63	0.96	-0.065 (-0.332 - 0.203)	0.73	0.98	-0.047 (-0.318 - 0.224)
	2 - ≤4m	0.07	0.85	0.303 (-0.021 - 0.626)	0.06	0.81	0.310 (-0.015 - 0.636)
	0m	0.18	0.85	0.201 (-0.092 - 0.494)	0.16	0.81	0.221 (-0.084 - 0.525)
IL-17C	0 - ≤2m	0.81	0.97	-0.033 (-0.305 - 0.239)	0.95	1.00	-0.009 (-0.284 - 0.267)
	2 - ≤4m	0.77	0.97	-0.050 (-0.379 - 0.279)	0.74	0.98	-0.057 (-0.388 - 0.274)
	0m	0.43	0.95	0.117 (-0.174 - 0.409)	0.42	0.90	0.122 (-0.173 - 0.417)
IL-18	0 - ≤2m	0.14	0.85	-0.204 (-0.474 - 0.066)	0.23	0.81	-0.164 (-0.430 - 0.102)
	2 - ≤4m	0.90	0.98	0.022 (-0.305 - 0.348)	0.90	1.00	0.020 (-0.300 - 0.340)
	0m	0.68	0.96	0.062 (-0.233 - 0.357)	0.73	0.98	0.053 (-0.247 - 0.353)
IL-18R1	0 - ≤2m	0.81	0.97	-0.033 (-0.307 - 0.240)	0.87	1.00	-0.022 (-0.292 - 0.248)
	2 - ≤4m	0.65	0.96	0.077 (-0.254 - 0.407)	0.73	0.98	0.057 (-0.269 - 0.382)
	0m	0.65	0.96	-0.068 (-0.363 - 0.226)	0.54	0.90	-0.094 (-0.400 - 0.211)
IL-4	0 - ≤2m	0.93	0.98	0.012 (-0.261 - 0.285)	1.00	1.00	0.000 (-0.275 - 0.276)
	2 - ≤4m	0.22	0.85	-0.205 (-0.535 - 0.126)	0.27	0.81	-0.186 (-0.518 - 0.146)
	0m	0.84	0.97	-0.030 (-0.325 - 0.265)	0.87	1.00	-0.022 (-0.295 - 0.251)
IL-6	0 - ≤2m	0.58	0.96	-0.076 (-0.350 - 0.197)	0.53	0.90	-0.079 (-0.326 - 0.167)
	2 - ≤4m	0.61	0.96	0.087 (-0.244 - 0.417)	0.49	0.90	0.104 (-0.192 - 0.400)
	0m	0.00	0.47	-0.457 (-0.747 - -0.167)	0.00	0.51	-0.460 (-0.754 - -0.167)
IL-7	0 - ≤2m	0.02	0.85	-0.329 (-0.598 - -0.061)	0.02	0.81	-0.321 (-0.586 - -0.057)
	2 - ≤4m	0.75	0.97	-0.053 (-0.378 - 0.272)	0.76	0.98	-0.050 (-0.369 - 0.268)
	0m	0.70	0.96	-0.059 (-0.353 - 0.236)	0.59	0.93	-0.055 (-0.256 - 0.145)
IL-8	0 - ≤2m	0.53	0.96	-0.087 (-0.359 - 0.186)	0.33	0.86	-0.090 (-0.271 - 0.090)
	2 - ≤4m	0.49	0.96	0.116 (-0.213 - 0.446)	0.23	0.81	0.134 (-0.084 - 0.352)
	0m	0.81	0.97	0.036 (-0.259 - 0.331)	0.49	0.90	0.107 (-0.196 - 0.411)
IL-10	0 - ≤2m	0.54	0.96	-0.085 (-0.359 - 0.189)	0.82	1.00	-0.032 (-0.306 - 0.242)
	2 - ≤4m	0.68	0.96	-0.070 (-0.401 - 0.261)	0.73	0.98	-0.058 (-0.388 - 0.272)
	0m	0.36	0.92	-0.135 (-0.429 - 0.158)	0.24	0.81	-0.173 (-0.466 - 0.119)
LAP TGF-β-1	0 - ≤2m	0.92	0.98	-0.013 (-0.285 - 0.259)	0.85	1.00	-0.025 (-0.288 - 0.239)
	2 - ≤4m	0.13	0.85	0.257 (-0.072 - 0.586)	0.09	0.81	0.275 (-0.043 - 0.592)
	0m	0.12	0.85	-0.230 (-0.523 - 0.063)	0.13	0.81	-0.233 (-0.537 - 0.072)
LIF-R	0 - ≤2m	0.17	0.85	-0.188 (-0.459 - 0.083)	0.19	0.81	-0.183 (-0.457 - 0.092)
	2 - ≤4m	0.73	0.96	0.058 (-0.270 - 0.387)	0.78	1.00	0.047 (-0.284 - 0.378)
	0m	0.71	0.96	0.055 (-0.239 - 0.349)	0.69	0.98	0.056 (-0.222 - 0.335)
MCP-1	0 - ≤2m	0.48	0.96	-0.098 (-0.370 - 0.175)	0.51	0.90	-0.084 (-0.335 - 0.167)
	2 - ≤4m	0.97	0.98	-0.007 (-0.336 - 0.322)	0.93	1.00	-0.013 (-0.316 - 0.289)
	0m	0.85	0.97	0.028 (-0.266 - 0.322)	0.81	1.00	0.038 (-0.268 - 0.344)
MCP-2	0 - ≤2m	0.66	0.96	-0.060 (-0.333 - 0.213)	0.76	0.98	-0.044 (-0.32 - 0.232)
	2 - ≤4m	0.12	0.85	-0.262 (-0.592 - 0.068)	0.11	0.81	-0.269 (-0.602 - 0.063)
	0m	0.28	0.90	-0.160 (-0.453 - 0.133)	0.18	0.81	-0.142 (-0.349 - 0.065)
MCP-3	0 - ≤2m	0.40	0.95	-0.117 (-0.388 - 0.154)	0.23	0.81	-0.115 (-0.302 - 0.072)
	2 - ≤4m	0.97	0.98	-0.007 (-0.335 - 0.322)	0.91	1.00	0.013 (-0.212 - 0.238)
	0m	0.67	0.96	0.065 (-0.230 - 0.359)	0.47	0.90	0.111 (-0.192 - 0.414)
MCP-4	0 - ≤2m	0.42	0.95	0.113 (-0.160 - 0.385)	0.28	0.81	0.150 (-0.124 - 0.423)
	2 - ≤4m	0.15	0.85	0.240 (-0.090 - 0.570)	0.18	0.81	0.224 (-0.105 - 0.554)
	0m	0.89	0.98	0.020 (-0.274 - 0.315)	0.92	1.00	-0.016 (-0.319 - 0.288)
MMP-1	0 - ≤2m	0.16	0.85	0.196 (-0.077 - 0.469)	0.15	0.81	0.201 (-0.073 - 0.476)
	2 - ≤4m	0.19	0.85	0.222 (-0.108 - 0.553)	0.23	0.81	0.201 (-0.129 - 0.531)
	0m	0.68	0.96	0.061 (-0.231 - 0.354)	0.43	0.90	0.120 (-0.180 - 0.421)
MMP-10	0 - ≤2m	0.48	0.96	0.097 (-0.174 - 0.369)	0.29	0.81	0.147 (-0.124 - 0.418)
	2 - ≤4m	0.13	0.85	0.254 (-0.074 - 0.583)	0.14	0.81	0.247 (-0.079 - 0.574)
NT-3	0m	0.19	0.85	-0.197 (-0.491 - 0.096)	0.16	0.81	-0.215 (-0.517 - 0.087)

	0 - ≤2m	0.97	0.98	0.005 (-0.267 - 0.277)	0.98	1.00	-0.003 (-0.275 - 0.270)
	2 - ≤4m	0.20	0.85	-0.214 (-0.543 - 0.115)	0.28	0.81	-0.179 (-0.507 - 0.149)
	0m	0.23	0.85	-0.181 (-0.476 - 0.115)	0.12	0.81	-0.240 (-0.546 - 0.065)
OPG	0 - ≤2m	0.36	0.92	-0.127 (-0.401 - 0.147)	0.28	0.81	-0.153 (-0.429 - 0.123)
	2 - ≤4m	0.50	0.96	-0.114 (-0.445 - 0.217)	0.42	0.90	-0.137 (-0.469 - 0.195)
	0m	0.60	0.96	0.079 (-0.215 - 0.374)	0.52	0.90	0.071 (-0.144 - 0.287)
OSM	0 - ≤2m	0.82	0.97	-0.032 (-0.304 - 0.241)	0.92	1.00	-0.010 (-0.204 - 0.185)
	2 - ≤4m	0.20	0.85	0.216 (-0.114 - 0.546)	0.07	0.81	0.214 (-0.020 - 0.449)
	0m	0.51	0.96	0.100 (-0.195 - 0.395)	0.47	0.90	0.111 (-0.188 - 0.411)
PD-L1	0 - ≤2m	0.44	0.95	-0.107 (-0.381 - 0.167)	0.64	0.95	-0.065 (-0.335 - 0.206)
	2 - ≤4m	0.78	0.97	-0.047 (-0.378 - 0.284)	0.80	1.00	-0.042 (-0.368 - 0.283)
	0m	0.08	0.85	0.262 (-0.029 - 0.554)	0.12	0.81	0.239 (-0.061 - 0.539)
SCF	0 - ≤2m	0.01	0.85	0.340 (0.069 - 0.610)	0.03	0.81	0.301 (0.030 - 0.572)
	2 - ≤4m	0.63	0.96	0.080 (-0.247 - 0.407)	0.54	0.90	0.101 (-0.225 - 0.427)
	0m	0.25	0.85	0.172 (-0.121 - 0.465)	0.41	0.90	0.124 (-0.172 - 0.42)
SIRT2	0 - ≤2m	0.81	0.97	-0.034 (-0.306 - 0.238)	0.82	1.00	-0.032 (-0.298 - 0.235)
	2 - ≤4m	0.43	0.95	0.133 (-0.196 - 0.462)	0.49	0.90	0.113 (-0.208 - 0.434)
	0m	0.15	0.85	-0.216 (-0.507 - 0.076)	0.06	0.81	-0.292 (-0.592 - 0.009)
SLAMF1	0 - ≤2m	0.10	0.85	-0.228 (-0.499 - 0.042)	0.09	0.81	-0.237 (-0.508 - 0.034)
	2 - ≤4m	0.78	0.97	-0.047 (-0.373 - 0.28)	0.60	0.93	-0.087 (-0.413 - 0.240)
	0m	0.73	0.96	-0.051 (-0.344 - 0.242)	0.54	0.90	-0.088 (-0.373 - 0.197)
ST1A1	0 - ≤2m	0.13	0.85	0.209 (-0.062 - 0.481)	0.14	0.81	0.193 (-0.064 - 0.451)
	2 - ≤4m	0.14	0.85	0.249 (-0.079 - 0.578)	0.19	0.81	0.207 (-0.103 - 0.516)
	0m	0.23	0.85	0.177 (-0.115 - 0.47)	0.36	0.89	0.141 (-0.160 - 0.442)
STAMBP	0 - ≤2m	0.98	0.99	-0.003 (-0.275 - 0.268)	0.96	1.00	0.007 (-0.265 - 0.278)
	2 - ≤4m	0.36	0.92	0.154 (-0.174 - 0.482)	0.37	0.89	0.150 (-0.177 - 0.477)
	0m	0.81	0.97	-0.037 (-0.330 - 0.257)	0.97	1.00	0.005 (-0.279 - 0.289)
TGF-α	0 - ≤2m	0.70	0.96	0.054 (-0.219 - 0.326)	0.45	0.90	0.098 (-0.158 - 0.354)
	2 - ≤4m	0.05	0.85	0.323 (-0.006 - 0.652)	0.05	0.81	0.303 (-0.006 - 0.611)
	0m	0.87	0.98	-0.024 (-0.319 - 0.271)	0.90	1.00	0.020 (-0.284 - 0.325)
TNF	0 - ≤2m	0.93	0.98	-0.013 (-0.287 - 0.260)	0.99	1.00	-0.002 (-0.277 - 0.273)
	2 - ≤4m	0.35	0.92	0.158 (-0.172 - 0.489)	0.28	0.81	0.183 (-0.148 - 0.514)
	0m	0.73	0.96	-0.051 (-0.346 - 0.243)	0.60	0.93	-0.081 (-0.384 - 0.222)
TNFB	0 - ≤2m	0.12	0.85	-0.216 (-0.488 - 0.057)	0.13	0.81	-0.212 (-0.486 - 0.061)
	2 - ≤4m	0.95	0.98	-0.010 (-0.340 - 0.320)	0.93	1.00	-0.016 (-0.344 - 0.313)
	0m	0.23	0.85	0.178 (-0.116 - 0.473)	0.25	0.81	0.176 (-0.123 - 0.475)
TNFRSF9	0 - ≤2m	0.35	0.92	0.131 (-0.142 - 0.404)	0.22	0.81	0.170 (-0.100 - 0.440)
	2 - ≤4m	0.18	0.85	0.224 (-0.106 - 0.554)	0.14	0.81	0.244 (-0.081 - 0.569)
	0m	0.50	0.96	0.100 (-0.194 - 0.394)	0.61	0.94	0.062 (-0.176 - 0.300)
TNFSF14	0 - ≤2m	0.45	0.95	0.106 (-0.167 - 0.378)	0.33	0.86	0.107 (-0.107 - 0.322)
	2 - ≤4m	0.07	0.85	0.307 (-0.023 - 0.637)	0.04	0.81	0.272 (0.014 - 0.530)
	0m	0.26	0.85	0.170 (-0.124 - 0.463)	0.15	0.81	0.218 (-0.082 - 0.518)
TRAIL	0 - ≤2m	0.68	0.96	0.057 (-0.215 - 0.329)	0.49	0.90	0.094 (-0.177 - 0.366)
	2 - ≤4m	0.54	0.96	-0.104 (-0.433 - 0.225)	0.52	0.90	-0.107 (-0.434 - 0.219)
	0m	0.34	0.92	0.144 (-0.151 - 0.439)	0.25	0.81	0.181 (-0.126 - 0.488)
TRANCE	0 - ≤2m	0.56	0.96	0.081 (-0.192 - 0.355)	0.48	0.90	0.099 (-0.178 - 0.376)
	2 - ≤4m	0.70	0.96	0.066 (-0.265 - 0.396)	0.64	0.95	0.079 (-0.254 - 0.412)
	0m	0.43	0.95	0.117 (-0.173 - 0.408)	0.63	0.95	0.074 (-0.226 - 0.375)
TWEAK	0 - ≤2m	0.73	0.96	-0.047 (-0.317 - 0.222)	0.71	0.98	-0.052 (-0.323 - 0.219)
	2 - ≤4m	0.01	0.85	0.440 (0.114 - 0.766)	0.01	0.81	0.443 (0.116 - 0.769)
	0m	0.41	0.95	0.124 (-0.171 - 0.419)	0.93	1.00	-0.012 (-0.299 - 0.274)
uPA	0 - ≤2m	0.35	0.92	0.130 (-0.143 - 0.403)	0.57	0.92	0.076 (-0.183 - 0.334)
	2 - ≤4m	0.34	0.92	0.159 (-0.171 - 0.490)	0.51	0.90	0.104 (-0.208 - 0.416)
	0m	0.34	0.92	-0.142 (-0.436 - 0.152)	0.41	0.90	-0.125 (-0.421 - 0.172)
VEGFA	0 - ≤2m	0.87	0.98	0.023 (-0.249 - 0.296)	0.67	0.97	0.057 (-0.210 - 0.325)
	2 - ≤4m	0.61	0.96	0.084 (-0.245 - 0.414)	0.54	0.90	0.099 (-0.223 - 0.422)

**46 infants had an NA value for FGF-5.

Supplementary Table 11. Linear regression associations of infant serum biomarker levels with categorical exclusive HMF duration (infants grouped in three-month intervals) among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use categorical exclusive HMF duration (infants grouped in three-month intervals) to predict biomarker levels (standardized NPX). The exclusive HMF >3 months group was used as reference.

Olink Biomarkers	Variable Groups	Univariable			Multivariable		
		P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	0m	0.18	0.97	0.190 (-0.085 - 0.466)	0.31	0.96	0.145 (-0.135 - 0.426)
	0 - ≤3m	0.93	0.98	0.011 (-0.231 - 0.253)	0.92	0.99	-0.012 (-0.252 - 0.228)
ADA	0m	0.11	0.97	0.225 (-0.048 - 0.499)	0.16	0.96	0.192 (-0.076 - 0.460)
	0 - ≤3m	0.73	0.97	0.043 (-0.198 - 0.283)	0.55	0.97	0.070 (-0.159 - 0.300)
AXIN1	0m	0.97	0.98	-0.005 (-0.283 - 0.273)	0.67	0.98	-0.057 (-0.322 - 0.208)
	0 - ≤3m	0.76	0.97	-0.038 (-0.283 - 0.206)	0.99	0.99	0.001 (-0.226 - 0.228)
CASP-8	0m	0.35	0.97	0.132 (-0.145 - 0.410)	0.36	0.96	0.088 (-0.100 - 0.275)
	0 - ≤3m	0.66	0.97	-0.054 (-0.298 - 0.190)	0.98	0.99	-0.002 (-0.163 - 0.158)
CCL11	0m	0.47	0.97	-0.102 (-0.380 - 0.176)	0.59	0.97	-0.078 (-0.360 - 0.204)
	0 - ≤3m	0.22	0.97	-0.151 (-0.395 - 0.093)	0.34	0.96	-0.116 (-0.358 - 0.125)
CCL19	0m	0.72	0.97	-0.051 (-0.328 - 0.225)	0.94	0.99	-0.010 (-0.280 - 0.260)
	0 - ≤3m	0.43	0.97	-0.097 (-0.34 - 0.146)	0.33	0.96	-0.115 (-0.346 - 0.116)
CCL20	0m	0.67	0.97	-0.061 (-0.339 - 0.218)	0.89	0.98	0.019 (-0.264 - 0.303)
	0 - ≤3m	0.93	0.98	-0.012 (-0.257 - 0.233)	0.91	0.98	0.015 (-0.228 - 0.257)
CCL23	0m	0.23	0.97	-0.168 (-0.446 - 0.110)	0.20	0.96	-0.186 (-0.469 - 0.096)
	0 - ≤3m	0.70	0.97	-0.049 (-0.293 - 0.195)	0.73	0.98	-0.042 (-0.284 - 0.200)
CCL25	0m	0.03	0.97	0.297 (0.021 - 0.572)	0.08	0.96	0.256 (-0.026 - 0.539)
	0 - ≤3m	0.13	0.97	0.188 (-0.054 - 0.430)	0.13	0.96	0.189 (-0.053 - 0.431)
CCL28	0m	0.54	0.97	-0.087 (-0.364 - 0.191)	0.77	0.98	-0.041 (-0.322 - 0.239)
	0 - ≤3m	0.84	0.97	0.026 (-0.219 - 0.270)	0.78	0.98	0.034 (-0.206 - 0.273)
CCL3	0m	0.66	0.97	-0.063 (-0.342 - 0.216)	0.66	0.98	-0.057 (-0.312 - 0.199)
	0 - ≤3m	0.85	0.97	-0.023 (-0.269 - 0.222)	0.79	0.98	-0.030 (-0.249 - 0.189)
CCL4	0m	0.96	0.98	-0.006 (-0.285 - 0.273)	0.92	0.99	-0.013 (-0.278 - 0.252)
	0 - ≤3m	0.85	0.97	0.023 (-0.222 - 0.269)	0.89	0.98	0.016 (-0.210 - 0.243)
CD244	0m	0.51	0.97	-0.094 (-0.372 - 0.185)	0.31	0.96	-0.130 (-0.383 - 0.122)
	0 - ≤3m	0.66	0.97	-0.055 (-0.299 - 0.190)	0.78	0.98	-0.030 (-0.246 - 0.186)
CD40	0m	0.82	0.97	0.032 (-0.244 - 0.309)	0.86	0.98	-0.018 (-0.223 - 0.186)
	0 - ≤3m	0.76	0.97	0.037 (-0.206 - 0.280)	0.35	0.96	0.083 (-0.092 - 0.258)
CD5	0m	0.08	0.97	0.243 (-0.033 - 0.520)	0.13	0.96	0.211 (-0.062 - 0.484)
	0 - ≤3m	0.97	0.98	-0.005 (-0.248 - 0.238)	0.97	0.99	0.005 (-0.229 - 0.238)
CD6	0m	0.58	0.97	-0.078 (-0.354 - 0.197)	0.34	0.96	-0.133 (-0.404 - 0.139)
	0 - ≤3m	0.33	0.97	-0.119 (-0.362 - 0.123)	0.32	0.96	-0.117 (-0.350 - 0.115)
CD8A	0m	0.16	0.97	-0.197 (-0.474 - 0.080)	0.21	0.96	-0.181 (-0.463 - 0.101)
	0 - ≤3m	0.53	0.97	-0.078 (-0.321 - 0.166)	0.44	0.97	-0.095 (-0.336 - 0.146)
CDCP1	0m	0.45	0.97	0.107 (-0.169 - 0.382)	0.54	0.97	0.090 (-0.195 - 0.375)
	0 - ≤3m	0.05	0.97	-0.239 (-0.482 - 0.003)	0.08	0.96	-0.218 (-0.462 - 0.026)
CSF-1	0m	0.46	0.97	0.104 (-0.172 - 0.381)	0.51	0.97	0.092 (-0.182 - 0.366)
	0 - ≤3m	0.14	0.97	-0.185 (-0.428 - 0.058)	0.15	0.96	-0.173 (-0.408 - 0.061)
CST5	0m	0.78	0.97	-0.039 (-0.317 - 0.240)	0.36	0.96	-0.133 (-0.416 - 0.150)
	0 - ≤3m	0.86	0.97	0.023 (-0.222 - 0.267)	0.98	0.99	0.003 (-0.240 - 0.245)
CX3CL1	0m	0.14	0.97	0.210 (-0.068 - 0.487)	0.18	0.96	0.191 (-0.089 - 0.471)
	0 - ≤3m	0.32	0.97	0.123 (-0.121 - 0.367)	0.37	0.96	0.108 (-0.131 - 0.348)
CXCL1	0m	0.44	0.97	-0.109 (-0.387 - 0.170)	0.61	0.98	-0.072 (-0.350 - 0.205)
	0 - ≤3m	0.30	0.97	-0.129 (-0.374 - 0.116)	0.46	0.97	-0.088 (-0.326 - 0.149)
CXCL10	0m	0.38	0.97	0.123 (-0.154 - 0.400)	0.25	0.96	0.169 (-0.119 - 0.456)
	0 - ≤3m	0.43	0.97	-0.098 (-0.342 - 0.145)	0.56	0.97	-0.073 (-0.319 - 0.173)
CXCL11	0m	0.44	0.97	0.110 (-0.169 - 0.388)	0.25	0.96	0.161 (-0.116 - 0.438)
	0 - ≤3m	0.90	0.98	-0.016 (-0.260 - 0.229)	0.76	0.98	0.037 (-0.200 - 0.274)

CXCL5	0m	0.26	0.97	-0.160 (-0.437 - 0.117)	0.39	0.96	-0.121 (-0.397 - 0.155)
	0 - ≤3m	0.16	0.97	-0.174 (-0.417 - 0.070)	0.36	0.96	-0.110 (-0.346 - 0.126)
CXCL6	0m	0.09	0.97	-0.237 (-0.514 - 0.040)	0.13	0.96	-0.220 (-0.502 - 0.062)
	0 - ≤3m	0.17	0.97	-0.172 (-0.416 - 0.071)	0.25	0.96	-0.142 (-0.384 - 0.099)
CXCL9	0m	0.82	0.97	-0.031 (-0.310 - 0.247)	0.98	0.99	0.003 (-0.282 - 0.289)
	0 - ≤3m	0.61	0.97	0.064 (-0.181 - 0.309)	0.42	0.96	0.100 (-0.145 - 0.344)
DNER	0m	0.72	0.97	-0.051 (-0.328 - 0.227)	0.65	0.98	-0.065 (-0.349 - 0.219)
	0 - ≤3m	0.77	0.97	-0.036 (-0.280 - 0.208)	0.68	0.98	-0.050 (-0.294 - 0.193)
EN-RAGE	0m	0.67	0.97	0.060 (-0.219 - 0.338)	0.62	0.98	0.058 (-0.170 - 0.285)
	0 - ≤3m	0.56	0.97	-0.072 (-0.317 - 0.173)	0.91	0.98	0.012 (-0.183 - 0.206)
FGF-19	0m	0.11	0.97	0.219 (-0.048 - 0.487)	0.09	0.96	0.239 (-0.039 - 0.517)
	0 - ≤3m	0.53	0.97	0.076 (-0.159 - 0.312)	0.57	0.97	0.069 (-0.169 - 0.307)
FGF-21	0m	0.74	0.97	-0.047 (-0.323 - 0.230)	0.64	0.98	-0.067 (-0.352 - 0.218)
	0 - ≤3m	0.58	0.97	-0.069 (-0.312 - 0.174)	0.52	0.97	-0.079 (-0.323 - 0.164)
FGF-23	0m	0.81	0.97	0.033 (-0.243 - 0.310)	0.95	0.99	0.009 (-0.275 - 0.292)
	0 - ≤3m	0.19	0.97	-0.161 (-0.404 - 0.082)	0.24	0.96	-0.145 (-0.388 - 0.098)
FGF-5**	0m	0.30	0.97	-0.154 (-0.447 - 0.138)	0.29	0.96	-0.163 (-0.464 - 0.139)
	0 - ≤3m	0.96	0.98	-0.007 (-0.261 - 0.248)	0.90	0.98	-0.016 (-0.272 - 0.239)
Flt3L	0m	0.59	0.97	-0.077 (-0.355 - 0.201)	0.46	0.97	-0.107 (-0.394 - 0.179)
	0 - ≤3m	0.31	0.97	-0.126 (-0.371 - 0.118)	0.31	0.96	-0.126 (-0.371 - 0.119)
HGF	0m	0.78	0.97	0.041 (-0.238 - 0.319)	0.77	0.98	0.039 (-0.222 - 0.299)
	0 - ≤3m	0.89	0.97	0.018 (-0.227 - 0.263)	0.56	0.97	0.067 (-0.156 - 0.290)
IFN-γ	0m	0.60	0.97	0.074 (-0.204 - 0.353)	0.36	0.96	0.133 (-0.156 - 0.423)
	0 - ≤3m	0.79	0.97	-0.033 (-0.277 - 0.212)	0.87	0.98	-0.021 (-0.268 - 0.227)
IL-10RA	0m	0.32	0.97	0.136 (-0.132 - 0.404)	0.38	0.96	0.126 (-0.153 - 0.404)
	0 - ≤3m	0.35	0.97	-0.113 (-0.348 - 0.122)	0.35	0.96	-0.114 (-0.352 - 0.125)
IL-10RB	0m	0.77	0.97	-0.042 (-0.320 - 0.236)	0.52	0.97	-0.094 (-0.380 - 0.192)
	0 - ≤3m	0.38	0.97	0.109 (-0.135 - 0.354)	0.54	0.97	0.077 (-0.168 - 0.321)
IL-12B	0m	0.61	0.97	-0.072 (-0.351 - 0.206)	0.83	0.98	-0.031 (-0.319 - 0.256)
	0 - ≤3m	0.36	0.97	-0.115 (-0.359 - 0.130)	0.48	0.97	-0.088 (-0.333 - 0.158)
IL-15RA	0m	0.96	0.98	0.007 (-0.271 - 0.286)	0.93	0.99	0.013 (-0.276 - 0.302)
	0 - ≤3m	0.30	0.97	-0.130 (-0.375 - 0.115)	0.32	0.96	-0.125 (-0.372 - 0.123)
IL-17A	0m	0.25	0.97	0.160 (-0.114 - 0.434)	0.20	0.96	0.184 (-0.100 - 0.469)
	0 - ≤3m	0.71	0.97	-0.046 (-0.287 - 0.195)	0.75	0.98	-0.039 (-0.283 - 0.204)
IL-17C	0m	0.17	0.97	0.193 (-0.083 - 0.47)	0.14	0.96	0.214 (-0.073 - 0.501)
	0 - ≤3m	0.58	0.97	-0.068 (-0.311 - 0.175)	0.71	0.98	-0.047 (-0.293 - 0.199)
IL-18	0m	0.35	0.97	0.130 (-0.145 - 0.405)	0.33	0.96	0.138 (-0.141 - 0.416)
	0 - ≤3m	0.27	0.97	-0.137 (-0.379 - 0.105)	0.40	0.96	-0.101 (-0.339 - 0.137)
IL-18R1	0m	0.81	0.97	0.034 (-0.245 - 0.312)	0.79	0.98	0.038 (-0.244 - 0.321)
	0 - ≤3m	0.65	0.97	-0.057 (-0.302 - 0.187)	0.84	0.98	-0.025 (-0.267 - 0.217)
IL-4	0m	0.96	0.98	0.007 (-0.272 - 0.285)	0.85	0.98	-0.028 (-0.317 - 0.260)
	0 - ≤3m	0.50	0.97	0.083 (-0.162 - 0.328)	0.64	0.98	0.059 (-0.188 - 0.306)
IL-6	0m	0.80	0.97	-0.035 (-0.314 - 0.243)	0.87	0.98	-0.021 (-0.279 - 0.236)
	0 - ≤3m	0.76	0.97	-0.038 (-0.283 - 0.207)	0.85	0.98	-0.021 (-0.242 - 0.199)
IL-7	0m	0.00	0.16	-0.459 (-0.732 - -0.186)	0.00	0.14	-0.468 (-0.744 - -0.192)
	0 - ≤3m	0.01	0.86	-0.311 (-0.551 - -0.071)	0.01	0.62	-0.320 (-0.556 - -0.083)
IL-8	0m	0.54	0.97	-0.087 (-0.365 - 0.191)	0.47	0.97	-0.070 (-0.260 - 0.119)
	0 - ≤3m	0.50	0.97	-0.085 (-0.329 - 0.159)	0.53	0.97	-0.052 (-0.215 - 0.110)
IL-10	0m	0.89	0.97	0.020 (-0.258 - 0.298)	0.58	0.97	0.081 (-0.205 - 0.367)
	0 - ≤3m	0.26	0.97	-0.140 (-0.384 - 0.105)	0.38	0.96	-0.110 (-0.354 - 0.135)
LAP TGF-β-1	0m	0.09	0.97	-0.238 (-0.515 - 0.040)	0.05	0.96	-0.282 (-0.559 - -0.005)
	0 - ≤3m	0.33	0.97	-0.121 (-0.365 - 0.123)	0.27	0.96	-0.132 (-0.369 - 0.104)
LIF-R	0m	0.07	0.97	-0.257 (-0.533 - 0.019)	0.09	0.96	-0.251 (-0.538 - 0.036)
	0 - ≤3m	0.12	0.97	-0.193 (-0.436 - 0.049)	0.16	0.96	-0.178 (-0.423 - 0.068)
MCP-1	0m	0.86	0.97	0.025 (-0.251 - 0.302)	0.76	0.98	0.040 (-0.222 - 0.302)
	0 - ≤3m	0.22	0.97	-0.151 (-0.395 - 0.092)	0.32	0.96	-0.113 (-0.338 - 0.111)
MCP-2	0m	0.58	0.97	0.078 (-0.200 - 0.356)	0.54	0.97	0.090 (-0.200 - 0.379)
	0 - ≤3m	0.63	0.97	-0.060 (-0.305 - 0.185)	0.71	0.98	-0.046 (-0.294 - 0.201)
MCP-3	0m	0.21	0.97	-0.176 (-0.452 - 0.100)	0.14	0.96	-0.146 (-0.341 - 0.049)
	0 - ≤3m	0.26	0.97	-0.139 (-0.381 - 0.104)	0.22	0.96	-0.104 (-0.271 - 0.063)
MCP-4	0m	0.82	0.97	-0.032 (-0.311 - 0.246)	0.89	0.98	0.020 (-0.267 - 0.306)
	0 - ≤3m	0.94	0.98	-0.009 (-0.254 - 0.236)	0.78	0.98	0.034 (-0.211 - 0.280)

MMP-1	0m	0.67	0.97	-0.061 (-0.34 - 0.218)	0.55	0.97	-0.088 (-0.375 - 0.200)
	0 - ≤3m	0.47	0.97	0.090 (-0.155 - 0.335)	0.38	0.96	0.111 (-0.135 - 0.356)
MMP-10	0m	0.98	0.99	0.003 (-0.274 - 0.280)	0.67	0.98	0.062 (-0.222 - 0.346)
	0 - ≤3m	0.57	0.97	0.070 (-0.173 - 0.313)	0.36	0.96	0.113 (-0.130 - 0.355)
NT-3	0m	0.36	0.97	-0.129 (-0.407 - 0.148)	0.26	0.96	-0.165 (-0.450 - 0.121)
	0 - ≤3m	0.64	0.97	0.058 (-0.186 - 0.302)	0.84	0.98	0.025 (-0.218 - 0.269)
OPG	0m	0.23	0.97	-0.171 (-0.449 - 0.108)	0.14	0.96	-0.216 (-0.504 - 0.072)
	0 - ≤3m	0.27	0.97	-0.138 (-0.383 - 0.107)	0.26	0.96	-0.141 (-0.387 - 0.106)
OSM	0m	0.89	0.97	0.020 (-0.259 - 0.298)	0.78	0.98	0.029 (-0.176 - 0.233)
	0 - ≤3m	0.62	0.97	-0.061 (-0.306 - 0.183)	0.96	0.99	-0.005 (-0.180 - 0.170)
PD-L1	0m	0.43	0.97	0.111 (-0.167 - 0.390)	0.40	0.96	0.120 (-0.162 - 0.403)
	0 - ≤3m	0.48	0.97	-0.087 (-0.332 - 0.158)	0.65	0.98	-0.056 (-0.298 - 0.186)
SCF	0m	0.10	0.97	0.228 (-0.047 - 0.504)	0.18	0.96	0.196 (-0.088 - 0.479)
	0 - ≤3m	0.04	0.97	0.253 (0.011 - 0.496)	0.08	0.96	0.214 (-0.029 - 0.456)
SIRT2	0m	0.34	0.97	0.133 (-0.144 - 0.410)	0.49	0.97	0.098 (-0.180 - 0.377)
	0 - ≤3m	0.66	0.97	-0.054 (-0.297 - 0.190)	0.79	0.98	-0.032 (-0.271 - 0.206)
SLAMF1	0m	0.11	0.97	-0.226 (-0.500 - 0.049)	0.05	0.96	-0.281 (-0.564 - 0.002)
	0 - ≤3m	0.05	0.97	-0.239 (-0.480 - 0.003)	0.07	0.96	-0.223 (-0.465 - 0.019)
ST1A1	0m	0.42	0.97	-0.113 (-0.390 - 0.164)	0.36	0.96	-0.124 (-0.393 - 0.145)
	0 - ≤3m	0.21	0.97	0.155 (-0.088 - 0.399)	0.12	0.96	0.183 (-0.047 - 0.413)
STAMBP	0m	0.26	0.97	0.157 (-0.119 - 0.434)	0.41	0.96	0.119 (-0.165 - 0.403)
	0 - ≤3m	0.86	0.97	0.022 (-0.221 - 0.265)	0.84	0.98	0.025 (-0.218 - 0.268)
TGF-α	0m	0.35	0.97	-0.133 (-0.411 - 0.146)	0.57	0.97	-0.078 (-0.347 - 0.190)
	0 - ≤3m	0.87	0.97	-0.021 (-0.266 - 0.224)	0.72	0.98	0.041 (-0.189 - 0.271)
TNF	0m	0.62	0.97	-0.069 (-0.348 - 0.209)	0.81	0.98	-0.034 (-0.322 - 0.253)
	0 - ≤3m	0.75	0.97	-0.040 (-0.284 - 0.205)	0.76	0.98	-0.038 (-0.284 - 0.209)
TNFB	0m	0.81	0.97	-0.033 (-0.311 - 0.245)	0.66	0.98	-0.064 (-0.349 - 0.222)
	0 - ≤3m	0.23	0.97	-0.150 (-0.394 - 0.095)	0.21	0.96	-0.155 (-0.399 - 0.090)
TNFRSF9	0m	0.42	0.97	0.113 (-0.165 - 0.392)	0.51	0.97	0.095 (-0.188 - 0.378)
	0 - ≤3m	0.57	0.97	0.071 (-0.174 - 0.315)	0.51	0.97	0.082 (-0.160 - 0.324)
TNFSF14	0m	0.95	0.98	0.008 (-0.270 - 0.287)	0.99	0.99	0.002 (-0.224 - 0.227)
	0 - ≤3m	0.83	0.97	0.028 (-0.217 - 0.273)	0.39	0.96	0.084 (-0.109 - 0.277)
TRAIL	0m	0.18	0.97	0.191 (-0.086 - 0.468)	0.11	0.96	0.234 (-0.049 - 0.518)
	0 - ≤3m	0.70	0.97	0.049 (-0.195 - 0.292)	0.57	0.97	0.070 (-0.173 - 0.312)
TRANCE	0m	0.38	0.97	0.124 (-0.154 - 0.402)	0.30	0.96	0.154 (-0.135 - 0.443)
	0 - ≤3m	0.66	0.97	0.055 (-0.190 - 0.299)	0.62	0.98	0.063 (-0.184 - 0.310)
TWEAK	0m	1.00	1.00	0.000 (-0.278 - 0.278)	0.77	0.98	-0.043 (-0.330 - 0.244)
	0 - ≤3m	0.42	0.97	-0.100 (-0.345 - 0.144)	0.42	0.96	-0.101 (-0.346 - 0.145)
uPA	0m	0.58	0.97	0.078 (-0.201 - 0.356)	0.86	0.98	-0.025 (-0.295 - 0.246)
	0 - ≤3m	0.52	0.97	0.081 (-0.164 - 0.326)	0.47	0.97	0.086 (-0.146 - 0.317)
VEGFA	0m	0.16	0.97	-0.197 (-0.474 - 0.081)	0.19	0.96	-0.186 (-0.465 - 0.094)
	0 - ≤3m	0.62	0.97	-0.062 (-0.306 - 0.182)	0.76	0.98	-0.037 (-0.276 - 0.202)

**46 infants had an NA value for FGF-5.

Supplementary Table 12. Linear regression associations of infant serum biomarker levels with HMF method at three months among one-year-old CHILD cohort infants (not currently HMF subset, n=347). Results from univariable and multivariable (adjusting for time until blood sample centrifugation, sex, and study site) linear regression models that use HMF method at three months to predict biomarker levels. The direct HMF group was used as reference.

Olink Biomarkers	Variable Groups	HMF method Univariable			HMF method Multivariable		
		P-value	FDR P-value	β-Coefficient (95% CI)	P-value	FDR P-value	β-Coefficient (95% CI)
4E-BP1	Only HMF - Some Indirect	0.92	0.99	-0.017 (-0.338 - 0.304)	0.97	1.00	-0.006 (-0.325 - 0.313)
	FF + HMF	0.83	0.99	-0.033 (-0.342 - 0.276)	0.99	1.00	-0.003 (-0.309 - 0.304)
	Only FF	0.89	0.99	0.025 (-0.324 - 0.373)	0.72	1.00	-0.064 (-0.418 - 0.291)
ADA	Only HMF - Some Indirect	0.88	0.99	-0.024 (-0.346 - 0.298)	0.58	1.00	-0.088 (-0.396 - 0.221)
	FF + HMF	0.30	0.99	0.164 (-0.147 - 0.474)	0.47	1.00	0.109 (-0.188 - 0.405)
	Only FF	0.56	0.99	-0.105 (-0.455 - 0.245)	0.39	1.00	-0.151 (-0.494 - 0.192)
AXIN1	Only HMF - Some Indirect	0.17	0.99	0.226 (-0.094 - 0.547)	0.32	1.00	0.152 (-0.147 - 0.451)
	FF + HMF	1.00	1.00	0.001 (-0.308 - 0.309)	0.94	1.00	0.010 (-0.277 - 0.298)
	Only FF	0.73	0.99	-0.061 (-0.409 - 0.288)	0.32	1.00	-0.168 (-0.500 - 0.164)
CASP-8	Only HMF - Some Indirect	0.52	0.99	0.107 (-0.216 - 0.43)	0.94	1.00	0.009 (-0.207 - 0.225)
	FF + HMF	0.61	0.99	0.082 (-0.23 - 0.393)	0.39	1.00	-0.091 (-0.299 - 0.117)
	Only FF	0.73	0.99	-0.063 (-0.414 - 0.288)	0.75	1.00	-0.039 (-0.280 - 0.201)
CCL11	Only HMF - Some Indirect	0.60	0.99	0.085 (-0.235 - 0.404)	0.94	1.00	0.012 (-0.306 - 0.330)
	FF + HMF	0.29	0.99	-0.164 (-0.473 - 0.144)	0.19	1.00	-0.203 (-0.509 - 0.103)
	Only FF	0.16	0.99	-0.247 (-0.595 - 0.100)	0.18	1.00	-0.243 (-0.597 - 0.110)
CCL19	Only HMF - Some Indirect	0.19	0.99	0.213 (-0.103 - 0.53)	0.13	1.00	0.231 (-0.072 - 0.533)
	FF + HMF	0.69	0.99	-0.062 (-0.367 - 0.243)	0.95	1.00	0.009 (-0.282 - 0.300)
	Only FF	0.08	0.99	0.304 (-0.040 - 0.649)	0.06	1.00	0.323 (-0.013 - 0.660)
CCL20	Only HMF - Some Indirect	0.81	0.99	0.040 (-0.282 - 0.362)	0.98	1.00	-0.004 (-0.324 - 0.315)
	FF + HMF	0.85	0.99	-0.029 (-0.339 - 0.281)	0.86	1.00	-0.027 (-0.334 - 0.280)
	Only FF	0.96	0.99	-0.010 (-0.359 - 0.340)	0.73	1.00	0.063 (-0.292 - 0.418)
CCL23	Only HMF - Some Indirect	0.53	0.99	0.104 (-0.219 - 0.427)	0.68	1.00	0.068 (-0.253 - 0.389)
	FF + HMF	0.60	0.99	-0.083 (-0.394 - 0.228)	0.76	1.00	-0.049 (-0.357 - 0.260)
	Only FF	0.98	0.99	-0.005 (-0.356 - 0.346)	0.70	1.00	-0.070 (-0.427 - 0.287)
CCL25	Only HMF - Some Indirect	0.19	0.99	0.212 (-0.108 - 0.533)	0.33	1.00	0.161 (-0.161 - 0.483)
	FF + HMF	0.15	0.99	0.226 (-0.082 - 0.535)	0.16	1.00	0.222 (-0.088 - 0.531)
	Only FF	0.03	0.92	0.391 (0.042 - 0.739)	0.08	1.00	0.321 (-0.036 - 0.679)
CCL28	Only HMF - Some Indirect	0.41	0.99	0.136 (-0.187 - 0.458)	0.53	1.00	0.102 (-0.215 - 0.42)
	FF + HMF	0.90	0.99	-0.019 (-0.330 - 0.292)	0.79	1.00	-0.041 (-0.346 - 0.264)
	Only FF	0.97	0.99	0.006 (-0.344 - 0.357)	0.74	1.00	0.059 (-0.294 - 0.411)
CCL3	Only HMF - Some Indirect	0.65	0.99	-0.073 (-0.392 - 0.246)	0.51	1.00	-0.095 (-0.380 - 0.191)
	FF + HMF	0.72	0.99	-0.055 (-0.363 - 0.253)	0.22	1.00	-0.172 (-0.446 - 0.103)
	Only FF	0.51	0.99	-0.116 (-0.463 - 0.231)	1.00	1.00	-0.001 (-0.318 - 0.317)
CCL4	Only HMF - Some Indirect	0.76	0.99	-0.050 (-0.369 - 0.268)	0.67	1.00	-0.064 (-0.359 - 0.232)
	FF + HMF	0.95	0.99	0.009 (-0.297 - 0.316)	0.52	1.00	-0.094 (-0.378 - 0.190)
	Only FF	0.56	0.99	-0.102 (-0.449 - 0.244)	0.89	1.00	-0.022 (-0.351 - 0.306)

CD244	Only HMF - Some Indirect	0.68	0.99	-0.066 (-0.381 - 0.249)	0.28	1.00	-0.154 (-0.435 - 0.126)
	FF + HMF	0.96	0.99	-0.007 (-0.311 - 0.296)	0.39	1.00	-0.119 (-0.389 - 0.151)
	Only FF	0.00	0.33	-0.500 (-0.842 - -0.158)	0.00	0.26	-0.508 (-0.820 - -0.196)
CD40	Only HMF - Some Indirect	0.93	0.99	-0.014 (-0.334 - 0.306)	0.30	1.00	-0.125 (-0.360 - 0.110)
	FF + HMF	0.71	0.99	0.059 (-0.250 - 0.367)	0.34	1.00	-0.110 (-0.336 - 0.116)
	Only FF	0.13	0.99	-0.268 (-0.616 - 0.079)	0.05	1.00	-0.265 (-0.527 - -0.004)
CD5	Only HMF - Some Indirect	0.56	0.99	0.096 (-0.227 - 0.420)	0.85	1.00	0.030 (-0.283 - 0.342)
	FF + HMF	0.70	0.99	0.062 (-0.250 - 0.374)	0.97	1.00	-0.005 (-0.306 - 0.295)
	Only FF	0.55	0.99	0.108 (-0.244 - 0.459)	0.58	1.00	0.098 (-0.250 - 0.445)
CD6	Only HMF - Some Indirect	0.68	0.99	0.067 (-0.255 - 0.389)	0.85	1.00	0.029 (-0.280 - 0.338)
	FF + HMF	0.37	0.99	-0.142 (-0.453 - 0.168)	0.15	1.00	-0.219 (-0.516 - 0.078)
	Only FF	0.60	0.99	-0.092 (-0.443 - 0.258)	0.56	1.00	-0.103 (-0.447 - 0.241)
CD8A	Only HMF - Some Indirect	0.70	0.99	0.063 (-0.259 - 0.385)	0.74	1.00	0.054 (-0.265 - 0.374)
	FF + HMF	0.24	0.99	-0.184 (-0.495 - 0.126)	0.36	1.00	-0.142 (-0.449 - 0.164)
	Only FF	0.65	0.99	0.081 (-0.269 - 0.431)	0.56	1.00	0.105 (-0.250 - 0.459)
CDCP1	Only HMF - Some Indirect	0.74	0.99	0.054 (-0.270 - 0.378)	0.90	1.00	0.020 (-0.307 - 0.346)
	FF + HMF	0.81	0.99	-0.038 (-0.350 - 0.274)	0.73	1.00	-0.056 (-0.370 - 0.258)
	Only FF	0.75	0.99	0.057 (-0.295 - 0.408)	0.93	1.00	0.015 (-0.347 - 0.378)
CSF-1	Only HMF - Some Indirect	0.20	0.99	0.213 (-0.110 - 0.536)	0.24	1.00	0.188 (-0.126 - 0.501)
	FF + HMF	0.29	0.99	0.169 (-0.142 - 0.480)	0.51	1.00	0.102 (-0.200 - 0.403)
	Only FF	0.70	0.99	0.069 (-0.282 - 0.420)	0.59	1.00	0.096 (-0.252 - 0.444)
CST5	Only HMF - Some Indirect	0.81	0.99	-0.039 (-0.359 - 0.281)	0.87	1.00	-0.027 (-0.346 - 0.291)
	FF + HMF	0.63	0.99	-0.075 (-0.383 - 0.234)	0.71	1.00	-0.059 (-0.365 - 0.247)
	Only FF	0.70	0.99	0.067 (-0.281 - 0.415)	0.86	1.00	-0.032 (-0.386 - 0.322)
CX3CL1	Only HMF - Some Indirect	0.70	0.99	0.064 (-0.258 - 0.386)	0.56	1.00	0.093 (-0.224 - 0.411)
	FF + HMF	0.36	0.99	0.145 (-0.165 - 0.455)	0.20	1.00	0.198 (-0.107 - 0.503)
	Only FF	0.09	0.99	0.300 (-0.050 - 0.650)	0.17	1.00	0.250 (-0.103 - 0.602)
CXCL1	Only HMF - Some Indirect	0.93	0.99	0.014 (-0.302 - 0.330)	0.65	1.00	-0.071 (-0.381 - 0.238)
	FF + HMF	0.81	0.99	0.037 (-0.267 - 0.342)	0.94	1.00	-0.011 (-0.309 - 0.286)
	Only FF	0.05	0.99	-0.34 (-0.683 - 0.004)	0.07	1.00	-0.318 (-0.661 - 0.026)
CXCL10	Only HMF - Some Indirect	0.27	0.99	0.183 (-0.141 - 0.506)	0.30	1.00	0.173 (-0.155 - 0.500)
	FF + HMF	0.62	0.99	0.079 (-0.232 - 0.391)	0.59	1.00	0.087 (-0.228 - 0.401)
	Only FF	0.25	0.99	0.208 (-0.144 - 0.559)	0.20	1.00	0.240 (-0.124 - 0.604)
CXCL11	Only HMF - Some Indirect	0.40	0.99	0.139 (-0.183 - 0.461)	0.63	1.00	0.076 (-0.238 - 0.39)
	FF + HMF	0.34	0.99	0.152 (-0.158 - 0.462)	0.48	1.00	0.109 (-0.192 - 0.411)
	Only FF	0.70	0.99	0.07 (-0.281 - 0.420)	0.51	1.00	0.117 (-0.232 - 0.466)
CXCL5	Only HMF - Some Indirect	0.21	0.99	-0.206 (-0.527 - 0.114)	0.10	1.00	-0.262 (-0.572 - 0.048)
	FF + HMF	0.13	0.99	-0.236 (-0.545 - 0.072)	0.18	1.00	-0.202 (-0.500 - 0.096)
	Only FF	0.02	0.70	-0.431 (-0.779 - -0.083)	0.01	0.26	-0.492 (-0.837 - -0.148)
CXCL6	Only HMF - Some Indirect	0.25	0.99	-0.185 (-0.502 - 0.131)	0.12	1.00	-0.251 (-0.565 - 0.063)
	FF + HMF	0.18	0.99	-0.208 (-0.513 - 0.097)	0.10	1.00	-0.252 (-0.554 - 0.050)
	Only FF	0.00	0.33	-0.521 (-0.865 - -0.177)	0.00	0.26	-0.521 (-0.871 - -0.172)
CXCL9	Only HMF - Some Indirect	0.51	0.99	0.108 (-0.214 - 0.430)	0.80	1.00	0.041 (-0.282 - 0.364)
	FF + HMF	0.35	0.99	0.148 (-0.162 - 0.459)	0.36	1.00	0.144 (-0.166 - 0.454)
	Only FF	0.61	0.99	-0.091 (-0.441 - 0.259)	0.62	1.00	-0.091 (-0.450 - 0.268)
DNER	Only HMF - Some Indirect	0.92	0.99	0.015 (-0.307 - 0.338)	0.99	1.00	-0.003 (-0.325 - 0.320)

	FF + HMF	0.78	0.99	-0.044 (-0.355 - 0.267)	0.54	1.00	-0.097 (-0.406 - 0.213)
	Only FF	0.51	0.99	-0.118 (-0.469 - 0.233)	0.62	1.00	-0.089 (-0.447 - 0.269)
EN-RAGE	Only HMF - Some Indirect	0.64	0.99	0.076 (-0.246 - 0.399)	0.85	1.00	-0.025 (-0.278 - 0.228)
	FF + HMF	0.91	0.99	-0.017 (-0.328 - 0.294)	0.49	1.00	-0.086 (-0.329 - 0.157)
	Only FF	0.78	0.99	-0.049 (-0.400 - 0.302)	0.73	1.00	-0.049 (-0.331 - 0.232)
FGF-19	Only HMF - Some Indirect	0.27	0.99	0.18 (-0.140 - 0.501)	0.21	1.00	0.209 (-0.116 - 0.534)
	FF + HMF	0.06	0.99	0.292 (-0.017 - 0.601)	0.06	1.00	0.294 (-0.018 - 0.606)
	Only FF	0.03	0.92	0.394 (0.046 - 0.743)	0.02	0.56	0.440 (0.079 - 0.801)
FGF-21	Only HMF - Some Indirect	0.48	0.99	-0.113 (-0.425 - 0.200)	0.49	1.00	-0.110 (-0.423 - 0.202)
	FF + HMF	0.93	0.99	0.013 (-0.288 - 0.314)	0.82	1.00	0.035 (-0.265 - 0.336)
	Only FF	0.55	0.99	-0.104 (-0.443 - 0.236)	0.38	1.00	-0.156 (-0.503 - 0.192)
FGF-23	Only HMF - Some Indirect	0.45	0.99	-0.123 (-0.444 - 0.199)	0.41	1.00	-0.136 (-0.458 - 0.186)
	FF + HMF	0.33	0.99	-0.153 (-0.463 - 0.157)	0.37	1.00	-0.142 (-0.451 - 0.167)
	Only FF	0.62	0.99	0.089 (-0.26 - 0.438)	0.89	1.00	0.025 (-0.332 - 0.383)
FGF-5**	Only HMF - Some Indirect	0.16	0.99	-0.240 (-0.574 - 0.095)	0.15	1.00	-0.245 (-0.582 - 0.091)
	FF + HMF	0.10	0.99	-0.272 (-0.595 - 0.050)	0.13	1.00	-0.251 (-0.575 - 0.073)
	Only FF	0.30	0.99	-0.191 (-0.555 - 0.173)	0.30	1.00	-0.198 (-0.573 - 0.176)
Flt3L	Only HMF - Some Indirect	0.97	0.99	0.007 (-0.315 - 0.328)	0.84	1.00	0.033 (-0.29 - 0.356)
	FF + HMF	0.60	0.99	-0.082 (-0.392 - 0.228)	0.50	1.00	-0.106 (-0.416 - 0.204)
	Only FF	0.55	0.99	-0.105 (-0.454 - 0.244)	0.52	1.00	-0.118 (-0.477 - 0.240)
HGF	Only HMF - Some Indirect	0.93	0.99	-0.014 (-0.336 - 0.308)	0.56	1.00	-0.087 (-0.382 - 0.207)
	FF + HMF	0.86	0.99	0.027 (-0.283 - 0.337)	0.67	1.00	-0.060 (-0.343 - 0.222)
	Only FF	0.40	0.99	-0.149 (-0.499 - 0.200)	0.44	1.00	-0.129 (-0.456 - 0.198)
IFN-γ	Only HMF - Some Indirect	0.54	0.99	0.100 (-0.224 - 0.424)	0.51	1.00	0.110 (-0.218 - 0.438)
	FF + HMF	0.41	0.99	0.132 (-0.180 - 0.444)	0.32	1.00	0.159 (-0.156 - 0.474)
	Only FF	0.43	0.99	0.141 (-0.211 - 0.493)	0.28	1.00	0.202 (-0.162 - 0.567)
IL-10RA	Only HMF - Some Indirect	0.39	0.99	0.140 (-0.183 - 0.464)	0.41	1.00	0.139 (-0.190 - 0.467)
	FF + HMF	0.97	0.99	0.006 (-0.306 - 0.318)	0.96	1.00	0.007 (-0.308 - 0.323)
	Only FF	0.59	0.99	0.097 (-0.255 - 0.448)	0.70	1.00	0.072 (-0.293 - 0.437)
IL-10RB	Only HMF - Some Indirect	0.22	0.99	-0.202 (-0.521 - 0.118)	0.17	1.00	-0.222 (-0.541 - 0.098)
	FF + HMF	0.83	0.99	0.034 (-0.274 - 0.342)	0.90	1.00	0.021 (-0.287 - 0.328)
	Only FF	0.09	0.99	-0.296 (-0.643 - 0.052)	0.06	1.00	-0.346 (-0.701 - 0.010)
IL-12B	Only HMF - Some Indirect	0.88	0.99	0.025 (-0.296 - 0.347)	0.93	1.00	0.013 (-0.310 - 0.337)
	FF + HMF	0.26	0.99	-0.179 (-0.489 - 0.130)	0.30	1.00	-0.164 (-0.475 - 0.147)
	Only FF	0.60	0.99	0.093 (-0.256 - 0.442)	0.39	1.00	0.156 (-0.203 - 0.515)
IL-15RA	Only HMF - Some Indirect	0.11	0.99	-0.260 (-0.581 - 0.061)	0.07	1.00	-0.295 (-0.620 - 0.030)
	FF + HMF	0.06	0.99	-0.293 (-0.602 - 0.017)	0.06	1.00	-0.297 (-0.609 - 0.015)
	Only FF	0.17	0.99	-0.243 (-0.592 - 0.106)	0.17	1.00	-0.252 (-0.613 - 0.109)
IL-17A	Only HMF - Some Indirect	0.81	0.99	-0.039 (-0.361 - 0.284)	0.79	1.00	-0.045 (-0.372 - 0.282)
	FF + HMF	0.43	0.99	-0.124 (-0.435 - 0.187)	0.53	1.00	-0.100 (-0.414 - 0.214)
	Only FF	0.49	0.99	-0.124 (-0.474 - 0.227)	0.48	1.00	-0.132 (-0.495 - 0.232)
IL-17C	Only HMF - Some Indirect	0.29	0.99	-0.173 (-0.496 - 0.149)	0.22	1.00	-0.204 (-0.530 - 0.123)
	FF + HMF	0.49	0.99	-0.110 (-0.421 - 0.201)	0.51	1.00	-0.106 (-0.419 - 0.208)
	Only FF	0.94	0.99	-0.014 (-0.365 - 0.337)	0.92	1.00	-0.019 (-0.382 - 0.344)
IL-18	Only HMF - Some Indirect	0.86	0.99	0.029 (-0.294 - 0.353)	0.80	1.00	-0.041 (-0.360 - 0.279)
	FF + HMF	0.85	0.99	-0.031 (-0.343 - 0.281)	0.70	1.00	-0.060 (-0.368 - 0.247)
	Only FF	0.97	0.99	0.008 (-0.344 - 0.359)	1.00	1.00	0.000 (-0.355 - 0.356)

IL-18R1	Only HMF - Some Indirect	0.57	0.99	0.094 (-0.229 - 0.417)	0.64	1.00	0.076 (-0.244 - 0.396)
	FF + HMF	0.60	0.99	0.084 (-0.228 - 0.395)	0.73	1.00	0.054 (-0.254 - 0.361)
	Only FF	0.85	0.99	0.034 (-0.317 - 0.386)	0.80	1.00	0.045 (-0.311 - 0.401)
IL-4	Only HMF - Some Indirect	0.75	0.99	0.052 (-0.271 - 0.376)	0.80	1.00	0.042 (-0.285 - 0.369)
	FF + HMF	0.91	0.99	-0.019 (-0.330 - 0.292)	0.81	1.00	-0.039 (-0.354 - 0.275)
	Only FF	0.24	0.99	0.208 (-0.143 - 0.559)	0.27	1.00	0.204 (-0.159 - 0.568)
IL-6	Only HMF - Some Indirect	0.42	0.99	0.131 (-0.19 - 0.452)	0.59	1.00	0.079 (-0.212 - 0.369)
	FF + HMF	0.55	0.99	0.093 (-0.216 - 0.402)	0.89	1.00	-0.019 (-0.299 - 0.260)
	Only FF	0.91	0.99	-0.021 (-0.369 - 0.328)	0.67	1.00	0.070 (-0.253 - 0.393)
IL-7	Only HMF - Some Indirect	0.29	0.99	-0.171 (-0.486 - 0.145)	0.26	1.00	-0.178 (-0.489 - 0.134)
	FF + HMF	0.00	0.33	-0.461 (-0.765 - -0.156)	0.01	0.26	-0.423 (-0.722 - -0.124)
	Only FF	0.01	0.37	-0.478 (-0.821 - -0.135)	0.00	0.26	-0.534 (-0.880 - -0.188)
IL-8	Only HMF - Some Indirect	0.68	0.99	0.068 (-0.254 - 0.39)	0.91	1.00	-0.012 (-0.229 - 0.205)
	FF + HMF	0.92	0.99	0.015 (-0.295 - 0.325)	0.12	1.00	-0.164 (-0.372 - 0.045)
	Only FF	0.32	0.99	-0.176 (-0.525 - 0.174)	0.74	1.00	-0.040 (-0.281 - 0.201)
IL-10	Only HMF - Some Indirect	0.08	0.99	0.288 (-0.034 - 0.61)	0.15	1.00	0.237 (-0.087 - 0.56)
	FF + HMF	0.15	0.99	0.229 (-0.082 - 0.539)	0.12	1.00	0.246 (-0.065 - 0.557)
	Only FF	0.95	0.99	0.011 (-0.340 - 0.361)	0.90	1.00	0.024 (-0.336 - 0.383)
LAP TGF-β-1	Only HMF - Some Indirect	0.49	0.99	-0.112 (-0.433 - 0.209)	0.28	1.00	-0.170 (-0.481 - 0.142)
	FF + HMF	0.04	0.99	-0.331 (-0.640 - -0.022)	0.01	0.29	-0.407 (-0.706 - -0.108)
	Only FF	0.15	0.99	-0.254 (-0.603 - 0.095)	0.10	1.00	-0.288 (-0.634 - 0.058)
LIF-R	Only HMF - Some Indirect	0.65	0.99	0.065 (-0.217 - 0.346)	0.79	1.00	0.038 (-0.247 - 0.323)
	FF + HMF	0.28	0.99	-0.151 (-0.422 - 0.121)	0.23	1.00	-0.169 (-0.443 - 0.105)
	Only FF	0.40	0.99	-0.131 (-0.437 - 0.175)	0.37	1.00	-0.145 (-0.462 - 0.172)
MCP-1	Only HMF - Some Indirect	0.28	0.99	0.175 (-0.147 - 0.497)	0.42	1.00	0.122 (-0.175 - 0.419)
	FF + HMF	0.87	0.99	-0.026 (-0.336 - 0.284)	0.41	1.00	-0.119 (-0.405 - 0.166)
	Only FF	0.56	0.99	0.104 (-0.246 - 0.453)	0.32	1.00	0.166 (-0.165 - 0.496)
MCP-2	Only HMF - Some Indirect	0.86	0.99	-0.028 (-0.350 - 0.293)	0.78	1.00	-0.046 (-0.372 - 0.28)
	FF + HMF	0.69	0.99	-0.062 (-0.372 - 0.248)	0.72	1.00	-0.058 (-0.371 - 0.256)
	Only FF	0.29	0.99	0.187 (-0.163 - 0.537)	0.31	1.00	0.188 (-0.175 - 0.550)
MCP-3	Only HMF - Some Indirect	0.49	0.99	0.114 (-0.208 - 0.436)	0.81	1.00	0.027 (-0.198 - 0.252)
	FF + HMF	0.90	0.99	-0.020 (-0.330 - 0.290)	0.07	1.00	-0.199 (-0.415 - 0.017)
	Only FF	0.19	0.99	-0.234 (-0.584 - 0.115)	0.43	1.00	-0.099 (-0.349 - 0.150)
MCP-4	Only HMF - Some Indirect	0.51	0.99	0.108 (-0.215 - 0.431)	0.59	1.00	0.088 (-0.236 - 0.413)
	FF + HMF	0.93	0.99	0.014 (-0.298 - 0.325)	0.87	1.00	0.026 (-0.286 - 0.337)
	Only FF	0.74	0.99	-0.06 (-0.411 - 0.291)	0.82	1.00	-0.042 (-0.403 - 0.318)
MMP-1	Only HMF - Some Indirect	0.80	0.99	0.041 (-0.28 - 0.363)	0.92	1.00	0.016 (-0.307 - 0.339)
	FF + HMF	0.56	0.99	0.091 (-0.218 - 0.401)	0.65	1.00	0.071 (-0.24 - 0.381)
	Only FF	0.55	0.99	-0.105 (-0.454 - 0.244)	0.38	1.00	-0.162 (-0.521 - 0.197)
MMP-10	Only HMF - Some Indirect	0.44	0.99	0.126 (-0.197 - 0.449)	0.60	1.00	0.087 (-0.236 - 0.410)
	FF + HMF	0.50	0.99	0.106 (-0.205 - 0.418)	0.38	1.00	0.139 (-0.171 - 0.450)
	Only FF	0.82	0.99	0.040 (-0.311 - 0.392)	0.80	1.00	0.047 (-0.312 - 0.406)
NT-3	Only HMF - Some Indirect	0.96	0.99	-0.009 (-0.332 - 0.314)	0.85	1.00	-0.032 (-0.357 - 0.293)
	FF + HMF	0.78	0.99	-0.044 (-0.355 - 0.267)	0.64	1.00	-0.074 (-0.386 - 0.238)
	Only FF	0.47	0.99	-0.129 (-0.480 - 0.223)	0.45	1.00	-0.140 (-0.500 - 0.221)
OPG	Only HMF - Some Indirect	0.89	0.99	-0.023 (-0.345 - 0.299)	0.98	1.00	-0.003 (-0.327 - 0.321)

	FF + HMF	0.29	0.99	-0.166 (-0.476 - 0.144)	0.23	1.00	-0.190 (-0.502 - 0.121)
	Only FF	0.59	0.99	-0.096 (-0.446 - 0.254)	0.50	1.00	-0.124 (-0.485 - 0.236)
OSM	Only HMF - Some Indirect	0.81	0.99	0.039 (-0.283 - 0.361)	0.60	1.00	-0.062 (-0.294 - 0.170)
	FF + HMF	0.84	0.99	0.031 (-0.279 - 0.342)	0.28	1.00	-0.122 (-0.345 - 0.101)
	Only FF	0.34	0.99	-0.169 (-0.519 - 0.181)	0.50	1.00	-0.088 (-0.346 - 0.17)
PD-L1	Only HMF - Some Indirect	0.51	0.99	0.108 (-0.216 - 0.432)	0.83	1.00	0.034 (-0.287 - 0.355)
	FF + HMF	0.83	0.99	0.033 (-0.279 - 0.346)	0.97	1.00	0.006 (-0.303 - 0.314)
	Only FF	0.89	0.99	0.026 (-0.326 - 0.378)	0.92	1.00	0.017 (-0.339 - 0.374)
SCF	Only HMF - Some Indirect	0.88	0.99	-0.025 (-0.345 - 0.296)	0.97	1.00	0.005 (-0.315 - 0.326)
	FF + HMF	0.19	0.99	0.208 (-0.101 - 0.517)	0.26	1.00	0.178 (-0.130 - 0.486)
	Only FF	0.08	0.99	0.311 (-0.037 - 0.66)	0.06	1.00	0.342 (-0.014 - 0.698)
SIRT2	Only HMF - Some Indirect	0.88	0.99	-0.025 (-0.349 - 0.299)	0.75	1.00	-0.052 (-0.370 - 0.266)
	FF + HMF	0.99	1.00	0.001 (-0.311 - 0.313)	0.80	1.00	-0.040 (-0.346 - 0.266)
	Only FF	0.37	0.99	-0.159 (-0.511 - 0.193)	0.26	1.00	-0.204 (-0.557 - 0.149)
SLAMF1	Only HMF - Some Indirect	0.25	0.99	0.186 (-0.134 - 0.505)	0.24	1.00	0.190 (-0.131 - 0.510)
	FF + HMF	0.18	0.99	-0.211 (-0.519 - 0.096)	0.17	1.00	-0.214 (-0.522 - 0.094)
	Only FF	0.69	0.99	-0.071 (-0.418 - 0.276)	0.40	1.00	-0.151 (-0.508 - 0.205)
ST1A1	Only HMF - Some Indirect	0.53	0.99	-0.101 (-0.419 - 0.217)	0.69	1.00	-0.061 (-0.363 - 0.241)
	FF + HMF	0.81	0.99	0.038 (-0.268 - 0.345)	0.86	1.00	0.027 (-0.264 - 0.317)
	Only FF	0.28	0.99	-0.191 (-0.536 - 0.155)	0.33	1.00	-0.167 (-0.503 - 0.169)
STAMBP	Only HMF - Some Indirect	0.87	0.99	0.027 (-0.297 - 0.351)	0.97	1.00	0.006 (-0.318 - 0.33)
	FF + HMF	0.71	0.99	0.059 (-0.253 - 0.371)	0.69	1.00	0.063 (-0.249 - 0.374)
	Only FF	0.61	0.99	-0.092 (-0.445 - 0.260)	0.36	1.00	-0.167 (-0.527 - 0.193)
TGF-α	Only HMF - Some Indirect	0.94	0.99	0.012 (-0.311 - 0.335)	0.89	1.00	-0.022 (-0.325 - 0.281)
	FF + HMF	0.70	0.99	-0.060 (-0.371 - 0.251)	0.59	1.00	-0.080 (-0.371 - 0.211)
	Only FF	0.41	0.99	-0.148 (-0.499 - 0.203)	0.67	1.00	-0.073 (-0.41 - 0.264)
TNF	Only HMF - Some Indirect	0.40	0.99	0.137 (-0.184 - 0.459)	0.47	1.00	0.120 (-0.204 - 0.444)
	FF + HMF	0.95	0.99	0.009 (-0.301 - 0.319)	0.95	1.00	-0.010 (-0.321 - 0.301)
	Only FF	0.68	0.99	0.073 (-0.276 - 0.422)	0.42	1.00	0.147 (-0.213 - 0.507)
TNFB	Only HMF - Some Indirect	0.74	0.99	0.054 (-0.269 - 0.377)	0.75	1.00	0.052 (-0.272 - 0.376)
	FF + HMF	0.30	0.99	-0.164 (-0.476 - 0.147)	0.38	1.00	-0.139 (-0.451 - 0.172)
	Only FF	0.76	0.99	-0.053 (-0.405 - 0.298)	0.55	1.00	-0.110 (-0.470 - 0.250)
TNFRSF9	Only HMF - Some Indirect	0.91	0.99	0.018 (-0.305 - 0.340)	0.70	1.00	-0.063 (-0.382 - 0.256)
	FF + HMF	0.99	1.00	-0.002 (-0.313 - 0.309)	0.90	1.00	-0.019 (-0.325 - 0.288)
	Only FF	0.47	0.99	0.128 (-0.223 - 0.478)	0.58	1.00	0.101 (-0.253 - 0.455)
TNFSF14	Only HMF - Some Indirect	0.89	0.99	0.023 (-0.298 - 0.344)	0.92	1.00	-0.014 (-0.267 - 0.240)
	FF + HMF	0.75	0.99	0.051 (-0.259 - 0.36)	0.63	1.00	-0.06 (-0.303 - 0.183)
	Only FF	0.77	0.99	-0.052 (-0.401 - 0.297)	0.92	1.00	0.014 (-0.267 - 0.296)
TRAIL	Only HMF - Some Indirect	0.56	0.99	-0.097 (-0.419 - 0.226)	0.53	1.00	-0.103 (-0.425 - 0.219)
	FF + HMF	0.87	0.99	-0.026 (-0.337 - 0.285)	0.87	1.00	0.027 (-0.283 - 0.336)
	Only FF	0.26	0.99	0.202 (-0.149 - 0.552)	0.23	1.00	0.221 (-0.137 - 0.579)
TRANCE	Only HMF - Some Indirect	0.78	0.99	-0.045 (-0.366 - 0.276)	0.70	1.00	-0.064 (-0.389 - 0.262)
	FF + HMF	0.76	0.99	0.047 (-0.262 - 0.357)	0.77	1.00	0.047 (-0.266 - 0.360)
	Only FF	0.58	0.99	0.098 (-0.251 - 0.447)	0.43	1.00	0.144 (-0.218 - 0.506)
TWEAK	Only HMF - Some Indirect	0.47	0.99	-0.117 (-0.438 - 0.204)	0.34	1.00	-0.156 (-0.479 - 0.166)
	FF + HMF	0.22	0.99	-0.193 (-0.502 - 0.116)	0.13	1.00	-0.238 (-0.548 - 0.072)
	Only FF	0.15	0.99	-0.254 (-0.602 - 0.095)	0.09	1.00	-0.311 (-0.670 - 0.048)

uPA	Only HMF - Some Indirect	0.17	0.99	-0.226 (-0.548 - 0.096)	0.20	1.00	-0.198 (-0.503 - 0.108)
	FF + HMF	0.79	0.99	-0.042 (-0.353 - 0.268)	0.49	1.00	-0.104 (-0.398 - 0.190)
	Only FF	0.74	0.99	-0.059 (-0.409 - 0.291)	0.43	1.00	-0.138 (-0.478 - 0.202)
VEGFA	Only HMF - Some Indirect	0.95	0.99	0.011 (-0.310 - 0.333)	0.67	1.00	-0.068 (-0.386 - 0.249)
	FF + HMF	0.85	0.99	-0.030 (-0.340 - 0.279)	0.60	1.00	-0.082 (-0.387 - 0.224)
	Only FF	0.12	0.99	-0.279 (-0.629 - 0.070)	0.14	1.00	-0.267 (-0.620 - 0.087)

**46 infants had an NA value for FGF-5.

References

1. Ames SR, Lotoski LC, Azad MB. Comparing early life nutritional sources and human milk feeding practices: personalized and dynamic nutrition supports infant gut microbiome development and immune system maturation. https://doi.org/101080/1949097620232190305 [Internet] 2023 [cited 2023 Jul 18]; 15. Available from: https://www.tandfonline.com/doi/abs/10.1080/19490976.2023.2190305
2. Understanding copyright for journal authors | Author Services [Internet]. [cited 2023 Sep 2]; Available from: https://authorservices.taylorandfrancis.com/publishing-your-research/moving-through-production/copyright-for-journal-authors/
3. Hornef MW, Torow N. 'Layered immunity' and the 'neonatal window of opportunity' – timed succession of non-redundant phases to establish mucosal host–microbial homeostasis after birth. Immunology [Internet] 2020 [cited 2022 Sep 3]; 159:15–25. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/imm.13149
4. Weström B, Arévalo Sureda E, Pierzynowska K, Pierzynowski SG, Pérez-Cano F-J. The Immature Gut Barrier and Its Importance in Establishing Immunity in Newborn Mammals. Front Immunol 2020; 11.
5. Sadeghi K, Berger A, Langgartner M, Prusa A, Hayde M, Herkner K, Pollak A, Spittler A, Förster-Waldl E. Immaturity of Infection Control in Preterm and Term Newborns Is Associated with Impaired Toll-Like Receptor Signaling. J Infect Dis 2007; 195.
6. Willems F, Vollstedt S, Suter M. Phenotype and function of neonatal DC. Eur J Immunol 2009; 39:26–35.
7. Nussbaum C, Gloning A, Pruenster M, Frommhold D, Bierschenk S, Genzel-Boroviczeny O, von Andrian UH, Quackenbush E, Sperandio M. Neutrophil and endothelial adhesive function during human fetal ontogeny. J Leukoc Biol 2013; 93.
8. Haynes BF, Martin ME, Kay HH, Kurtzberg J. Early events in human T cell ontogeny. Phenotypic characterization and immunohistologic localization of T cell precursors in early human fetal tissues. Journal of Experimental Medicine 1988; 168:1061–80.
9. Mold JE, Venkatasubrahmanyam S, Burt TD, Michaëlsson J, Rivera JM, Galkina SA, Weinberg K, Stoddart CA, McCune JM. Fetal and Adult Hematopoietic Stem Cells Give Rise to Distinct T Cell Lineages in Humans. Science (1979) 2010; 330:1695–9.
10. Dawod B, Marshall JS, Azad MB. Breastfeeding and the developmental origins of mucosal immunity: how human milk shapes the innate and adaptive mucosal immune systems. Curr Opin Gastroenterol 2021; 37.
11. Zaghouani H, Hoeman CM, Adkins B. Neonatal immunity: faulty T-helpers and the shortcomings of dendritic cells. Trends Immunol [Internet] 2009 [cited 2023 Sep 2]; 30:585. Available from: /pmc/articles/PMC2787701/
12. Sedney CJ, Harvill ET. The Neonatal Immune System and Respiratory Pathogens. Microorganisms 2023, Vol 11, Page 1597 [Internet] 2023 [cited 2023 Sep 2]; 11:1597. Available from: https://www.mdpi.com/2076-2607/11/6/1597/htm
13. Brambell FWR. THE TRANSMISSION OF IMMUNITY FROM MOTHER TO YOUNG AND THE CATABOLISM OF IMMUNOGLOBULINS. The Lancet 1966; 288:1087–93.
14. Yao Y, Cai X, Ye Y, Wang F, Chen F, Zheng C. The Role of Microbiota in Infant Health: From Early Life to Adulthood. Front Immunol 2021; 12:4114.
15. Strachan DP. Hay fever, hygiene, and household size. BMJ [Internet] 1989 [cited 2023 Nov 16]; 299:1259–60. Available from: https://pubmed.ncbi.nlm.nih.gov/2513902/

16. Houghteling PD, Walker WA. Why is initial bacterial colonization of the intestine important to infants' and children's health? J Pediatr Gastroenterol Nutr [Internet] 2015 [cited 2022 Sep 8]; 60:294–307. Available from: https://pubmed.ncbi.nlm.nih.gov/25313849/
17. He X, Parenti M, Grip T, Domellöf M, Lönnerdal B, Hernell O, Timby N, M. Slupsky C. Metabolic phenotype of breast-fed infants, and infants fed standard formula or bovine MFGM supplemented formula: a randomized controlled trial. Scientific Reports 2019 9:1 [Internet] 2019 [cited 2022 Dec 15]; 9:1–13. Available from: https://www.nature.com/articles/s41598-018-36292-5
18. Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of Breast Milk on Intelligence Quotient, Brain Size, and White Matter Development. Pediatric Research 2010 67:4 [Internet] 2010 [cited 2022 Dec 15]; 67:357–62. Available from: https://www.nature.com/articles/pr201066
19. Netea MG, Quintin J, Van Der Meer JWM. Trained immunity: A memory for innate host defense. Cell Host Microbe [Internet] 2011 [cited 2023 Nov 16]; 9:355–61. Available from: http://www.cell.com/article/S1931312811001284/fulltext
20. MacGillivray DM, Kollmann TR. The Role of Environmental Factors in Modulating Immune Responses in Early Life. Front Immunol [Internet] 2014 [cited 2023 Nov 16]; 5. Available from: /pmc/articles/PMC4161944/
21. Tuazon JA, Kilburg-Basnyat B, Oldfield LM, Wiscovitch-Russo R, Dunigan-Russell K, Fedulov A V., Oestreich KJ, Gowdy KM. Emerging Insights into the Impact of Air Pollution on Immune-Mediated Asthma Pathogenesis. Curr Allergy Asthma Rep [Internet] 2022 [cited 2023 Nov 16]; 22:77. Available from: /pmc/articles/PMC9246904/
22. Medeleanu M V., Qian YC, Moraes TJ, Subbarao P. Early-immune development in asthma: A review of the literature. Cell Immunol 2023; 393–394:104770.
23. Janssen-Weets B, Kerff F, Swiontek K, Kler S, Czolk R, Revets D, Kuehn A, Bindslev-Jensen C, Ollert M, Hilger C. Mammalian derived lipocalin and secretoglobin respiratory allergens strongly bind ligands with potentially immune modulating properties. Frontiers in allergy [Internet] 2022 [cited 2023 Nov 16]; 3. Available from: https://pubmed.ncbi.nlm.nih.gov/35991307/
24. Laursen MF, Zachariassen G, Bahl MI, Bergström A, Host A, Michaelsen KF, Licht TR. Having older siblings is associated with gut microbiota development during early childhood. BMC Microbiol [Internet] 2015 [cited 2023 Nov 16]; 15. Available from: /pmc/articles/PMC4522135/
25. Jain N. The early life education of the immune system: Moms, microbes and (missed) opportunities. Gut Microbes [Internet] 2020 [cited 2023 Nov 16]; 12. Available from: /pmc/articles/PMC7781677/
26. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proceedings of the Royal Society B: Biological Sciences [Internet] 2015 [cited 2023 Nov 16]; 282. Available from: /pmc/articles/PMC4707740/
27. Rosenblum MD, Way SS, Abbas AK. Regulatory T cell memory. Nat Rev Immunol [Internet] 2016 [cited 2023 Nov 16]; 16:90. Available from: /pmc/articles/PMC5113825/
28. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med [Internet] 2015 [cited 2023 Nov 16]; 372:803–13. Available from: https://pubmed.ncbi.nlm.nih.gov/25705822/

29. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science [Internet] 2016 [cited 2023 Nov 16]; 352:539. Available from: /pmc/articles/PMC5050524/
30. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, Kuzeljevic B, Gold MJ, Britton HM, Lefebvre DL, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med [Internet] 2015 [cited 2023 Feb 7]; 7. Available from: https://www.science.org/doi/10.1126/scitranslmed.aab2271
31. Brodin P, Davis MM. Human immune system variation. Nat Rev Immunol [Internet] 2017 [cited 2023 Sep 2]; 17:21. Available from: /pmc/articles/PMC5328245/
32. Fragkou PC, Karaviti D, Zemlin M, Skevaki C. Impact of Early Life Nutrition on Children's Immune System and Noncommunicable Diseases Through Its Effects on the Bacterial Microbiome, Virome and Mycobiome. Front Immunol [Internet] 2021 [cited 2023 Sep 2]; 12. Available from: /pmc/articles/PMC8012492/
33. Laouar A. Maternal Leukocytes and Infant Immune Programming during Breastfeeding. Trends Immunol 2020; 41:225–39.
34. Witkowska-Zimny M, Kaminska-El-Hassan E. Cells of human breast milk. Cell Mol Biol Lett [Internet] 2017 [cited 2022 Sep 13]; 22:1–11. Available from: https://cmbl.biomedcentral.com/articles/10.1186/s11658-017-0042-4
35. Cabinian A, Sinsimer D, Tang M, Zumba O, Mehta H, Toma A, Sant'Angelo D, Laouar Y, Laouar A. Transfer of Maternal Immune Cells by Breastfeeding: Maternal Cytotoxic T Lymphocytes Present in Breast Milk Localize in the Peyer's Patches of the Nursed Infant. PLoS One [Internet] 2016 [cited 2022 Aug 4]; 11:e0156762. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0156762
36. Arvola M, Gustafsson E, Svensson L, Jansson L, Holmdahl R, Heyman B, Okabe M, Mattsson R. Immunoglobulin-Secreting Cells of Maternal Origin Can Be Detected in B Cell-Deficient Mice1. Biol Reprod 2000; 63:1817–24.
37. Field CJ. The Immunological Components of Human Milk and Their Effect on Immune Development in Infants. J Nutr [Internet] 2005 [cited 2023 Jan 8]; 135:1–4. Available from: https://academic.oup.com/jn/article/135/1/1/4663581
38. Tuaillon E, Valea D, Becquart P, Tabaa Y Al, Meda N, Bollore K, Perre P Van de, Vendrell J-P. Human Milk-Derived B Cells: A Highly Activated Switched Memory Cell Population Primed to Secrete Antibodies. The Journal of Immunology [Internet] 2009 [cited 2022 Sep 14]; 182:7155–62. Available from: https://www.jimmunol.org/content/182/11/7155
39. Atyeo C, Alter G. The multifaceted roles of breast milk antibodies. Cell 2021; 184:1486–99.
40. Ballard O, Morrow AL. Human Milk Composition: Nutrients and Bioactive Factors. Pediatr Clin North Am [Internet] 2013 [cited 2022 Aug 6]; 60:49. Available from: /pmc/articles/PMC3586783/
41. Oddy WH, Rosales F. A systematic review of the importance of milk TGF-β on immunological outcomes in the infant and young child. Pediatric Allergy and Immunology 2010; 21:47–59.
42. Järvinen KM, Suárez-Fariñas M, Savilahti E, Sampson HA, Berin MC. Immune factors in breast milk related to infant milk allergy are independent of maternal atopy. J Allergy Clin

Immunol [Internet] 2015 [cited 2022 Dec 16]; 135:1390. Available from: /pmc/articles/PMC4426237/
43. Sitarik AR, Bobbitt KR, Havstad SL, Fujimura KE, Levin AM, Zoratti EM, Kim H, Woodcroft KJ, Wegienka G, Ownby DR, et al. Breast Milk Transforming Growth Factor β Is Associated With Neonatal Gut Microbial Composition. J Pediatr Gastroenterol Nutr 2017; 65:e60–7.
44. Rautava S, Nanthakumar NN, Dubert-Ferrandon A, Lu L, Rautava J, Walker WA. Breast Milk-Transforming Growth Factor-β2 Specifically Attenuates IL-1β-Induced Inflammatory Responses in the Immature Human Intestine via an SMAD6- and ERK-Dependent Mechanism. Neonatology [Internet] 2011 [cited 2022 Dec 15]; 99:192. Available from: /pmc/articles/PMC3214931/
45. Hoeflich A, Meyer Z. Functional analysis of the IGF-system in milk. Best Pract Res Clin Endocrinol Metab 2017; 31:409–18.
46. Riskin A, Almog M, Peri R, Halasz K, Srugo I, Kessel A. Changes in immunomodulatory constituents of human milk in response to active infection in the nursing infant. Pediatr Res 2012; 71:220–5.
47. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int J Mol Sci [Internet] 2021 [cited 2023 Nov 16]; 22:1–16. Available from: /pmc/articles/PMC7962638/
48. Manzoni P. Clinical Benefits of Lactoferrin for Infants and Children. Journal of Pediatrics [Internet] 2016 [cited 2022 Sep 9]; 173:S43–52. Available from: http://www.jpeds.com/article/S0022347616002985/fulltext
49. Ellison RT, Giehl TJ. Killing of gram-negative bacteria by lactoferrin and lysozyme. J Clin Invest 1991; 88:1080–91.
50. Vega-Bautista A, de la Garza M, Carrero JC, Campos-Rodríguez R, Godínez-Victoria M, Drago-Serrano ME. The Impact of Lactoferrin on the Growth of Intestinal Inhabitant Bacteria. Int J Mol Sci [Internet] 2019 [cited 2022 Sep 13]; 20. Available from: /pmc/articles/PMC6801499/
51. Demers-Mathieu V, Huston RK, Markell AM, McCulley EA, Martin RL, Spooner M, Dallas DC. Differences in Maternal Immunoglobulins within Mother's Own Breast Milk and Donor Breast Milk and across Digestion in Preterm Infants. Nutrients 2019; 11:920.
52. Takemura T, Eishi Y. Distribution of secretory component and immunoglobulins in the developing lung. Am Rev Respir Dis 1985; 131:125–30.
53. Granato A, Chen Y, Wesemann DR. Primary immunoglobulin repertoire development: time and space matter. Curr Opin Immunol [Internet] 2015 [cited 2022 Sep 15]; 33:126. Available from: /pmc/articles/PMC4414491/
54. Donald K, Petersen C, Turvey SE, Finlay BB, Azad MB. Secretory IgA: Linking microbes, maternal health, and infant health through human milk. Cell Host Microbe 2022; 30:650–9.
55. Dzidic M, Mira A, Artacho A, Abrahamsson TR, Jenmalm MC, Collado MC. Allergy development is associated with consumption of breastmilk with a reduced microbial richness in the first month of life. Pediatric Allergy and Immunology [Internet] 2020 [cited 2022 Dec 16]; 31:250–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/pai.13176

56. Koch MA, Reiner GL, Lugo KA, Kreuk LSM, Stanbery AG, Ansaldo E, Seher TD, Ludington WB, Barton GM. Maternal IgG and IgA Antibodies Dampen Mucosal T Helper Cell Responses in Early Life. Cell [Internet] 2016 [cited 2022 Sep 14]; 165:827–41. Available from: http://www.cell.com/article/S0092867416305001/fulltext
57. Verhasselt V. Neonatal tolerance under breastfeeding influence. Curr Opin Immunol [Internet] 2010 [cited 2022 Aug 4]; 22:623–30. Available from: https://pubmed.ncbi.nlm.nih.gov/20851590/
58. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, Ross MC, Lloyd RE, Doddapaneni HV, Metcalf GA, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature [Internet] 2018 [cited 2022 Aug 6]; 562:583–8. Available from: https://pubmed.ncbi.nlm.nih.gov/30356187/
59. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. Cell Host Microbe 2015; 17:690–703.
60. Davis EC, Dinsmoor AM, Wang M, Donovan SM. Microbiome Composition in Pediatric Populations from Birth to Adolescence: Impact of Diet and Prebiotic and Probiotic Interventions. Dig Dis Sci [Internet] 2020 [cited 2022 Aug 29]; 65:706. Available from: /pmc/articles/PMC7046124/
61. Moossavi S, Sepehri S, Robertson B, Bode L, Goruk S, Field CJ, Lix LM, de Souza RJ, Becker AB, Mandhane PJ, et al. Composition and Variation of the Human Milk Microbiota Are Influenced by Maternal and Early-Life Factors. Cell Host Microbe 2019; 25.
62. Treven P, Mahnič A, Rupnik M, Golob M, Pirš T, Matijašić BB, Lorbeg PM. Evaluation of Human Milk Microbiota by 16S rRNA Gene Next-Generation Sequencing (NGS) and Cultivation/MALDI-TOF Mass Spectrometry Identification. Front Microbiol 2019; 10:2612.
63. Moossavi S, Azad MB. Origins of human milk microbiota: new evidence and arising questions. Gut Microbes [Internet] 2020 [cited 2022 Aug 6]; 12:1667722. Available from: /pmc/articles/PMC7524145/
64. Stinson LF, Trevenen ML, Geddes DT. The Viable Microbiome of Human Milk Differs from the Metataxonomic Profile. Nutrients 2021, Vol 13, Page 4445 [Internet] 2021 [cited 2022 Sep 11]; 13:4445. Available from: https://www.mdpi.com/2072-6643/13/12/4445/htm
65. Bode L. Human milk oligosaccharides: Every baby needs a sugar mama. Glycobiology [Internet] 2012 [cited 2022 Sep 11]; 22:1147. Available from: /pmc/articles/PMC3406618/
66. Almeida CC, Mendonça Pereira BF, Leandro KC, Costa MP, Spisso BF, Conte-Junior CA. Bioactive Compounds in Infant Formula and Their Effects on Infant Nutrition and Health: A Systematic Literature Review. Int J Food Sci [Internet] 2021 [cited 2022 Sep 11]; 2021. Available from: /pmc/articles/PMC8140835/
67. Lee H, Padhi E, Hasegawa Y, Larke J, Parenti M, Wang A, Hernell O, Lönnerdal B, Slupsky C. Compositional dynamics of the milk fat globule and its role in infant development. Front Pediatr 2018; 6:313.
68. Calder PC. Functional Roles of Fatty Acids and Their Effects on Human Health. Journal of Parenteral and Enteral Nutrition [Internet] 2015 [cited 2022 Dec 17]; 39:18S-32S.

Available from: https://onlinelibrary-wiley-com.uml.idm.oclc.org/doi/full/10.1177/0148607115595980
69. Moossavi S, Atakora F, Miliku K, Sepehri S, Robertson B, Duan QL, Becker AB, Mandhane PJ, Turvey SE, Moraes TJ, et al. Integrated analysis of human milk microbiota with oligosaccharides and fatty acids in the child cohort. Front Nutr 2019; 6:58.
70. Churchward CP, Alany RG, Snyder LAS. Alternative antimicrobials: the properties of fatty acids and monoglycerides. https://doi-org.uml.idm.oclc.org/101080/1040841X20181467875 [Internet] 2018 [cited 2022 Dec 17]; 44:561–70. Available from: https://www-tandfonline-com.uml.idm.oclc.org/doi/abs/10.1080/1040841X.2018.1467875
71. Perez-Burillo S, Rajakaruna S, Paliy O. Growth of Bifidobacterium species is inhibited by free fatty acids and bile salts but not by glycerides. AIMS Microbiol [Internet] 2022 [cited 2022 Dec 17]; 8:53. Available from: /pmc/articles/PMC8995189/
72. Bobiński R, Bobińska J. Fatty acids of human milk – a review. https://doi.org/101024/0300-9831/a000651 [Internet] 2020 [cited 2022 Dec 17]; 92:280–91. Available from: https://econtent.hogrefe.com/doi/10.1024/0300-9831/a000651
73. Harbige LS. Fatty acids, the immune response, and autoimmunity: A question of n−6 essentiality and the balance between n−6 and n−3. Lipids [Internet] 2003 [cited 2023 Jan 6]; 38:323–41. Available from: https://onlinelibrary.wiley.com/doi/full/10.1007/s11745-003-1067-z
74. Walker WA, Iyengar RS. Breast milk, microbiota, and intestinal immune homeostasis. Pediatric Research 2015 77:1 [Internet] 2014 [cited 2022 Dec 17]; 77:220–8. Available from: https://www.nature.com/articles/pr2014160
75. Wegh CAM, Geerlings SY, Knol J, Roeselers G, Belzer C. Postbiotics and Their Potential Applications in Early Life Nutrition and Beyond. Int J Mol Sci [Internet] 2019 [cited 2022 Sep 10]; 20. Available from: /pmc/articles/PMC6801921/
76. Żółkiewicz J, Marzec A, Ruszczyński M, Feleszko W. Postbiotics—A Step Beyond Pre- and Probiotics. Nutrients [Internet] 2020 [cited 2022 Sep 15]; 12:1–17. Available from: /pmc/articles/PMC7468815/
77. Kataria J, Li N, Wynn JL, Neu J. Probiotic microbes: do they need to be alive to be beneficial? Nutr Rev 2009; 67:546–50.
78. Sugahara H, Yao R, Odamaki T, Xiao JZ. Differences between live and heat-killed bifidobacteria in the regulation of immune function and the intestinal environment. Benef Microbes 2017; 8:463–72.
79. Zagato E, Mileti E, Massimiliano L, Fasano F, Budelli A, Penna G, Rescigno M. Lactobacillus paracasei CBA L74 Metabolic Products and Fermented Milk for Infant Formula Have Anti-Inflammatory Activity on Dendritic Cells In Vitro and Protective Effects against Colitis and an Enteric Pathogen In Vivo. PLoS One [Internet] 2014 [cited 2022 Sep 14]; 9. Available from: /pmc/articles/PMC3919712/
80. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 2018; 9:388354.
81. Pittard WB, Geddes KM, Brown S, Mintz S, Hulsey TC. Bacterial contamination of human milk: container type and method of expression. Am J Perinatol [Internet] 1991 [cited 2022 Sep 11]; 8:25–7. Available from: https://pubmed.ncbi.nlm.nih.gov/1987962/
82. World Health Organization. World Health Statistics 2014. 2014;

83. Chan K, Labonté JM, Francis J, Zora H, Sawchuk S, Whitfield KC. Breastfeeding in Canada: predictors of initiation, exclusivity, and continuation from the 2017-2018 Canadian Community Health Survey.
84. Altobelli E, Angeletti PM, Verrotti A, Petrocelli R. The Impact of Human Milk on Necrotizing Enterocolitis: A Systematic Review and Meta-Analysis. Nutrients [Internet] 2020 [cited 2023 Sep 16]; 12:1–13. Available from: /pmc/articles/PMC7284425/
85. Alotiby AA. The role of breastfeeding as a protective factor against the development of the immune-mediated diseases: A systematic review. Front Pediatr [Internet] 2023 [cited 2023 Sep 16]; 11. Available from: /pmc/articles/PMC9981158/
86. Pena-Leon V, Folgueira C, Barja-Fernández S, Pérez-Lois R, Da Silva Lima N, Martin M, Heras V, Martinez-Martinez S, Valero P, Iglesias C, et al. Prolonged breastfeeding protects from obesity by hypothalamic action of hepatic FGF21. [cited 2023 Aug 27]; Available from: https://doi.org/10.1038/s42255-022-00602-z
87. Krol KM, Grossmann T. Psychological effects of breastfeeding on children and mothers. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz [Internet] 2018 [cited 2023 Sep 2]; 61:977. Available from: /pmc/articles/PMC6096620/
88. Ehlaye MS, Bener A. Duration of breast-feeding and the risk of childhood allergic diseases in a developing country. Allergy Asthma Proc [Internet] 2008 [cited 2023 Sep 2]; 29:386–91. Available from: https://pubmed.ncbi.nlm.nih.gov/18702886/
89. Hossain S, Mihrshahi S. Exclusive Breastfeeding and Childhood Morbidity: A Narrative Review. Int J Environ Res Public Health [Internet] 2022 [cited 2023 Sep 25]; 19:14804. Available from: /pmc/articles/PMC9691199/
90. Khan MN, Islam MM. Effect of exclusive breastfeeding on selected adverse health and nutritional outcomes: A nationally representative study. BMC Public Health [Internet] 2017 [cited 2023 Sep 25]; 17:1–7. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-017-4913-4
91. Alotiby AA. The role of breastfeeding as a protective factor against the development of the immune-mediated diseases: A systematic review. Front Pediatr [Internet] 2023 [cited 2023 Sep 2]; 11. Available from: /pmc/articles/PMC9981158/
92. Liu F, Lv D, Wang L, Feng X, Zhang R, Liu W, Han W. Breastfeeding and overweight/obesity among children and adolescents: a cross-sectional study. BMC Pediatr [Internet] 2022 [cited 2023 Nov 16]; 22. Available from: /pmc/articles/PMC9202207/
93. Moore S, Prentice A, Wagatsuma Y, Fulford A, Collinson A, Raqib R, Vahter M, Persson L, Arifeen S. Early-life nutritional and environmental determinants of thymic size in infants born in rural Bangladesh. Acta Paediatr 2009; 98:1168–75.
94. Nabukeera-Barungi N, Lanyero B, Grenov B, Friis H, Namusoke H, Mupere E, Michaelsen KF, Mølgaard C, Wiese M, Nielsen DS, et al. Thymus size and its correlates among children admitted with severe acute malnutrition: a cross-sectional study in Uganda. BMC Pediatr 2021; 21:1.
95. Jeppesen DL, Hasselbalch H, Lisse IM, Ersboll AK, Engelmann MDM. T-lymphocyte subsets, thymic size and breastfeeding in infancy. Pediatric Allergy and Immunology 2004; 15:127–32.
96. Wood H, Acharjee A, Pearce H, Quraishi MN, Powell R, Rossiter A, Beggs A, Ewer A, Moss P, Toldi G. Breastfeeding promotes early neonatal regulatory T-cell expansion and immune tolerance of non-inherited maternal antigens. Allergy [Internet] 2021 [cited 2023

Aug 27]; 76:2447–60. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.14736
97. Eberl G. Immunity by equilibrium. Nat Rev Immunol 2016; 16:524–32.
98. Zhang J-M, An J. Cytokines, Inflammation, and Pain. Int Anesthesiol Clin 2007; 45.
99. Davis MM, Tato CM, Furman D. Systems immunology: just getting started. Nature Immunology 2017 18:7 [Internet] 2017 [cited 2023 Sep 2]; 18:725–32. Available from: https://www.nature.com/articles/ni.3768
100. Torres-Castro P, Abril-Gil M, Rodríguez-Lagunas M, Castell M, Pérez-Cano F, Franch À. TGF-β2, EGF, and FGF21 Growth Factors Present in Breast Milk Promote Mesenteric Lymph Node Lymphocytes Maturation in Suckling Rats. Nutrients 2018; 10:1171.
101. Torres-Castro P, Grases-Pintó B, Abril-Gil M, Castell M, Rodríguez-Lagunas MJ, Pérez-Cano FJ, Franch À. Modulation of the Systemic Immune Response in Suckling Rats by Breast Milk TGF-β2, EGF and FGF21 Supplementation. Nutrients 2020; 12:1888.
102. Trares K, Bhardwaj M, Perna L, Stocker H, Petrera A, Hauck SM, Beyreuther K, Brenner H, Schöttker B. Association of the inflammation-related proteome with dementia development at older age: results from a large, prospective, population-based cohort study. Alzheimers Res Ther [Internet] 2022 [cited 2023 Sep 25]; 14. Available from: /pmc/articles/PMC9461133/
103. Siegmund B, Ryan R, Abreu MT, Vermeire S, Dotan I, Goetsch M, Crosby C, Woolcott J, Komori HK, Danese S. P574 Characterization of plasma inflammatory protein abundance in patients with ulcerative colitis treated with etrasimod: an exploratory analysis of the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials. J Crohns Colitis [Internet] 2023 [cited 2023 Sep 25]; 17:i700–1. Available from: https://dx.doi.org/10.1093/ecco-jcc/jjac190.0704
104. Zhao J, Schank M, Wang L, Dang X, Cao D, Khanal S, Nguyen LNT, Zhang Y, Wu XY, Adkins JL, et al. Plasma biomarkers for systemic inflammation in COVID-19 survivors. Proteomics Clin Appl [Internet] 2022 [cited 2023 Sep 25]; 16:2200031. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/prca.202200031
105. Sears M, Lefebvre D, Duncan J, Quinn M. CHILD study webpage [Internet]. [cited 2023 Jun 25]; Available from: http://www.canadianchildstudy.ca/
106. Moraes TJ, Lefebvre DL, Chooniedass R, Becker AB, Brook JR, Denburg J, Hayglass KT, Hegele RG, Kollmann TR, Macri J, et al. The canadian healthy infant longitudinal development birth cohort study: Biological samples and biobanking. Paediatr Perinat Epidemiol [Internet] 2015 [cited 2023 Jun 25]; 29:84–92. Available from: https://onlinelibrary-wiley-com.uml.idm.oclc.org/doi/full/10.1111/ppe.12161
107. Takaro TK, Scott JA, Allen RW, Anand SS, Becker AB, Befus AD, Brauer M, Duncan J, Lefebvre DL, Lou W, et al. The Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study: assessment of environmental exposures. J Expo Sci Environ Epidemiol [Internet] 2015 [cited 2023 Jun 25]; 25:580. Available from: /pmc/articles/PMC4611361/
108. Fink AL, Klein SL. The evolution of greater humoral immunity in females than males: implications for vaccine efficacy. Curr Opin Physiol [Internet] 2018 [cited 2023 Jun 26]; 6:16–20. Available from: /pmc/articles/PMC6181235/
109. Ramsey JM, Cooper JD, Penninx BWJH, Bahn S. Variation in serum biomarkers with sex and female hormonal status: implications for clinical tests. Sci Rep 2016; 6:26947.

110. Wooldridge AL, McMillan M, Kaur M, Giles LC, Marshall HS, Gatford KL. Relationship between birth weight or fetal growth rate and postnatal allergy: A systematic review. Journal of Allergy and Clinical Immunology 2019; 144:1703–13.
111. Jain N. The early life education of the immune system: Moms, microbes and (missed) opportunities. Gut Microbes [Internet] 2020 [cited 2023 Jun 26]; 12. Available from: /pmc/articles/PMC7781677/
112. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and risk of allergic rhinitis in young adulthood. Journal of Allergy and Clinical Immunology 2011; 127:1173–9.
113. Shekhar S, Petersen FC. The Dark Side of Antibiotics: Adverse Effects on the Infant Immune Defense Against Infection. Front Pediatr [Internet] 2020 [cited 2023 Jun 26]; 8:544460. Available from: /pmc/articles/PMC7593395/
114. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. Nature [Internet] 2008 [cited 2023 Jun 26]; 454:445. Available from: /pmc/articles/PMC3573758/
115. Laupèze B, Del Giudice G, Doherty MT, Van der Most R. Vaccination as a preventative measure contributing to immune fitness. NPJ Vaccines [Internet] 2021 [cited 2023 Jun 26]; 6. Available from: /pmc/articles/PMC8316335/
116. Song SJ, Dominguez-Bello MG, Knight R. How delivery mode and feeding can shape the bacterial community in the infant gut. CMAJ : Canadian Medical Association Journal [Internet] 2013 [cited 2023 Sep 20]; 185:373. Available from: /pmc/articles/PMC3602250/
117. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clinical & Experimental Allergy 2008; 38:629–33.
118. Neerven RJJ van, Savelkoul H. Nutrition and Allergic Diseases. Nutrients 2017; 9.
119. Calder PC, Krauss-Etschmann S, de Jong EC, Dupont C, Frick J-S, Frokiaer H, Heinrich J, Garn H, Koletzko S, Lack G, et al. Early nutrition and immunity - progress and perspectives. Br J Nutr 2006; 96:774–90.
120. El-Heneidy A, Abdel-Rahman M, Mihala G, Ross L, Comans T. Milk Other Than Breast Milk and the Development of Asthma in Children 3 Years of Age. A Birth Cohort Study (2006–2011). Nutrients 2018; 10:1798.
121. Al Nabhani Z, Dulauroy S, Marques R, Cousu C, Al Bounny S, Déjardin F, Sparwasser T, Bérard M, Cerf-Bensussan N, Eberl G. A Weaning Reaction to Microbiota Is Required for Resistance to Immunopathologies in the Adult. Immunity 2019; 50:1276-1288.e5.
122. Bauer RN, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: The role of Toll-like receptors and nucleotide-binding oligomerization domain–like receptors. J Allergy Clin Immunol [Internet] 2012 [cited 2023 Jun 26]; 129:14. Available from: /pmc/articles/PMC4341993/
123. Laursen MF, Zachariassen G, Bahl MI, Bergström A, Host A, Michaelsen KF, Licht TR. Having older siblings is associated with gut microbiota development during early childhood. BMC Microbiol [Internet] 2015 [cited 2023 Jun 26]; 15. Available from: /pmc/articles/PMC4522135/
124. Azad MB, Lissitsyn Y, Miller GE, Becker AB, HayGlass KT, Kozyrskyj AL. Influence of Socioeconomic Status Trajectories on Innate Immune Responsiveness in Children. PLoS One [Internet] 2012 [cited 2023 Jun 26]; 7:38669. Available from: /pmc/articles/PMC3369855/

125. Nafstad P, Magnus P, Gaarder PI, Jaakkola JJK. Exposure to pets and atopy-related diseases in the first 4 years of life. Allergy [Internet] 2001 [cited 2023 Jun 26]; 56:307–12. Available from: https://pubmed.ncbi.nlm.nih.gov/11284797/
126. Abraham RA, Agrawal PK, Acharya R, Sarna A, Ramesh S, Johnston R, de Wagt A, Khan N, Porwal A, Kurundkar SB, et al. Effect of temperature and time delay in centrifugation on stability of select biomarkers of nutrition and non-communicable diseases in blood samples. Biochem Med (Zagreb) 2019; 29:020708.
127. Levenson D, Romero R, Garcia-Flores V, Miller D, Xu Y, Sahi A, Hassan SS, Gomez-Lopez N. The effects of advanced maternal age on T-cell subsets at the maternal–fetal interface prior to term labor and in the offspring: a mouse study. Clin Exp Immunol [Internet] 2020 [cited 2023 Jun 26]; 201:58. Available from: /pmc/articles/PMC7290081/
128. Pasetti MF, Ackerman ME, Hoen AG, Alter G, Tsang JS, Marchant A. Maternal determinants of infant immunity: implications for effective immunization and maternal-child health. Vaccine [Internet] 2020 [cited 2023 Jun 26]; 38:4491. Available from: /pmc/articles/PMC9946685/
129. Bennett T. Marital status and infant health outcomes. Soc Sci Med [Internet] 1992 [cited 2023 Jun 26]; 35:1179–87. Available from: https://pubmed.ncbi.nlm.nih.gov/1439936/
130. Noghanibehambari H, Salari M, Tavassoli N. Maternal human capital and infants' health outcomes: Evidence from minimum dropout age policies in the US. SSM Popul Health [Internet] 2022 [cited 2023 Jun 26]; 19:101163. Available from: /pmc/articles/PMC9287432/
131. Yeyeodu ST, Kidd LCR, Sean Kimbro K. Protective Innate Immune Variants in Racial/Ethnic Disparities of Breast and Prostate Cancer. Cancer Immunol Res [Internet] 2019 [cited 2023 Jun 26]; 7:1384. Available from: /pmc/articles/PMC6730653/
132. Chahal N, McLain AC, Ghassabian A, Michels KA, Bell EM, Lawrence DA, Yeung EH. Maternal Smoking and Newborn Cytokine and Immunoglobulin Levels. Nicotine & Tobacco Research [Internet] 2017 [cited 2023 Jun 26]; 19:789. Available from: /pmc/articles/PMC5939663/
133. Sunyer J, Garcia-Esteban R, Castilla AM, Aurrekoetxea JJ, Iñiguez C, Tardón A, Espada M, Lertxundi A, Chatzi L, Rebagliato M, et al. Exposure to second-hand smoke and reproductive outcomes depending on maternal asthma. European Respiratory Journal [Internet] 2012 [cited 2023 Jun 26]; 40:371–6. Available from: https://erj.ersjournals.com/content/40/2/371
134. Gauthier TW. Prenatal Alcohol Exposure and the Developing Immune System. Alcohol Res [Internet] 2015 [cited 2023 Jun 26]; 37:279. Available from: /pmc/articles/PMC4590623/
135. Hurley KM, Oberlander SE, Merry BC, Wrobleski MM, Klassen AC, Black MM. The Healthy Eating Index and Youth Healthy Eating Index Are Unique, Nonredundant Measures of Diet Quality among Low-Income, African American Adolescents. J Nutr [Internet] 2009 [cited 2023 Jun 26]; 139:359. Available from: /pmc/articles/PMC2646206/
136. Azad MB, Sharma AK, De Souza RJ, Dolinsky VW, Becker AB, Mandhane PJ, Turvey SE, Subbarao P, Lefebvre DL, Sears MR, et al. Association Between Artificially Sweetened Beverage Consumption During Pregnancy and Infant Body Mass Index. JAMA Pediatr [Internet] 2016 [cited 2023 Sep 19]; 170:662–70. Available from: https://jamanetwork-com.uml.idm.oclc.org/journals/jamapediatrics/fullarticle/2521471

137. Prentice S. They Are What You Eat: Can Nutritional Factors during Gestation and Early Infancy Modulate the Neonatal Immune Response? Front Immunol [Internet] 2017 [cited 2023 Jun 26]; 8. Available from: /pmc/articles/PMC5712338/
138. Wilson RM, Messaoudi I. The impact of maternal obesity during pregnancy on offspring immunity. Mol Cell Endocrinol [Internet] 2015 [cited 2023 Jun 26]; 418:134. Available from: /pmc/articles/PMC4674375/
139. Cook-Mills JM. Maternal Influences over Offspring Allergic Responses. Curr Allergy Asthma Rep [Internet] 2015 [cited 2023 Jun 26]; 15:501. Available from: /pmc/articles/PMC4445968/
140. Barrett EG, Rudolph K, Bowen LE, Bice DE. Parental allergic status influences the risk of developing allergic sensitization and an asthmatic-like phenotype in canine offspring. Immunology [Internet] 2003 [cited 2023 Jun 26]; 110:493. Available from: /pmc/articles/PMC1783065/
141. Milcic TL. The Complete Blood Count. Neonatal Network [Internet] 2010 [cited 2023 Jun 25]; 29:109–15. Available from: https://connect.springerpub.com/content
142. Pediatric Reference Ranges [Internet]. [cited 2023 Jun 25]; Available from: https://www.healthcare.uiowa.edu/path_handbook/appendix/heme/pediatric_normals.html
143. Olink Proteomics. Target 96 Inflammation [white paper] [Internet]. 2021 [cited 2023 Jun 25]; Available from: https://www.olink.com/content/uploads/2021/09/1029-v1.3-inflammation-panel-content.pdf
144. Olink Proteomics. PEA – a high-multiplex immunoassay technology with qPCR or NGS readout [Internet]. 2021 [cited 2023 Jun 25]; Available from: https://www.olink.com/content/uploads/2021/09/olink-white-paper-pea-a-high-multiplex-immunoassay-technology-with-qpcr-or-ngs-readout-v1.0.pdf
145. Olink Proteomics. Data normalization and standardization [white paper]. [Internet]. Olink Proteomics.2022 [cited 2023 Jun 25]; Available from: https://olink.com/application/data-normalization-and-standardization/
146. Olink. Olink Target 96 Inflammation [Internet]. 2021 [cited 2021 Nov 26]; Available from: https://www.olink.com/products-services/target/inflammation/
147. Yi H, Raman AT, Zhang H, Allen GI, Liu Z. Detecting hidden batch factors through data-adaptive adjustment for biological effects. Bioinformatics [Internet] 2018 [cited 2023 Sep 17]; 34:1141. Available from: /pmc/articles/PMC6454417/
148. removeBatchEffect: Remove Batch Effect in limma: Linear Models for Microarray Data [Internet]. [cited 2023 Jun 25]; Available from: https://rdrr.io/bioc/limma/man/removeBatchEffect.html
149. Olink Proteomics. How is the Limit of Detection (LOD) estimated and how is this handled in the data analysis? [Internet]. 2023 [cited 2023 Jun 25]; Available from: https://olink.com/faq/how-is-the-limit-of-detection-lod-estimated-and-handled/
150. RStudio Team - RStudio [Internet]. [cited 2023 Jun 25]; Available from: https://www.rstudio.com/authors/rstudio-team/
151. CRAN - Package dplyr [Internet]. [cited 2023 Jun 25]; Available from: https://cran.r-project.org/web/packages/dplyr/index.html
152. CRAN - Package tidyr [Internet]. [cited 2023 Jun 25]; Available from: https://cran.r-project.org/web/packages/tidyr/index.html
153. lm function - RDocumentation [Internet]. [cited 2023 Jun 25]; Available from: https://www.rdocumentation.org/packages/stats/versions/3.6.2/topics/lm

154. CRAN - Package glmnet [Internet]. [cited 2023 Jun 25]; Available from: https://cran.r-project.org/web/packages/glmnet/index.html
155. CRAN - Package tidyverse [Internet]. [cited 2023 Jun 25]; Available from: https://cran.r-project.org/web/packages/tidyverse/index.html
156. CRAN - Package vegan [Internet]. [cited 2023 Jun 25]; Available from: https://cran.r-project.org/web/packages/vegan/index.html
157. CRAN - Package ggplot2 [Internet]. [cited 2023 Aug 28]; Available from: https://cran.r-project.org/web/packages/ggplot2/index.html
158. Chen SY, Feng Z, Yi X. A general introduction to adjustment for multiple comparisons. J Thorac Dis [Internet] 2017 [cited 2023 Jun 26]; 9:1725. Available from: /pmc/articles/PMC5506159/
159. Platt RW. ANOVA, t tests, and linear regression. Injury Prevention [Internet] 1998 [cited 2023 Jun 26]; 4:52. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1730336/
160. Zhang Z. Too much covariates in a multivariable model may cause the problem of overfitting. J Thorac Dis [Internet] 2014 [cited 2023 Jun 26]; 6:E196. Available from: /pmc/articles/PMC4178069/
161. Trares K, Bhardwaj M, Perna L, Stocker H, Petrera A, Hauck SM, Beyreuther K, Brenner H, Schöttker B. Association of the inflammation-related proteome with dementia development at older age: results from a large, prospective, population-based cohort study. Alzheimers Res Ther [Internet] 2022 [cited 2023 Jun 25]; 14:1–17. Available from: https://alzres.biomedcentral.com/articles/10.1186/s13195-022-01063-y
162. Haq Z, Yang D, Psaras C, Stewart JM. Sex-Based Analysis of Potential Inflammation-Related Protein Biomarkers in the Aqueous Humor of Patients With Diabetes Mellitus. Transl Vis Sci Technol [Internet] 2021 [cited 2023 Jun 25]; 10:1–8. Available from: /pmc/articles/PMC7961117/
163. Erfani N, Maleki S, Zakian A, Yazdkhasti M. Evaluation of the effects of time and ambient temperature on the concentration stability of β-hydroxybutyrate and total protein in serum and plasma samples of sheep: a preliminary study about technical method. Comp Clin Path [Internet] 2023 [cited 2023 Nov 16]; 32:211–6. Available from: https://link.springer.com/article/10.1007/s00580-022-03427-0
164. R: Step Function [Internet]. [cited 2023 Jun 26]; Available from: https://search.r-project.org/CRAN/refmans/emdi/html/step.html
165. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. Fam Med Community Health [Internet] 2020 [cited 2023 Jun 26]; 8:262. Available from: /pmc/articles/PMC7032893/
166. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Müller M. pROC: An open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011; 12.
167. Type Package Title Display and Analyze ROC Curves. 2023 [cited 2023 Sep 23]; Available from: https://github.com/xrobin/pROC/issues
168. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: Current methods and applications. BMC Med Res Methodol [Internet] 2017 [cited 2023 Jun 25]; 17:1–19. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0332-6

169. Xia J, Broadhurst DI, Wilson M, Wishart DS. Translational biomarker discovery in clinical metabolomics: an introductory tutorial. Metabolomics [Internet] 2013 [cited 2023 Aug 27]; 9:280. Available from: /pmc/articles/PMC3608878/
170. Lourenço AG, Komesu MC, Duarte G, Del Ciampo LA, Mussi-Pinhata MM, Yamamoto AY. High Levels of Chemokine C-C Motif Ligand 20 in Human Milk and Its Production by Oral Keratinocytes. Breastfeed Med 2017; 12:116–21.
171. Maheshwari A, Christensen RD, Calhoun DA. ELR+ CXC chemokines in human milk. Cytokine 2003; 24:91–102.
172. Gavaldà-Navarro A, Hondares E, Giralt M, Mampel T, Iglesias R, Villarroya F. Fibroblast growth factor 21 in breast milk controls neonatal intestine function. Sci Rep 2015; 5:13717.
173. Izadpanah A, Dwinell MB, Eckmann L, Varki NM, Kagnoff MF. Regulated MIP-3alpha/CCL20 production by human intestinal epithelium: mechanism for modulating mucosal immunity. Am J Physiol Gastrointest Liver Physiol [Internet] 2001 [cited 2023 Aug 27]; 280. Available from: https://pubmed.ncbi.nlm.nih.gov/11254498/
174. Sokol CL, Luster AD. The Chemokine System in Innate Immunity. Cold Spring Harb Perspect Biol [Internet] 2015 [cited 2023 Aug 27]; 7:1–20. Available from: /pmc/articles/PMC4448619/
175. Liu J, Zhang N, Li Q, Zhang W, Ke F, Leng Q, Wang H, Chen J, Wang H. Tumor-Associated Macrophages Recruit CCR6+ Regulatory T Cells and Promote the Development of Colorectal Cancer via Enhancing CCL20 Production in Mice. PLoS One [Internet] 2011 [cited 2023 Aug 27]; 6:e19495. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0019495
176. Lee AYS, Eri R, Lyons AB, Grimm MC, Korner H. CC Chemokine Ligand 20 and Its Cognate Receptor CCR6 in Mucosal T Cell Immunology and Inflammatory Bowel Disease: Odd Couple or Axis of Evil? Front Immunol [Internet] 2013 [cited 2023 Aug 27]; 4. Available from: /pmc/articles/PMC3711275/
177. Na H, Cho M, Chung Y. Regulation of Th2 Cell Immunity by Dendritic Cells. Immune Netw [Internet] 2016 [cited 2023 Nov 16]; 16:1. Available from: /pmc/articles/PMC4770095/
178. Zehra S, Khambati I, Vierhout M, Mian MF, Buck R, Forsythe P. Human Milk Oligosaccharides Attenuate Antigen–Antibody Complex Induced Chemokine Release from Human Intestinal Epithelial Cell Lines. J Food Sci [Internet] 2018 [cited 2023 Aug 27]; 83:499–508. Available from: https://onlinelibrary-wiley-com.uml.idm.oclc.org/doi/full/10.1111/1750-3841.14039
179. Sibartie S, O'Hara AM, Ryan J, Fanning Á, O'Mahony J, O'Neill S, Sheil B, O'Mahony L, Shanahan F. Modulation of pathogen-induced CCL20 secretion from HT-29 human intestinal epithelial cells by commensal bacteria. BMC Immunol [Internet] 2009 [cited 2023 Sep 21]; 10:54. Available from: /pmc/articles/PMC2763856/
180. Williams IR. CCR6 and CCL20: partners in intestinal immunity and lymphorganogenesis. Ann N Y Acad Sci 2006; 1072:52–61.
181. Kaser A, Ludwiczek O, Holzmann S, Moschen AR, Weiss G, Enrich B, Graziadei I, Dunzendorfer S, Wiedermann CJ, Mürzl E, et al. Increased expression of CCL20 in human inflammatory bowel disease. J Clin Immunol [Internet] 2004 [cited 2023 Aug 27]; 24:74–85. Available from: https://pubmed.ncbi.nlm.nih.gov/14997037/

182. Crane-Godreau MA, Wira CR. CCL20/Macrophage Inflammatory Protein 3α and Tumor Necrosis Factor Alpha Production by Primary Uterine Epithelial Cells in Response to Treatment with Lipopolysaccharide or Pam3Cys. Infect Immun [Internet] 2005 [cited 2023 Sep 7]; 73:476. Available from: /pmc/articles/PMC538962/
183. Agresta L, Hoebe KHN, Janssen EM. The Emerging Role of CD244 Signaling in Immune Cells of the Tumor Microenvironment. Front Immunol 2018; 9.
184. Dung NT, Van Chi P. A survey of membrane proteins in human serum. Proteomics Insights 2012; 5:1–19.
185. Köstlin-Gille N, Flaig L-A, Ginzel M, Arand J, Poets CF, Gille C. Granulocytic Myeloid-Derived Suppressor Cells in Breast Milk (BM-MDSC) Correlate with Gestational Age and Postnatal Age and Are Influenced by Infant's Sex. Nutrients 2020; 12:2571.
186. Wuyts A, Struyf S, Gijsbers K, Schutyser E, Put W, Conings R, Lenaerts JP, Geboes K, Opdenakker G, Menten P, et al. The CXC Chemokine GCP-2/CXCL6 Is Predominantly Induced in Mesenchymal Cells by Interleukin-1β and Is Down-Regulated by Interferon-γ: Comparison with Interleukin-8/CXCL8. Laboratory Investigation [Internet] 2003 [cited 2023 Aug 27]; 83:23–34. Available from: http://www.laboratoryinvestigation.org/article/S0023683722035905/fulltext
187. Sun MY, Wang SJ, Li XQ, Shen YL, Lu JR, Tian XH, Rahman K, Zhang LJ, Nian H, Zhang H. CXCL6 promotes renal interstitial fibrosis in diabetic nephropathy by activating JAK/STAT3 signaling pathway. Front Pharmacol [Internet] 2019 [cited 2023 Aug 27]; 10. Available from: /pmc/articles/PMC6442023/
188. Mittal P, Romero R, Kusanovic JP, Edwin SS, Gotsch F, Mazaki-Tovi S, Espinoza J, Erez O, Nhan-Chang C-L, Than NG, et al. ORIGINAL ARTICLE: CXCL6 (Granulocyte Chemotactic Protein-2): A Novel Chemokine Involved in the Innate Immune Response of the Amniotic Cavity. American Journal of Reproductive Immunology 2008; 60:246–57.
189. Sánchez B, González-Rodríguez I, Arboleya S, López P, Suárez A, Ruas-Madiedo P, Margolles A, Gueimonde M. The Effects of Bifidobacterium breve on Immune Mediators and Proteome of HT29 Cells Monolayers. Biomed Res Int [Internet] 2015 [cited 2023 Sep 21]; 2015. Available from: /pmc/articles/PMC4352474/
190. Linge HM, Collin M, Nordenfelt P, Mörgelin M, Malmsten M, Egesten A. The Human CXC Chemokine Granulocyte Chemotactic Protein 2 (GCP-2)/CXCL6 Possesses Membrane-Disrupting Properties and Is Antibacterial. Antimicrob Agents Chemother 2008; 52:2599–607.
191. Liu G, An L, Zhang H, Du P, Sheng Y. Activation of CXCL6/CXCR1/2 Axis Promotes the Growth and Metastasis of Osteosarcoma Cells in vitro and in vivo. Front Pharmacol 2019; 10.
192. Weiss ARR, Dahlke MH. Immunomodulation by Mesenchymal Stem Cells (MSCs): Mechanisms of Action of Living, Apoptotic, and Dead MSCs. Front Immunol 2019; 10.
193. Tezze C, Romanello V, Sandri M. FGF21 as Modulator of Metabolism in Health and Disease. Front Physiol 2019; 10:419.
194. Gavaldà-Navarro A, Hondares E, Giralt M, Mampel T, Iglesias R, Villarroya F. Fibroblast growth factor 21 in breast milk controls neonatal intestine function. Sci Rep 2015; 5:13717.
195. Coate KC, Hernandez G, Thorne CA, Sun S, Le TDV, Vale K, Kliewer SA, Mangelsdorf DJ. FGF21 is an Exocrine Pancreas Secretagogue. Cell Metab [Internet] 2017 [cited 2023 Sep 7]; 25:472. Available from: /pmc/articles/PMC5299054/

196. Nakayama Y, Masuda Y, Ohta H, Tanaka T, Washida M, Nabeshima YI, Miyake A, Itoh N, Konishi M. Fgf21 regulates T-cell development in the neonatal and juvenile thymus. Scientific Reports 2017 7:1 [Internet] 2017 [cited 2023 Nov 16]; 7:1–14. Available from: https://www.nature.com/articles/s41598-017-00349-8
197. IL10RB interleukin 10 receptor subunit beta [Homo sapiens (human)] - Gene - NCBI [Internet]. [cited 2023 Aug 27]; Available from: https://www.ncbi.nlm.nih.gov/gene/3588
198. Wong BR, Josien R, Lee SY, Sauter B, Li H-L, Steinman RM, Choi Y. TRANCE (Tumor Necrosis Factor [TNF]-related Activation-induced Cytokine), a New TNF Family Member Predominantly Expressed in T cells, Is a Dendritic Cell–specific Survival Factor. J Exp Med 1997; 186:2075–80.
199. Ono T, Hayashi M, Sasaki F, Nakashima T. RANKL biology: bone metabolism, the immune system, and beyond. Inflamm Regen 2020; 40:2.
200. Meijer B, Gearry RB, Day AS. The Role of S100A12 as a Systemic Marker of Inflammation. Int J Inflam 2012; 2012:1–6.
201. Foell D, Wittkowski H, Kessel C, Lüken A, Weinhage T, Varga G, Vogl T, Wirth T, Viemann D, Björk P, et al. Proinflammatory S100A12 can activate human monocytes via Toll-like receptor 4. Am J Respir Crit Care Med 2013; 187:1324–34.
202. Day AS, Ehn M, Gearry RB, Lemberg DA, Leach ST. Fecal S100A12 in Healthy Infants and Children. Dis Markers 2013; 35:295–9.
203. Gonçalves CM, Henriques SN, Santos RF, Carmo AM. CD6, a Rheostat-Type Signalosome That Tunes T Cell Activation. Front Immunol [Internet] 2018 [cited 2023 Nov 16]; 9. Available from: https://pubmed.ncbi.nlm.nih.gov/30619347/
204. Castelletti E, Caputo S Lo, Kuhn L, Borelli M, Gajardo J, Sinkala M, Trabattoni D, Kankasa C, Lauri E, Clivio A, et al. The Mucosae-Associated Epithelial Chemokine (MEC/CCL28) Modulates Immunity in HIV Infection. PLoS One [Internet] 2007 [cited 2023 Nov 16]; 2:e969. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0000969
205. Flom JD, Niedzwiecki M, Colicino E, Berin C, Wright RJ. Characterizing the prenatal inflammatory milieu associated with maternal asthma: A proteomics approach. Journal of Allergy and Clinical Immunology [Internet] 2019 [cited 2023 Aug 27]; 143:AB6. Available from: http://www.jacionline.org/article/S0091674918317603/fulltext
206. Kapur N, Leach SM, Vanderhoef D, Thyagarajan B, Crouser ED, Maier LA, Bhargava M, Perlman DM. Differentiating Sarcoidosis from Healthy Subjects and Sarcoidosis Subtypes Using Immune Response and Metabolic Proteins. [cited 2023 Aug 27]; Available from: www.atsjournals.org
207. Grund B, Sabin C. Analysis of Biomarker Data: logs, odds ratios and ROC curves. Curr Opin HIV AIDS [Internet] 2010 [cited 2023 Aug 27]; 5:473. Available from: /pmc/articles/PMC3157029/
208. Hara T, Shitara S, Imai K, Miyachi H, Kitano S, Yao H, Tani-ichi S, Ikuta K. Identification of IL-7–Producing Cells in Primary and Secondary Lymphoid Organs Using IL-7–GFP Knock-In Mice. The Journal of Immunology [Internet] 2012 [cited 2023 Nov 16]; 189:1577–84. Available from: https://dx.doi.org/10.4049/jimmunol.1200586
209. Hossny EM, El-Ghoneimy DH, El-Owaidy RH, Mansour MG, Hamza MT, El-Said AF. Breast milk interleukin-7 and thymic gland development in infancy. Eur J Nutr 2020; 59:111–8.

210. Oliveira ML, Akkapeddi P, Ribeiro D, Melão A, Barata JT. IL-7R-mediated signaling in T-cell acute lymphoblastic leukemia: An update. Adv Biol Regul 2019; 71:88–96.
211. Setoguchi R, Tachibana M, Naoe Y, Muroi S, Akiyama K, Tezuka C, Okuda T, Taniuchi I. Repression of the Transcription Factor Th-POK by Runx Complexes in Cytotoxic T Cell Development. Science (1979) 2008; 319:822–5.
212. ElKassar N, Gress RE. An overview of IL-7 biology and its use in immunotherapy. J Immunotoxicol 2010; 7:1–7.
213. Hong C, Luckey MA, Park J-H. Intrathymic IL-7: the where, when, and why of IL-7 signaling during T cell development. Semin Immunol 2012; 24:151–8.
214. Hsu PS, Nanan R. Does Breast Milk Nurture T Lymphocytes in Their Cradle? Front Pediatr [Internet] 2018 [cited 2023 Sep 7]; 6:268. Available from: /pmc/articles/PMC6170640/
215. Yan F, Mo X, Liu J, Ye S, Zeng X, Chen D. Thymic function in the regulation of T cells, and molecular mechanisms underlying the modulation of cytokines and stress signaling. Mol Med Rep 2017; 16:7175–84.
216. Hasselbalch H, Jeppesen DL, Engelmann MDM, Michaelsen KF, Nielsen MB. Decreased thymus size in formula-fed infants compared with breastfed infants. Acta Paediatr [Internet] 1996 [cited 2023 Sep 10]; 85:1029–32. Available from: https://pubmed.ncbi.nlm.nih.gov/8888912/
217. Verduci E, Banderali G, Barberi S, Radaelli G, Lops A, Betti F, Riva E, Giovannini M. Epigenetic Effects of Human Breast Milk. Nutrients 2014; 6:1711–24.
218. Masopust D, Soerens AG. Tissue-Resident T Cells and Other Resident Leukocytes. Annu Rev Immunol [Internet] 2019 [cited 2023 Nov 16]; 37:521. Available from: /pmc/articles/PMC7175802/
219. Schmitz T, Harmel E, Heier M, Peters A, Linseisen J, Meisinger C. Inflammatory plasma proteins predict short-term mortality in patients with an acute myocardial infarction. J Transl Med [Internet] 2022 [cited 2023 Aug 27]; 20:1–12. Available from: https://link.springer.com/articles/10.1186/s12967-022-03644-9
220. Camacho-Morales A, Caba M, García-Juárez M, Caba-Flores MD, Viveros-Contreras R, Martínez-Valenzuela C. Breastfeeding Contributes to Physiological Immune Programming in the Newborn. Front Pediatr 2021; 9.
221. Yokanovich LT, Newberry RD, Knoop KA. Regulation of oral antigen delivery early in life: Implications for oral tolerance and food allergy. Clin Exp Allergy [Internet] 2021 [cited 2023 Sep 20]; 51:518. Available from: /pmc/articles/PMC8743004/
222. Bluestone JA, Anderson M. Tolerance in the Age of Immunotherapy. New England Journal of Medicine 2020; 383:1156–66.
223. Esch BCAM van, Porbahaie M, Abbring S, Garssen J, Potaczek DP, Savelkoul HFJ, Neerven RJJ van. The Impact of Milk and Its Components on Epigenetic Programming of Immune Function in Early Life and Beyond: Implications for Allergy and Asthma. Front Immunol [Internet] 2020 [cited 2022 Sep 10]; 11:2141. Available from: /pmc/articles/PMC7641638/
224. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. The Lancet 2016; 387.
225. Curotto de Lafaille MA, Lafaille JJ. Natural and Adaptive Foxp3+ Regulatory T Cells: More of the Same or a Division of Labor? Immunity 2009; 30:626–35.

226. Van Den Broek T, Borghans JAM, Van Wijk F. The full spectrum of human naive T cells. Nature Reviews Immunology 2018 18:6 [Internet] 2018 [cited 2023 Nov 16]; 18:363–73. Available from: https://www.nature.com/articles/s41577-018-0001-y
227. Hoskinson C, Dai DLY, Del Bel KL, Becker AB, Moraes TJ, Mandhane PJ, Finlay BB, Simons E, Kozyrskyj AL, Azad MB, et al. Delayed gut microbiota maturation in the first year of life is a hallmark of pediatric allergic disease. Nature Communications 2023 14:1 [Internet] 2023 [cited 2023 Nov 16]; 14:1–14. Available from: https://www.nature.com/articles/s41467-023-40336-4
228. Canada: total income distribution by income level | Statista [Internet]. [cited 2023 Sep 16]; Available from: https://www.statista.com/statistics/484838/income-distribution-in-canada-by-income-level/
229. Breastfeeding your baby - Canada.ca [Internet]. [cited 2023 Feb 9]; Available from: https://www.canada.ca/en/public-health/services/health-promotion/childhood-adolescence/stages-childhood/infancy-birth-two-years/breastfeeding-infant-nutrition.html
230. López OAM, López AM, Crossa DrJ. Overfitting, Model Tuning, and Evaluation of Prediction Performance. Multivariate Statistical Machine Learning Methods for Genomic Prediction [Internet] 2022 [cited 2023 Aug 27]; :109–39. Available from: https://www.ncbi.nlm.nih.gov/books/NBK583970/
231. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci [Internet] 2004 [cited 2023 Nov 19]; 1024:138–46. Available from: https://pubmed.ncbi.nlm.nih.gov/15265778/
232. Ferrara G, Petrillo MG, Giani T, Marrani E, Filippeschi C, Oranges T, Simonini G, Cimaz R. Clinical Use and Molecular Action of Corticosteroids in the Pediatric Age. Int J Mol Sci [Internet] 2019 [cited 2023 Nov 16]; 20. Available from: /pmc/articles/PMC6359239/
233. Ferrara G, Petrillo MG, Giani T, Marrani E, Filippeschi C, Oranges T, Simonini G, Cimaz R. Resolution of inflammation: the beginning programs the end. Nature Immunology 2005 6:12 [Internet] 2005 [cited 2023 Nov 16]; 6:1191–7. Available from: https://www.nature.com/articles/ni1276
234. Mayeux R. Biomarkers: Potential Uses and Limitations. NeuroRx [Internet] 2004 [cited 2023 Sep 14]; 1:182. Available from: /pmc/articles/PMC534923/
235. Bono R, Blanca MJ, Arnau J, Gómez-Benito J. Non-normal Distributions Commonly Used in Health, Education, and Social Sciences: A Systematic Review. Front Psychol [Internet] 2017 [cited 2023 Sep 14]; 8:1602. Available from: /pmc/articles/PMC5603665/
236. Anderson LS, Reynolds MB, Rivara KR, Miller LS, Simon SI. A Mouse Model to Assess Innate Immune Response to Staphylococcus aureus Infection. J Vis Exp [Internet] 2019 [cited 2023 Sep 27]; 2019. Available from: /pmc/articles/PMC6605055/