TURUN YLIOPISTO
UNIVERSITY OF TURKU

Maternal Pre-Pregnancy Body Mass Index and Neonatal Brain

Findings from FinnBrain Birth Cohort Study

Aylin Rosberg

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For those who marvel at the wonders of the brain.

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ABSTRACT

Neonatal brain development is a dynamic process shaped by genetic and environmental factors, with early structural and microstructural changes influencing long-term cognitive and behavioral outcomes. Maternal pre-pregnancy body weight has emerged as a key prenatal exposure but remains scarcely studied. Magnetic resonance imaging (MRI) has been an indispensable tool for studying the developmental processes in the human brain. Yet, methodological challenges limit the reliability and comparability of neonatal neuroimaging studies. This dissertation aims to enhance the methodology and to enable new insights into associations between maternal pre-pregnancy weight status and neonatal brain development.

In Study I, we developed the FinnBrain Neonate (FBN-125) MRI template and atlas collection, which includes structural and diffusion brain templates, reproducible transforms to standard volumetric and cortical surface spaces, and atlas labels. Building on this foundation, Studies II, III, and IV investigated the associations between maternal pre-pregnancy body mass index (MBMI) as a proxy for metabolic health and microstructural properties of different brain regions represented by mean diffusivity (MD), which reflects the magnitude of water diffusion. Study II on 116 neonates found a positive association between MBMI and MD in the left caudate nucleus. Study III (n=122) revealed a positive association between MBMI and hippocampal MD. Study IV (n=157) showed a positive association between MBMI and MD in the leftmost parts of the body of the corpus callosum. These findings suggest that elevated MBMI may slow neonatal microstructural development in specific subcortical and white matter regions.

This work advances developmental neuroscience by integrating methodological innovations with investigations of how maternal weight impacts early brain development. The findings underscore the importance of standardized imaging approaches and the role of early-life risk factors in shaping neurodevelopment, providing a foundation for future research. This work encourages future efforts in investigating the molecular mediators of the associations between MBMI and neonatal brain structure, and to assess whether these associations relate to later child health outcomes and development.

KEYWORDS: diffusion tensor imaging, magnetic resonance imaging, neonatal MRI, maternal obesity, maternal BMI, striatum, hippocampus, neurodevelopment.

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AYLIN ROSBERG: Äidin raskautta edeltävä painoindeksi ja vastasyntyneen aivot. Tuloksia FinnBrain-syntymäkohorttitutkimuksesta.
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TIIVISTELMÄ

Vastasyntyneen aivojen kehitys on dynaaminen prosessi, johon vaikuttavat geneettiset ja ympäristötekijät ja jossa varhaiset rakenteelliset ja mikrorakenteelliset muutokset muovaavat pitkän aikavälin kognitiivista ja käyttäytymiseen liittyvää kehitystä. Äidin raskaudenaikainen ylipaino on keskeinen raskauden aikainen altiste, mutta silti sitä on tutkittu vasta vähän. Magneettikuvaus (MRI) on korvaamaton työkalu kehittyvien aivojen tutkimuksessa. Menetelmälliset haasteet kuitenkin rajoittavat vastasyntyneiden aivokuvantamistutkimusten luotettavuutta ja vertailtavuutta. Tämä väitöskirja ratkoo näitä vastasyntyneiden aivokuvantamisen haasteita ja syventää ymmärrystä aivojen tyypillisestä kehityksestä. Väitöskirjan soveltavat tutkimukset keskittyvät äidin painoindeksin ja vastasyntyneen aivojen mikrorakenteellisten yhteyksien kartoittamiseen.

Osatyössä I kehitimme FinnBrain Neonate (FBN-125) MRI-mallin ja atlaskokoelman. Tämän mallin pohjalta osatöissä II, III ja IV tarkastelimme äidin raskaudenaikaista metabolista terveyttä. Mittarina käytimme äidin raskautta edeltävää painoindeksiä (MBMI) ja tämän yhteyttä eri aivoalueiden rakenteisiin, jota mittasimme diffuusiotensorikuvantamisesta määritetyn MD-mittarin (Mean Diffusivity) avulla. Osatyössä II oli mukana 116 vastasyntynyttä, ja siinä havaitsimme, että korkeampi MBMI oli yhteydessä kohonneeseen MD-arvoon vasemmassa häntätumakkeessa. Osatyössä III (n=122) osoitimme positiivisen yhteyden MBMI:n ja hippokampuksen MD:n välillä. Osatyössä IV (n=157) havaitsimme, että MBMI oli yhteydessä kohonneisiin MD-arvoihin aivokurkiaisen vasemmanpuoleisimmissa osissa. Tulokset viittaavat siihen, että kohonnut MBMI voi hidastaa vastasyntyneiden aivojen kehitystä harmaan aineen tumakkeissa ja valkean aineen alueilla.

Tässä työssä loimme uutta tietoa yhdistämällä menetelmällisiä innovaatioita tutkimuksiin äidin ylipainon vaikutuksista vastasyntyneen varhaiseen aivojen kehitykseen. Tulokset korostavat standardoitujen kuvantamismenetelmien merkitystä ja varhaisten riskitekijöiden roolia aivojen kehityksessä, tarjoten pohjan tuleville tutkimuksille. Tämä työ kannustaa jatkossa tutkimaan äidin painoindeksin ja vastasyntyneen aivojen kehityksen välisiä molekyylitason välittäviä mekanismeja sekä arvioimaan, liittyvätkö nämä lapsen myöhempään terveyteen ja kehitykseen.
AVAINSANAT: diffuusiotensorikuvaus, magneettikuvaus, vastasyntyneiden MRI, äidin lihavuus, äidin painoindeksi, tyvitumakkeet, hippokampus, neurokehitys.

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
BCC	Body of corpus callosum
BET	Brain extraction tool
BMI	Body mass index
CNR	Contrast-to-noise ratio
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FDR	False discovery rate
FDT	FMRIB’s diffusion tool
FMRIB	Functional magnetic resonance imaging of the brain
FOV	Field of view
FSL	FMRIB software library
GCI	Generalized conformity index
GDM	Gestational diabetes mellitus
GLM	General linear model
HCP	Human Connectome Project
MBMI	Maternal pre-pregnancy BMI
MD	Mean diffusivity
MNI	Montreal Neurological Institute
MPRAGE	Magnetization prepared rapid gradient echo
MRI	Magnetic resonance imaging
OLS	Ordinary least squares
PD	Proton density
TSE	Turbo spin echo
TR	Repetition time
ROI	Region of interest
SD	Standard deviation
SE-EPI	Spin Echo-Echo Planar Imaging

SNR	Signal-to-noise ratio
TBSS	Tract-based spatial statistics
TFCE	Threshold free cluster enhancement
TI	Inversion time
VBM	Voxel-based morphometry

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Tuulari, J.J.*, Rosberg, A.*, Pulli, E.P., Hashempour, N., Ukharova, E., Lidauer, K., Jolly, A., Luotonen, S., Audah, H.K., Vartiainen, E., Bano, W., Suuronen, I.,Wigley, I.L.C.M., Fonov, V.S., Collins, D.L., Merisaari, H., Karlsson, L., Karlsson, H., Lewis, J.D. The FinnBrain Multimodal Neonatal Template and Atlas Collection. *Commun Biol*, 2025; 8. https://doi.org/10.1038/s42003-025-07963-7 (* shared contribution)

II Rosberg, A., Merisaari, H., Lewis, J.D., Hashempour, N., Lukkarinen, M., Rasmussen, J.M., Scheinin, N.M., Karlsson, L., Karlsson, H., Tuulari, J.J. Associations between maternal pre-pregnancy BMI and infant striatal mean diffusivity. *BMC Medicine*, 2024; 22. https://doi.org/10.1186/s12916-024-03340-z

III Rosberg, A., Merisaari, H., Lewis, J.D., Hashempour, N., Lukkarinen, M., Rasmussen, J.M., Scheinin, N.M., Karlsson, L., Karlsson, H., Tuulari, J.J. Associations between maternal pre-pregnancy BMI and mean diffusivity of the hippocampus and amygdala in infants. *International Journal of Obesity*, 2025. https://doi.org/10.1038/s41366-025-01730-8

IV Rosberg, A., Merisaari, H., Lewis, J.D., Hashempour, N.,Jolly, A., Pulli, E.P., Audah, H.K., Mariani Wigley, I.L.C., Li, R., Luotonen, S., Bano, W., Lukkarinen, M., Rasmussen, J.M., Scheinin, N.M., Karlsson, L., Karlsson, H., Tuulari, J.J. Associations between Maternal pre-pregnancy BMI and Neonatal White Matter Integrity. Manuscript.

1 Introduction

Early brain development marks a critical period characterized by rapid structural and functional changes. Understanding these processes is essential for identifying factors that may influence long-term neurodevelopmental outcomes. Magnetic resonance imaging (MRI) has become an invaluable tool in studying neonatal brain maturation, providing insights into both structural and microstructural aspects of the developing brain. However, neonatal MRI faces several challenges, including technical limitations, physiological constraints, and difficulties in data interpretation, which necessitate the development of specialized tools and methodologies to enhance accuracy and reproducibility. Significant advancements in neonatal neuroimaging will happen through the creation of standardized MRI templates and atlases, which facilitate spatial normalization and comparative analysis across studies.

In addition to methodological advancements, understanding the impact of maternal factors, such as mental and metabolic health on early brain development has recently gained considerable attention. Maternal obesity, in particular, has been linked to alterations in fetal brain development through several mechanisms including the fetal programming of brain development, potentially influencing cognitive and behavioral trajectories later in life. While previous research has explored these associations in childhood and beyond, fewer studies have investigated the neonatal period, a crucial window for detecting early neurodevelopmental outcomes. Examining the relationship between maternal pre-pregnancy weight status and neonatal brain microstructure may provide valuable insights into the mechanisms underlying these associations and inform strategies for early intervention.

This dissertation aims to contribute to the field of neonatal neuroimaging by developing high-resolution neonatal brain templates and atlases while also exploring the influence of maternal pre-pregnancy weight status on early brain development. By addressing both methodological and clinical aspects of neonatal MRI research, this work seeks to enhance the interpretability of neonatal neuroimaging data and provide a foundation for future studies investigating the early origins of neurodevelopmental outcomes.

2 Review of the Literature

2.1 Brief Overview of Early Brain Development

Early brain development is a fundamental biological process that is essential for proper brain function and behavior in postnatal life. It is a complex and dynamic process that begins as early as the third week of the embryonic development and rapidly continues throughout the gestation into the postnatal life [1]. Nowadays, there is no need to rely solely on histology and other traditional methods to study fetal brain development; advancements in neuroimaging now allow us to gain a comprehensive and well-rounded understanding of the developing fetal brain [2,3].

The first trimester is the period from conception to 12 weeks of gestation and is pivotal for building the basic cellular and structural framework of the developing brain [4]. The neurulation, formation of the neural tube, happens around the 3rd and 4th week of gestation [5]. The neural tube continues its transformation by partitioning into primary vesicles. The primary vesicles, prosencephalon (forebrain) which eventually forms the basal ganglia, cerebral hemisphere, hippocampus, hypothalamus, infundibulum, lateral ventricles, pineal gland, thalamus and third ventricle; midbrain (mesencephalon) which gives rise to cerebral aqueduct**,** crus cerebri, tectum and tegmentum; and hindbrain (rhombencephalon) from where cerebellum, the fourth ventricle, medulla oblongata, pons and spinal cord will take shape [6]. Neural progenitor cells undergo rapid proliferation. As they proliferate, these cells begin to express specific markers indicating their differentiation towards mature neuronal and glial lineages, the intricate balance between proliferation and differentiation is essential for the proper formation of neuronal populations [7]. Migration process brings those populations together in the right spatial locations to interact to continue the development phase smoothly [8]. As neurons finish migrating, they begin to grow as axons and dendrites, reaching out to form often temporary synaptic connections. These connections are the first attempts for stable and lasting connections which will emerge in mature neural circuits [9]. Another milestone that takes place in this trimester is the brain splitting into right and left cerebral hemispheres [10].

In the second trimester, gestational weeks 13 to 28, the fetal brain undergoes a critical maturation period characterized by substantial growth, peak neurogenesis, synapse formation, and neuronal migration to their respective locations within the developing structure to establish the foundational architecture of the subcortical structures [11.] The subcortical structures, including caudate nucleus, putamen, hippocampus and amygdala that were already detectable in the first trimester take clear form and undergo significant growth, though the growth patterns are not uniform [12–14]. Synaptogenesis, formation of new synapses, lays the foundation for future communication within the subcortical structures mentioned and other brain regions [15]. In addition to the rapidly ongoing processes, a very substantial change occurs on the surface of the brain. The first signs of gyrification, emergence of sulci and gyri, are already visible on week 13 [16]. This cortical folding process is particularly evident by the 22nd week when many sulci are already present [17]. On a histological level, neuroepithelial stem cell maturation drives a massive cell turnover, generating millions of neurons, while apoptosis ensures precise regulation of the neuronal population through programmed cell death [18]. Another important milestone in this trimester is the rapid formation and development of white matter tracts (Figure 1) connect the structures within the limbic system, (stria terminalis and fornix) and commissural tracts, the tracts that connect the two hemispheres of the brain, (middle cerebellar peduncle, optic chiasm and anterior commissure) are among the first to develop and already visible by week 13 [19]. They are followed by the early appearance of projection tracts, the tracts that connect the cerebral cortex with the subcortical structures and the spinal cord, (internal capsule and corticospinal tract) and association tracts, the tracts that connect different cortical regions within the same hemisphere, (external capsule, uncinate fasciculus) [3]. Brainstem tracts (pontine crossing tract and cerebellar peduncles) become more defined [3]. The corpus callosum starts forming at 15-16 weeks [20]. Between weeks 17-19 more association fibres (inferior fronto-occipital fasciculus, inferior longitudinal fasciculus) become detectable. The corpus callosum extends anteriorly and posteriorly, forming the genu and splenium of the corpus callosum respectively [21]. Radial structures in the cerebral wall become pronounced. As the second trimester comes to an end limbic tracts are fully developed while peripheral white matter and association fibres are still maturing and the corpus callosum continues its rapid development. The intense period of construction that takes place in the second trimester leaves the developing brain highly susceptible to adverse maternal and environmental influences. Maternal smoking and high body mass index (BMI), for instance, can severely disrupt thyroid gland development and endocrine function, both essential for healthy brain maturation [22].

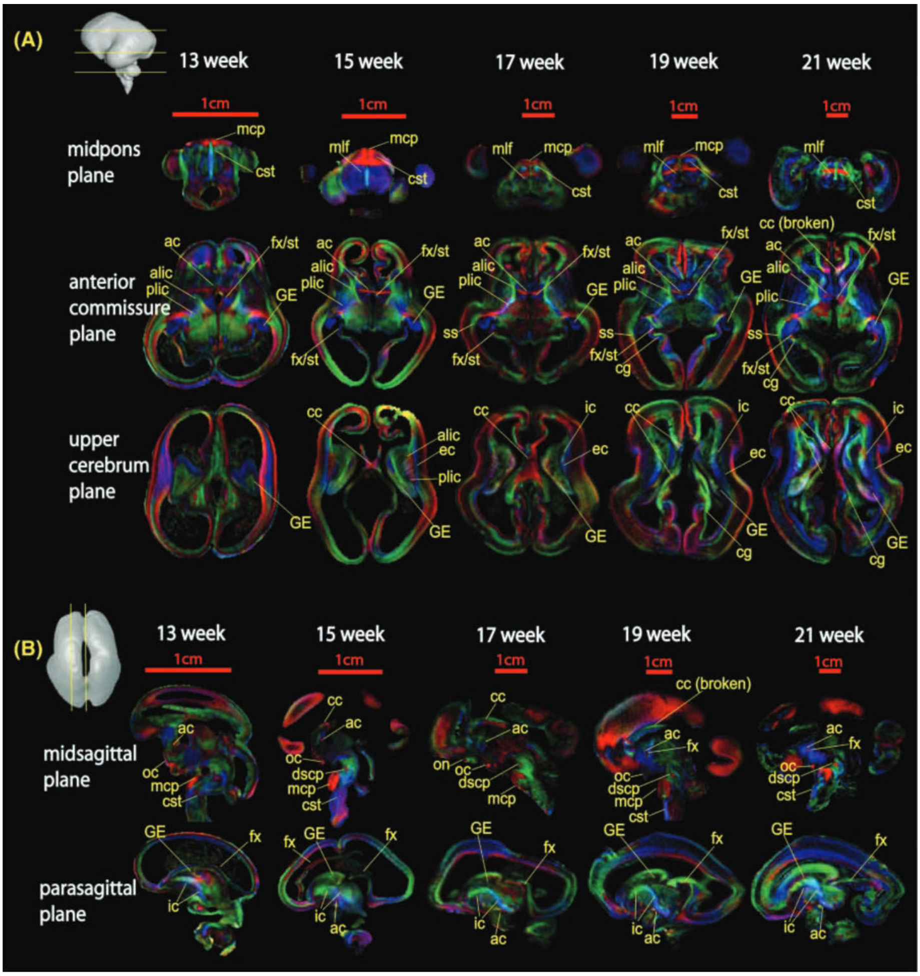

Figure 1. Annotation of major white matter tracts and the ganglionic eminence in axial (A) and sagittal (B) slices of fetal brains at 13, 15, 17, 19, and 21 weeks of gestation. The anatomical planes corresponding to each slice are indicated by yellow lines in the upper-left corner of each panel. White matter tracts are visualized using diffusion tensor imaging color maps. Abbreviations: ac, anterior commissure; acr, anterior region of the corona radiata; alic, anterior limb of the internal capsule; cbt, corticobulbar tracts; cc, corpus callosum; cg, cingulum; cp, cerebral peduncle; cst, corticospinal tract; dscp, decussation of the superior cerebellar peduncle; ec, external capsule; fx, fornix; GE, ganglionic eminence; icp, inferior cerebellar peduncle; ifo, inferior fronto-occipital fasciculus; ilf, inferior longitudinal fasciculus; mcp, middle cerebellar peduncle; ml, medial lemniscus; oc, optic chiasm; on, optic nerve; plic, posterior limb of the internal capsule; scp, superior cerebellar peduncle; scr, superior region of the corona radiata; ss, sagittal striatum; st, stria terminalis; unc, uncinate fasciculus. The figure is taken from Huang et al. 2010 The Neuroscientist.

The third trimester, weeks 28 to 40, is characterized by crucial advancements in both brain structure and function, setting the foundation for cognitive abilities post-birth. The main even of this period is the accelerated brain growth, with the most substantial increases in brain volume occurring during this time [1,23] (Figure 2). As an ongoing theme from the second trimester, maternal factors such as maternal stress and nutrition play an important role in the vulnerable state of neurodevelopment [24–26]. This phase is characterized by myelination and synaptic pruning. Myelination is the process of forming a myelin sheath around axons, which enhances the speed and efficiency of neural signal transmission. Synaptic pruning refers to the elimination of excess neurons and synaptic connections, promoting more efficient and specialized neural communication. These processes support the establishment of functional neural networks, including intra- and interhemispheric corticocortical connectivity [19,27]. The fetal brain becomes increasingly responsive to external stimuli, and the development of sensory systems becomes active [28]. For instance, cognitive functions related to vision begin to emerge [29]. Research reveals that the fetal brain begins responding to light stimuli, with eye movements becoming observable around 34 weeks of gestation [30].

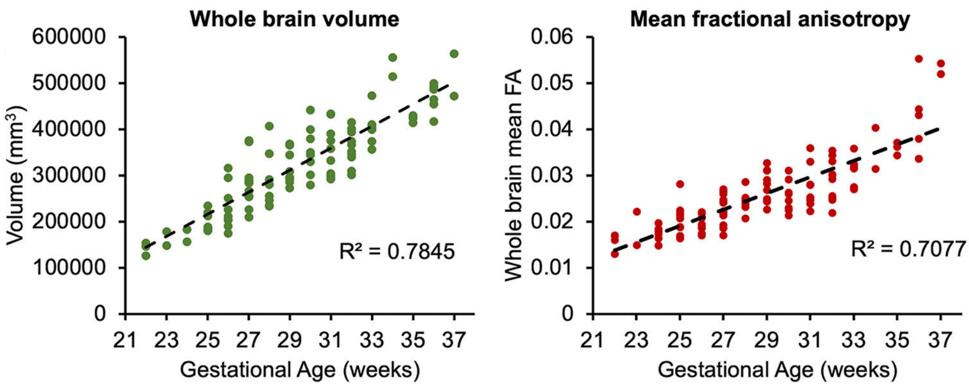

Figure 2. The statistically significant linear relationship of gestational age in weeks and the growth whole brain volume (left) and the mean fractional anisotropy (right) of 131 subjects. The figure is taken from Wilson et al. 2021 PNAS.

To summarize, early brain development is a complex and dynamic process that begins shortly after conception and progresses through distinct stages, including neurogenesis, migration, and maturation. This period is highly sensitive to genetic and environmental influences, with factors such as maternal health characteristics and chemical exposures [31]. The biological signals the fetal brain receives are critical in shaping the trajectory of brain development [32].

2.2 Magnetic Resonance Imaging

MRI is a non-invasive in vivo imaging technique. It is a safe method for it does not use ionizing radiation. The underlying mechanism of MRI involves the interaction between the magnetic field and the protons in the body [33] . When the protons realign with the magnetic field after being disturbed by the radio frequency pulses, they release energy. The time it takes for the protons to realign, and the amount of energy released vary depending on the tissue type, providing the contrast that is used for image formation [34]. Thanks to the contrast created, MRI can deliver high spatial resolution images of the brain, which enables the differentiation between various types of brain tissues, such as grey matter and white matter. This allows researchers and clinicians to examine anatomical structures with exquisite detail MRI has become a cornerstone in both clinical and research settings.

2.2.1 Diffusion Tensor Imaging

Diffusion-weighted MRI is a specialized form of MRI that focuses on the diffusion of water molecules in brain tissue [35]. Magnetic field gradients are applied in multiple directions to sensitively detect the diffusion of water molecules, generating diffusion-weighted images that measure their movement. For diffusion tensor imaging (DTI) analysis, the diffusion data collected from multiple diffusion encoding directions are used to construct a three-dimensional diffusion tensor, representing the magnitude and directionality of water diffusion within each voxel of the image [36,37]. From this tensor, key parameters such as fractional anisotropy (FA), the directional preference of diffusion, and mean diffusivity (MD), the overall magnitude of diffusion are derived [38]. DTI provides unique insights into the microstructural integrity of white matter tracts and the quantification of grey matter microstructure.

2.2.2 MRI templates in Developmental Neuroscience

An MRI template is a standardized reference image or set of images used in neuroimaging studies [39]. The creation of these templates often involves averaging multiple scans from a specific population, which helps to mitigate individual variability and enhances the reliability of neuroimaging findings [40]. Brain templates are commonly used for two main purposes. The first one is spatial normalization, which is aligning individual brain images to a common anatomical space enabling comparison of brain morphology and function across subjects and studies. The second one is providing standardized anatomical references to facilitate multimodal studies [41]. For instance, integrating functional and structural MRI data using the standardized templates enhances the overall understanding of brain development and its relationship with various developmental trajectories [42]. The Montreal Neurological Institute (MNI) template is a widely utilized neuroimaging reference space that serves as a standardized anatomical template [43]. Constructed from 152 high-resolution T1-weighted MRI scans of healthy adults, the MNI template is often regarded as the default template for neuroimaging analyses, enabling researchers to compare brain structures and functions across diverse populations and methodologies [44]. A significant advantage of the MNI template is its accessibility and wide acceptance in the neuroimaging community. Researchers commonly reference the MNI in their methodology sections to indicate that their results are spatially normalized to this standard, making it easier to relate findings across different research settings [45].

The use of the MNI template in paediatric neuroimaging is a crucial topic, as the applicability of adult-derived templates must be scrutinized when examining the developing brains of the babies and children. The MNI template serves as a standard reference for spatial normalization in neuroimaging studies. However, due to the registration problems caused by the disparity between paediatric and adult brain anatomy raises concerns about using a singular adult template for analysing paediatric populations. Research indicates that the registration of paediatric brains to the MNI adult template can result in significant errors due to purely size and age-specific anatomical differences [46–48]. In developmental neuroscience, the ability of MRI templates to facilitate accurate comparisons and interpretations of neuroimaging data is of utmost importance. This is because the templates do not only need to address the population-specific differences but also age-specific differences that are observed as varying tissue content properties and brain sizes [49].

2.3 Challenges of Neonatal MRI

MRI is an indispensable tool for assessing early brain development; however, it also comes with various challenges. Inherently, MRI requires stillness of the subject to obtain better-quality images without motion artefacts, providing that stillness with natural sleep without any sedation which is not applied in research settings due to the ethical considerations and related health risks. This limits the scanning options or hardens the scanning preparations [50].

MRI coils are designed for adults and might not be optimal for neonates [51]. Special technical measures such as head coils to ensure high signal-to-noise ratio (SNR) images [52], multiple layered sound protection to provide necessary sound attenuation [53], and special blankets to support immobility [54] should be considered. In addition to practical challenges there are three main categories of challenges in neonatal MRI that are not easily solvable even with advance instrumentation: technical limitations, physiological constraints, and interpretation of the MRI data.

2.3.1 Technical limitations

To minimize motion artifacts and avoid sedation, fast imaging sequences with incomplete k-space sampling are commonly used, but this comes at the cost of reduced image quality [55]. Additionally, thick slice 2D sequences are often employed to shorten acquisition time, leading to partial volume effects that can obscure small brain structures. The contrast-to-noise ratio (CNR) between grey matter and white matter may be suboptimal if imaging parameters, such as repetition and echo times, are not carefully optimized. The head coils and sequence parameters directly affect the SNR, affecting overall image clarity [56].

2.3.2 Physiological and Anatomical Constraints

The primary physiological constraint of neonatal brain MRI is the unique anatomical characteristics that separate them from the children or adult MRI images. Neonatal brains are characterized by incomplete myelination and a higher water content, leading to lower SNR in MRI images compared to adult brains [57]. This incomplete myelination and uneven pattern of development result in variable intensity contrasts between different tissue types, complicating the segmentation and interpretation of MRI scans [45]. In addition, due to the smaller size of neonatal brains, the relative voxel size is larger compared to brain size making the images more susceptible to partial volume effects, which occur when a single voxel contains a mixture of different tissue types or multiple anatomical brain structures, lead to signal averaging and reduced accuracy in distinguishing fine structural details [57].

2.3.3 Interpretation of the MRI data

In neonatal MRI images, the white matter looks darker than the grey matter on T1-weighted images and lighter than the grey matter on T2-weighted images due to the lack of myelin. This makes the contrast in neonatal images appear in reverse order compared to adult images (Figure 3). It becomes very challenging to distinguish these tissue types where myelination has started [45]. In addition, unlike adult MRI studies, which have established best practices, the field of neonatal neuroimaging lacks standardization [58]. This lack of common frameworks can lead to inconsistencies in data collection and analysis, making it difficult to compare results across studies [59].

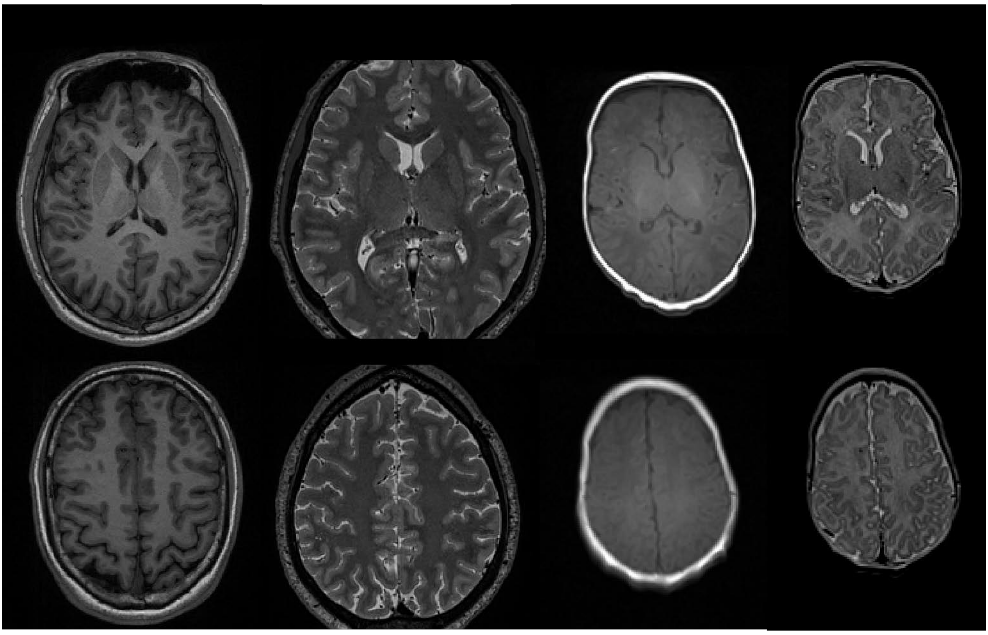

Figure 3. Comparison of structural MRI images of adult and neonate brains in the axial plane at two different slice levels. The left panel shows adult T1-weighted (left) and T2-weighted (right) images from an open-source database (openneuro.org) where in T1-weighted image white matter appears brighter and grey matter darker and in T2-weighted image grey matter appears brighter and white matter darker. In contrast, the right panel presents neonatal T1-weighted (left) and T-2 weighted (right) images from the FinnBrain infant dataset, where the tissue contrast is less pronounced due to ongoing myelination. The T2-weighted neonatal image contrast is comparable to the T1-weighted adult image.

2.3.3.1 Segmentation Methods

MRI image segmentation partitions an image into meaningful regions based on shared attributes like intensity or texture, classifying voxels into white matter, grey matter, cerebrospinal fluid and anatomical regions. As segmentation inherently involves classification, accurate and efficient methods are crucial [60]. Although there are automated segmentation tools available, the necessity for manual segmentation remains significant due to the complexities involved in accurately delineating brain structures in neonates. Therefore, currently semi-automated approaches, where initial automatic segmentations were refined manually to enhance accuracy, especially where the anatomical variability is pronounced, are commonly used. Reliable anatomical atlases for neonates are needed to ensure accurate and smooth segmentation processes, particularly in regions with low contrast [61].

2.3.3.2 Neonate Templates and Atlases

There is not a unified standard space for neonates as there is one for adults, which is most frequently the MNI space. Our literature search yielded 26 different pediatric atlases and templates, only eight out of which were exclusively from healthy term-born neonates [45]. None of them provided comprehensive combination of multimodal templates and atlas labels highlighting the need of standard template spaces in neonatal/infant neuroimaging studies. Also, the correspondence to adult MNI space would be helpful in supporting comparisons to adult studies, performing meta-analyses, and assuring reproducibility [45].

2.4 Maternal Gestational Obesity and Child Outcomes: A Brief Review

Obesity, defined as excessive accumulation of body fat, is a major public health concern associated with increased risks of cardiovascular diseases, type 2 diabetes, and metabolic disorders [62]. BMI (kg/m^2) is the standard metric for assessing weight status, with thresholds of 25 for overweight and 30 for obesity [63]. Once established, obesity, including childhood obesity, is difficult and costly to treat [64], highlighting the critical need for early identification of risk factors and biomarkers.

Obesity has reached epidemic proportions globally, requiring urgent interventions. An analysis of publicly available data from the World Health Organization, the World Bank, and the Food and Agricultural Organization estimated that in 2014, 38.9 million pregnant women were overweight, including 14.6 million classified as obese [65]. Given the prevailing trend of obesity over recent decades, it is foreseeable that the population of pregnant women with overweight and obese will rise, as will the number of infants born who are subjected to in utero exposure to maternal obesity.

2.4.1 The Influence of Maternal Obesity on Child Brain Development and Clinical Outcomes

Maternal obesity has been increasingly recognized as a significant factor associated with various neonatal complications including prematurity, neonatal hypoglycemia, higher rate of intensive care unit admissions and higher neonatal morbidity [66–68]. The implications of maternal obesity, however, extend beyond immediate neonatal complications, affecting long-term mental and physical health trajectories [69–71]. Within the scope of this dissertation, two main outcome categories are explained further: weigh trajectories, and psychosocial and cognitive outcomes in children.

2.4.1.1 Neural Mechanisms Linking Maternal Obesity to Childhood Weight Gain

The evidence suggests that children who were born to mothers with obesity are at high risk for developing obesity as early as age two [72]. Another cohort study analyzed data from 1557 mother-child pairs and a validation cohort with over 50,000 BMI measurements. They found that more than 20% of children exposed to obesity during pregnancy showed a distinct pattern of higher BMI from early infancy, leading to a significantly increased risk of being overweight or obese by age five. Similar associations were observed in older populations as well [73,74]. However, evidence suggests that this predisposition cannot be solely attributed to genetic and lifestyle factors. Instead, neural mechanisms play a crucial role in shaping eating behavior [75].

The striatum: caudate nucleus and lentiform nucleus, comprising the putamen and globus pallidus, is repeatedly linked to hedonic eating, food-related motivation, and reward processes [76–79]. Differences in how the brain processes unhealthy, high-sugar foods have been observed between individuals of healthy weight and those who are overweight or obese [80,81]. Obesity has been connected to structural changes in the striatum in both adolescents[82] and adults[83–85] and striatum stands out as a key area for predicting future weight gain [75,86]. Moreover, preclinical studies on maternal obesity have shown that it can lead to changes in neurotransmitter signaling and functioning, particularly in the striatum [87]. While the causal relationship between striatal structural and functional differences and positive energy balance remains complex, findings from normal-weight individuals with and without a parental history of obesity indicate that these neural mechanisms may already be at play before lifestyle factors come into effect.

2.4.1.2 Neural Mechanisms Linking Maternal Obesity to Child Neurodevelopment and Psychosocial Outcomes

Evidence suggests that *in utero* exposure to maternal obesity significantly impacts children's psychosocial and cognitive outcomes. Findings from the Early Childhood Longitudinal Study-Birth Cohort Children revealed that children who were born to mothers with obesity are more susceptible to mental delays at age two (n=6850) [88] and learning and behavioral disabilities between ages 2 – 4 (n=5200) [89]. A meta-analysis drawing from 32 different studies indicated that children of mothers with high pre-pregnancy BMI are at greater risk for neurodevelopmental disorders, for instance attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), as well as cognitive delay, learning difficulties, and emotional and behavioral problems [90,91]. The underlying neural mechanisms may involve alterations in the limbic system, particularly the hippocampus and amygdala, which play key roles in emotion regulation, learning, and memory. Preclinical studies, suggest that maternal obesity is associated with structural and functional changes in these regions, contributing to cognitive impairments and increased susceptibility to anxiety- and depression-like behaviors in offspring [92–94].

Beyond subcortical structures, white matter also appears to be particularly sensitive to prenatal exposures, including maternal nutrition [95,96] and mental health factors such as depression and anxiety [97–99]. As a key component of the brain's connectivity, white matter integrity is essential for cognitive and behavioral functioning.

2.4.2 Fetal Programming of the Brain Development

The concept of fetal programming, stemming from Barker's hypothesis, also known as the "foetal origins of adult disease", posits that adverse *in utero* environments, particularly those related to maternal nutrition, can have profound and lasting effects on an offspring's health, increasing vulnerability to conditions like obesity, cardiovascular disease, and type 2 diabetes [100]. During gestation, the embryo or fetus adapts to environmental cues through structural and functional modifications at cellular, tissue, and organ system levels [101,102], with these adaptations potentially persisting throughout the lifespan. Recent research across epidemiological, clinical and preclinical studies supports the role of fetal programming in the development of obesity risk [103,104].

Recently Rasmussen et al. further highlighted the importance of foetal brain programming in this context, suggesting that prenatal exposure to adverse conditions, including maternal obesity, inflammation, or nutritional deficiencies, can critically affect brain development [105]. Studying neonatal populations offers a unique opportunity to isolate the impact of maternal weight status from postnatal lifestyle confounders, allowing for a more direct assessment of in utero effects.

Research on the association between maternal obesity and neonatal brain development is still emerging, to the best of our knowledge, only few studies have examined the association between maternal obesity and early brain development in healthy term-born infants, and the limited available evidence suggests that in utero exposure to maternal obesity leads to significant neurodevelopmental changes in children [106] . These changes have been observed using various imaging modalities (Table 1). Na et al. examined the relationship between maternal obesity during pregnancy and the cortical thickness of neonates' brains in 44 otherwise healthy mother-neonate dyads. The main finding of the study was that maternal BMI was negatively associated with lower cortical thickness in specific regions of the frontal lobe [107]. Interestingly they pointed out that the structural and functional changes in the aforementioned frontal areas that are involved in language and executive functions, were observed in children with obesity. Therefore, the authors concluded that maternal obesity during pregnancy may negatively impact foetal cortical development, leading to reduced cortical thickness in neonates and the potential link between maternal obesity and persistent brain changes that may contribute to increased risk of childhood obesity and related behavioural issues [107]. There are two studies focused on the impact of maternal obesity on neonatal brain functional connectivity. Salzwedel et al. found that high maternal BMI was associated with significant alterations in functional connectivity across brain regions crucial for sensory cue processing, reward processing, cognitive control, and motor control in neonates [108]. Rajasilta et al., revealed that higher maternal pre-pregnancy BMI correlated with both increased local brain activity in left superior frontal gyrus (SFG) and distinct patterns of both increased and decreased functional connectivity between SFG and prefrontal regions, amygdalae, basal, ganglia, insular cortex, temporal regions and the ventral striatum [109]. Notably, both studies identified changes in brain areas implicated in behaviours related to obesity such as reward processing and food intake or inhibitory control, suggesting early-life programming of neural pathways due to maternal adiposity. These findings indicate that maternal obesity may lead to altered brain function in neonates, potentially contributing to increased risk of cognitive and behavioural issues, including obesity-related behaviours, in offspring. Two studies utilized the DTI method. One of them showed compromised microstructural integrity in widespread white matter regions in addition to a linear negative association between the maternal body fat percentage and FA values in multiple white matter regions in neonates who were born to mothers with high pre-pregnancy BMI [110]. The authors underscore that the associations are mainly in frontal lobe which is important for cognitive functioning [110]. The other study showed a positive relationship between the MD values in hypothalamus, central regulator of energy homeostasis, and maternal pre-pregnancy BMI drawing from two birth cohort data from two different countries [111]. Collectively, these studies converge on the finding that maternal obesity during pregnancy is associated with significant alterations in neonatal brain structure and function, affecting regions critical for cognitive control, reward processing, and energy homeostasis. This suggests that in utero exposure to maternal obesity may contribute to the intergenerational transmission of obesity risk by programming the newborn’s neurodevelopment, potentially predisposing offspring to adverse cognitive, behavioral, and metabolic outcomes. There is a need for more research to elucidate the specific mechanisms underlying these associations.

Table 1. Overview and main results of the neuroimaging studies that explored the relationship with maternal pre-pregnancy weight status and neurodevelopment in healthy term-born infants.

Authors	Maternal demographics	Neonatal demographics	Main results
Na et al. 2021	N=44 (28 normal weight, 16 obese)	N=44 (23 boys, 21 girls) Mean age at scan=14 days	Neonates born to obese mothers had significantly lower cortical thickness in three frontal lobe regions: left pars opercularis gyrus, left pars triangularis gyrus, left rostral middle frontal gyrus. Cortical thickness in these regions negatively correlated with maternal body fat percentage measured in early pregnancy.
Salzwedel et al. 2018	N=38 (23 normal weight, 15 obese)	N=38 (20 boys, 18 girls) Mean age at scan=2 weeks	Functional connectivity differences between neonates born to mothers with high BMI (14/15 obese) compared to those with normal BMI. Alterations observed across four key domains implicated in obesity mechanisms: • Sensory cue processing, particularly visual processing. • Reward processing, linked to eating behavior and motivation. • Cognitive control, involved in decision-making and self-regulation. • Motor output control, associated with movement and energy expenditure.
Rajasilta et al. 2021	N=21 (10 normal weight, 7 overweight, 4 obese)	N=21 (12 boys, 9 girls) Mean age at scan=27 days	Maternal pre-pregnancy BMI was positively associated with altered local functional synchronization in the neonate's left superior frontal gyrus (SFG). Maternal pre-pregnancy BMI associated with both positive and negative connectivity changes between the left SFG and, prefrontal regions, amygdalae, basal ganglia, and insular cortex.
Ou et al. 2015	N=28 (17 normal weight, 11 obese)	N=28 (18 boys, 10 girls) Mean age at scan=2 weeks	Neonates born to obese mothers had significantly lower fractional anisotropy (FA) values in inferior fronto-occipital longitudinal fasciculus, the superior longitudinal fasciculus, the external and anterior internal capsule, the forceps minor, the genu of the corpus callosum, the fornix, and the anterior and superior corona radiata. Global and regional (genu of corpus callosum, inferior frontal-occipital fasciculus, superior longitudinal fasciculus, anterior limb of internal capsule, external capsule, body of corpus callosum, and superior corona radiata) FA values

			negatively correlated with maternal fat mass percentage.
Rasmussen et al. 2023	Site 1: N=152 (4 underweight, 95 normal weight, 38 overweight, 15 obese) Site 2: N=79 (3 underweight, 42 normal, 25 overweight, 9 obese)	Site 1: N=152 (82 boys, 70 girls) Mean age at scan=26,7 days Site 2: N=79 (45 boys, 34 girls) Mean age at scan=25,6 days	Maternal pre-pregnancy BMI was positively associated with hypothalamic mean diffusivity values in neonates.

* Weight classification in maternal demographics were based on body mass index categories: underweight (BMI < 18), normal weight (18 ≤ BMI < 25), overweight (25 ≤ BMI < 30), obese (BMI ≥ 30)

2.5 Summary of the Literature Review

Early brain development is a dynamic and complex process that begins during the third week of gestation with neural tube formation and continues through fetal and neonatal periods. It is also very susceptible to maternal and environmental factors from very early stages. MRI is a powerful non-invasive tool for studying neonatal brain development. It provides high-resolution anatomical images, enabling differentiation of brain structures. Diffusion-weighted imaging, a specialized MRI technique and DTI analysis, allows for the examination of microstructure by mapping water diffusion patterns. MRI templates are essential in developmental neuroscience, aiding in spatial normalization and multimodal integration. However, neonatal MRI poses significant challenges, including motion artifacts, technical limitations, and physiological constraints. The low myelination of neonatal brains and their high water content impact image quality and complicate data interpretation. Segmentation of neonatal MRI data is particularly challenging, requiring a combination of automated and manual techniques to ensure accuracy. The lack of standardized neonatal templates further complicates neuroimaging analyses, highlighting the need for improved age-specific frameworks and resources.

Obesity is a major global health concern and maternal obesity is linked to immediate neonatal complications, including increased risks of prematurity, neonatal hypoglycemia, and intensive care admissions. However, the impact of *in utero* exposure to maternal obesity has long-term effects on offspring health through many complicated mechanisms including the fetal programming of brain development. Children born to mothers with obesity are at risk for obesity, they show differences in food-related reward processing compared to the children without parental obesity risk. Additionally, maternal prenatal obesity associates with increased rates of neurodevelopmental disorders such as ADHD and ASD, as well as emotional problems, cognitive delay poor academic performance. Given these associations, it is crucial to investigate maternal pre-pregnancy weight status and the fetal programming of the brain development in key brain regions, particularly the striatum and limbic structures.

3 Aims

The main aim of this dissertation was to create multimodal neonatal templates and labelled atlases from the neonatal structural and diffusion-weighted MRI data of FinnBrain Birth Cohort Study to help improve neonatal MRI data interpretation and analysis, and to utilize the templates and atlases to make a thorough assessment of the impact of *in utero* exposure to maternal obesity on the early brain development. The specific aims for the studies in this dissertation are as follows:

I. To advance developmental neuroscience by achieving reliable means for spatial normalization and measures of neonate brain structure via automated computational methods and to enable investigators to transform their statistical maps to the adult MNI space, improving the consistency and comparability of neonatal studies or the use of adult MNI space atlases in neonatal neuroimaging via the standard volumetric and surface co-registration files.

II. To investigate how pre-pregnancy maternal weight status influences the microstructure of reward-related striatal areas of caudate nucleus, putamen, and globus pallidus in neonates.

III. To investigate how pre-pregnancy maternal weight status influences the microstructure of the limbic structures of hippocampus and amygdala in neonates.

To investigate how pre-pregnancy maternal weight status influences the whole brain white matter development in neonatest.

4 Materials and Methods

4.1 Ethics Statement

All studies were conducted in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the Hospital District of Southwest Finland (15.03.2011) §95, ETMK: 31/180/2011.

4.2 Participants

The already obtained and well curated data of FinnBrain Birth Cohort Study was used in the studies [112]. The families all had Caucasian background and were from the Southwest Finland, including the Åland Islands. Term-born 2 – 5-week-old infants (N=180) were scanned between 2012 – 2016 [50]. The infants had no perinatal complications with neurological consequences (e.g., hypoxia), central nervous system anomaly or an abnormal finding in a previous MRI scan. They all had minimum 5 points in the 5 min Apgar [113]. Out of 180 neonates, 167 completed the structural and diffusion MRI scans.

The maternal demographics were obtained from the wellbeing services county of Southwest Finland records. The maternal data were based on both self-reported and recorded measurements initially acquired in the maternity clinics as a routine service, although the specific method for obtaining these at the individual level is not specified. None of the mothers had a known history of alcohol or drug abuse, severe psychiatric disorders, epilepsy, or related medication use during pregnancy [114]. The exact number of neonates differed based on the study specific requirements for neuroimaging and maternal demographic data. Table 2 shows the demographics of the 21 neonates whose brain MRI scans were used as the basis to create the 21 sub-templates and in the demographics of mother-neonate dyads are presented in Table 3.

Table 2. Demographic information of the 21 neonates included in Study I for template creation, presented as mean values with standard deviations (SD).

Neonatal demographics	Mean	SD
Birth height (cm)	50.5	1.7
Birth weight (g)	3512.8	376.8
Age from due date to scan (weeks)	3.29	1.03
Postmenstrual age at scan (weeks)	43.35	0.97

Table 3. Demographic information of the mother-neonate dyads in Studies II, III, and IV, presented as mean values with standard deviations (SD) or as frequencies.

Neonatal demographics	Study II		Study III		Study IV	
	mean	SD	mean	SD	mean	SD
Birth height (cm)	50	1.9	50	1.9	50	1.9
Birth weight (g)	3482	435	3485	441	3533	477
Gestational weeks at birth	39.9	1.1	39.9	1.1	39.9	1.1
Postnatal age at scan (days)	24.9	7.4	24.8	7.3	25.3	6.7
Girls	50/116		53/122		73 / 157	
Boys	66/116		69/122		84 /157	
Maternal demographics						
	mean	SD	mean	SD	mean	SD
Age at birth	29.7	4.4	29.6	4.5	29.9	4.4
Pre-pregnancy BMI	24.2	4	24.3	4	24.4	3.6
BMI categories						
Underweight (BMI < 18)	3/116		3/122		4 /157	
Normal weight (18 ≤ BMI < 25)	76/116		79/122		98 /157	
Overweight (25 ≤ BMI < 30)	25/116		27/122		38 /157	
Obese (BMI > 30)	12/116		13/122		17 /157	
Education level at birth						
< 12 years	32/116		34/122		44 /157	
12–15 years	36/116		36/122		49 /157	
15 years <	48/116		48/122		59 / 157	
SSRI/SNRI use in 1st trimester	8/116		9/122		10 /157	
SSRI/SNRI use in 3rd trimester	6/116		8/122		8 /157	
Tobacco use in 1st trimester	8/116		8/122		9 / 157	

Tobacco use in 3rd trimester	3/116	5/122	4 / 157

*BMI: body mass index, SSRI: selective serotonin reuptake inhibitor, SNRI: serotonin-norepinephrine reuptake inhibitor

4.3 MRI Data Acquisition

The MRI scans were performed at the Medical Imaging Centre of the Hospital District of Southwest Finland by an experienced radiographer using a Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). Scanning was conducted during natural sleep using the "feed and swaddle" method without anesthesia [113]. The imaging protocol lasted an hour.

The structural imaging protocol included a PD-T2-TSE (Dual-Echo Turbo Spin Echo) sequence with a repetition time (TR) of 12.070 ms and effective echo times (TE) of 13 ms for PD-weighted images and 102 ms for T2-weighted images with flip angle of 150° and matrix size 256 × 192 × 256. T-2 weighted images had 128 slices with 1.0 mm^3 isotropic resolution. Additionally, a sagittal 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (field of view [FoV]: 256 mm; 64 slices; TR: 1900 ms; TE: 3.26 ms; inversion time [TI]: 900 ms: flip angle: 9°; matrix size 256 × 256 × 176) was acquired. T1-weighted images had an isotropic resolution of 1.0 mm^3 across 176 slices. Sequence parameters were optimized to minimize acoustic noise by employing the "whisper" gradient mode in both the PD-T2-TSE and 3D T1 sequences.

Diffusion-weighted imaging protocol included a single-shell acquisition with a standard twice-refocused Spin Echo-Echo Planar Imaging (SE-EPI) sequence (FoV: 208 mm; 64 slices; TR: 9300 ms; TE: 87 ms) at an isotropic resolution of 2 mm^3 and a b-value of 1000 s/mm^2. The diffusion acquisition consisted of 96 unique diffusion encoding directions distributed across a three-part DTI sequence, with each segment containing 31, 32, or 33 directions. Additionally, three b0 images (without diffusion weighting) were acquired at the beginning, middle, and end of each of the three-part DTI sequence [115,116].

4.4 MRI Data Processing

The process of constructing the population-specific structural and diffusion templates and atlases involved rigorous steps. The templates and atlas labels created were used in all of the studies comprising this dissertation. First, of the initial 180 structural MRI scans available, 125 met the quality criteria for template creation, based on visual inspection. The primary reason for exclusion was the excessive artifacts in the images, which stemmed from undetected technical issues during data collection [50].

4.4.1 Structural Template Creation

Established methods of Fonov et al. were followed to create a population specific dual contrast template [40,117]. The T1 template that was created from the T1-weighted images was linearly registered to the adult standard template MNI. The average scaling factor from individual neonate MRIs to MNI was calculated, and its inverse was applied to resize the MNI template to match the neonate population. T2-weighted images were registered to T1-weighted images and the transforms estimated from the T1-weighted images were used to register the T2-weighted images to the neonatal template space. The template construction used an iterative approach that minimized the intensity differences between the template and individual scans while also reducing the magnitude of deformations needed to align subjects to the template.

A total of 21 clusters were identified based on non-linear transformations derived in the template construction. The clustering was performed using Jacobian determinant values (which measure local volume changes in the deformation field), combining cosine similarity and Euclidean distance. The choice of 21 clusters was made because it provided a good balance analysis reliability, and the manual effort required for segmentation. Within each of the 21 clusters, the subject with the smallest sum-squared distance to others was chosen as the central subject. These central subjects served as the basis for creating the sub-templates. The dual-contrast template was warped (i.e., transformed and aligned) to fit each of these 21 central subjects. The resulting 21 sub-templates were manually segmented. The people who performed the segmentation were blinded to the fact that these were variations of the same original template. A detailed flowchart of the template creation procedure is presented in Figure 4.

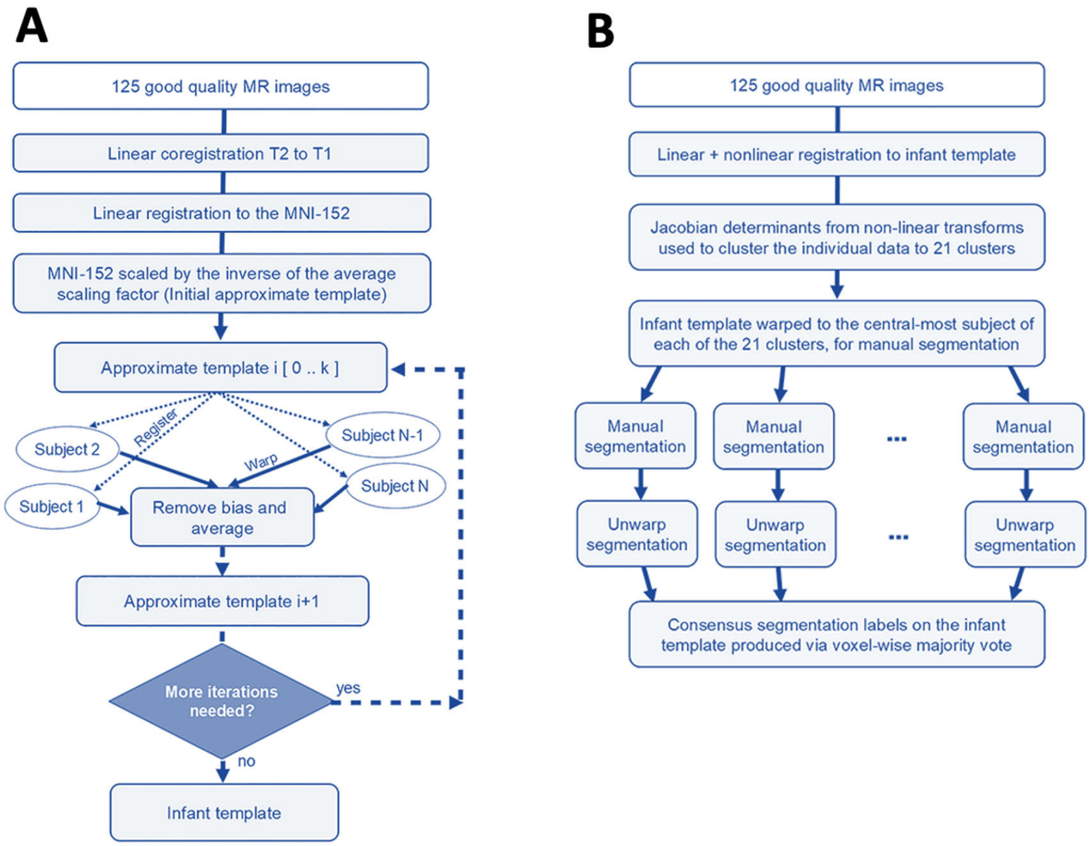

Figure 4. Schematic overview of the FBN-125 neonatal template creation. Structural MRI scans passing quality control (N = 125) were used to construct a population-specific dual-contrast template aligned with MNI space. Nonlinear transformations derived during template construction were used to cluster subjects into 21 groups, from which the central-most subject in each cluster was selected to generate 21 sub-templates for manual segmentation. Manually segmented labels from the 21 sub-templates were merged via voxel-wise majority voting to generate the final symmetric and asymmetric atlas labels. T2: T2-weighted magnetic resonance images, T1: T1-weighted magnetic resonance images. This figure is from Tuulari et al. 2025 Communications Biology.

4.4.2 Manual Segmentation and Creation of the Atlas Labels

Manual segmentation of neonatal brain MRI is a highly labor-intensive process requiring specialized expertise in developmental neuroanatomy. To optimize this process, we adopted a structured workflow that incorporated automated pre-segmentation of gross structures, manual refinement, and rigorous quality control.

The manual segmentation was performed by trained research assistants with close supervision.

Automated tissue segmentation was performed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) – voxel-based morphometry (VBM) pipeline, guided by the University of North Carolina (UNC) neonatal template grey matter probability mask. These estimates provided an initial delineation of cortical grey matter, white matter, and cerebrospinal fluid, which were subsequently refined through manual segmentation.

For subcortical structure segmentation, a reference segmentation of the hippocampus, amygdala, and subcortical grey matter nuclei was first created on a single template by a more experienced rater, primary rater, and a senior investigator, with external validation by an independent expert. This reference served as a guide for manually segmenting the same structures across the 21 sub-templates. Using Display software (part of the MINC Tool Kit), three trained research assistants manually segmented these structures under continuous supervision. The final segmentations were critically reviewed and revised by a senior investigator to ensure consistency. The accuracy between 21 manual segmentations was measured with generalized conformity index (GCI). The segmentation of specific brain structures followed established protocols. The hippocampus and amygdala were bilaterally segmented according to Hashempour et al.[118], while the caudate nucleus was segmented following Perlaki et al.[119]. The putamen was segmented primarily in the coronal plane, and the globus pallidus was delineated posterior-to-anterior using circular tracings. Thalamus segmentation was guided by previous work by Owens-Walton et al.[120].

Cortical and gross anatomical segmentations followed a similar process. Initial estimates of these structures were manually corrected to ensure anatomical accuracy. Three research assistants performed the segmentations with guidance from a senior investigator, who also developed a comprehensive segmentation manual and instructional videos to standardize procedures across raters. Weekly quality control sessions were conducted, and a final review of all segmentations ensured consistency. Cortical and gross anatomical segmentations were completed using FSL [121] tools, with manual corrections performed in FSLeyes.

4.4.3 Benchmarking Transfer of Statistical Maps of fMRI Activations from Neonatal to Adult MNI Space

To enable the transformation of neonatal fMRI statistical maps into adult MNI space, we generated standard coregistration files linking the FinnBrain Neonate (FBN)-125 neonatal template to the adult MNI template. Transformations were first estimated from the adult MNI template to FBN-125 space to account for anatomical differences. Coregistrations were performed using antsRegistrationSyNQuick.sh script and antsApplyTransforms program from ANTs software [122,123]. To ensure compatibility with existing neonatal studies, we selected the UNC-0-1-2-year template as the reference for coregistration [124,125], since it is recognized as the most frequently used infant atlas [48]. The transformation pipeline was validated using statistical maps from a recent neonatal fMRI study, applying concatenated warps from UNC to FBN-125 to adult MNI space [126]. This approach enhances the accuracy of neonatal-to-adult transformations, supporting longitudinal and comparative analyses.

4.4.4 Creation of the Surface Files

The FreeSurfer recon-all-clinical pipeline [127] was applied to the T2-weighted FBN-125 template to enable cortical surface reconstruction despite the absence of a true T1-weighted image. This process produced a synthetic T1-weighted image of the template, in which the white matter contrast was normalized to a value of 110. The synthetic T1-weighted image was then used as input for the recon-all pipeline of FreeSurfer 6.3. This version of FreeSurfer was selected to ensure compatibility with subsequent processing steps. Finally, the outputs from FreeSurfer were used as input for ciftify tool, which generated multiple standard-space surface files and transformations [128]. This workflow ensured consistency between the volumetric and surface representations of the FBN-125 template, facilitating further analyses in both domains.

4.4.5 Preprocessing of the Diffusion MRI Data and Diffusion Template Creation

4.4.5.1 Preprocessing of the DTI Data for Study I, II and III

Good quality b0 images were manually selected, coregistered, averaged, and placed at the beginning of each 4D diffusion series. Brain masks were then generated using the Brain Extraction Tool (BET) [129] from FSL to isolate brain tissue.

Quality control of the diffusion images was a two-step process. First, DTIPrep [130] tool was utilized for automated screening and low-quality volumes were discarded accordingly. All remaining images underwent a second round of visual inspection, with additional diffusion directions excluded as necessary. Based on previous findings datasets containing at least 20 diffusion encoding directions were considered sufficient for reliable tensor estimation [115,116]. Therefore, only infants with at least 20 valid diffusion encoding directions were included in the final analysis, resulting in a sample size of 122 neonates. Eddy current and motion correction were conducted using FSL, and the b-vector matrix rotated accordingly [131,132]. A diffusion tensor model was then fitted to each voxel within the brain mask using the DTIFIT tool in FDT (FMRIB's Diffusion Toolbox) with ordinary least squares (OLS) fit. The preprocessing workflow, which has demonstrated good test-retest reliability, ensured consistency and reproducibility of the DTI estimates [115].

4.4.5.2 Preprocessing of DTI data for Study IV

Without the limitation of needing good quality structural MRI images, the data set for study IV was larger. The data of 167 neonates went into DTI preprocessing pipeline used for the previous studies. The creation of brain masks based on good quality b0 images was followed by automated and manual quality control steps and the diffusion MRI data of 157 neonates with at least 40 diffusion encoding directions moved on to the artefact correction. A diffusion tensor model was fitted to each voxel with DTIFIT. Both the FA maps and the MD maps created by DTIFIT were fed into the Tract-Based Spatial Statistics (TBSS) pipeline of FSL [133] . Instead of the commonly used FMRIB58_FA standard-space, which is derived from adult MRI data, we utilized the FBN-125 template [45] to register the FA images to ensure more anatomically appropriate registration. The TBSS pipeline assumes that the highest DTI scalar values are located in the middle of the white matter tracts and allows investigators to create a white matter skeleton that estimates the individual tract centres before further analysis. It provides robust results, reduces the partial volume effect, and does not necessitate spatial smoothing [134]. The TBSS pipeline created all participants' mean scalar template and mean scalar skeleton as the final output. A commonly used FA threshold of 0.15 was applied to the MD and FA skeletons.

4.4.5.3 Diffusion Template Creation

For DTI template creation, the b0 images were rigidly registered to nonuniformity-corrected T1-weighted images (T1). The transformations from b0-to-T1 and T1-to-FinnBrain Neonatal (FBN-125) template space were combined to align the FA and MD maps to the standardized neonatal template [135,136]. The image registrations were performed using 'antsRegistration,' and the FA and MD templates were generated by averaging the transformed images with FSL's fslmaths tool. This approach ensured spatial consistency across participants, allowing for robust group-level analysis.

4.4.6 Extracting Diffusion Metrics for Study II and Study III

After aligning the b0 images to the nonuniformity-corrected T1-weighted data using rigid registration and combining the transformations from b0-to-T1 and T1-to-template space for MD maps, the individual anatomical structures were masked in the group average space to extract the values within the region of interest (ROI). For Study II, two different approaches were used to extract MD values. The first one was to use the defined anatomical masks, and the second one was to apply a 1.5 mm erosion to the anatomical masks to reduce partial volume effects [137]. Then the mean MD values within each ROI were calculated with both the non-eroded masks and the eroded masks. For Study III, the MD values were extracted only from the non-eroded masks and averaged for the ROI-based analysis.

4.5 Statistical Analysis

4.5.1 Region of Interest-based Analysis

In Study II and Study III, a linear regression model that was adjusted for the sex and postnatal age in days of the neonates was used to investigate the associations between maternal pre-pregnancy BMI (MBMI) and the mean MD of the striatum and limbic structures. Also, the findings were confirmed by using a sensitivity analysis where covariates infant's birthweight and gestational age at birth in weeks, mother's age at birth in years, socioeconomic status represented with education level (years of formal education), and the use of selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, or other drugs that affect the central nervous system were added one by one to the model. Additionally, in Study II, a subsample (n=100) was created for the mothers without gestational diabetes mellitus (GDM) to evaluate a possible confounding effect of GDM [138,139], and linear model was applied to the subsample data.

The appropriateness of the regression models was assured by visually inspecting the distribution of residuals and Q-Q plots for normality and checking the variance inflation factor. Multiple comparisons were corrected with the false discovery rate (FDR). P-values less than 0.05 after FDR correction were considered statistically significant. All statistical analyses and data visualization were performed with Rstudio 4.0.3 [140].

4.5.2 Voxel-based Permutation Analysis

We utilized FSL randomise to conduct voxel-wise general linear models (GLM) and related non-parametric permutation analyses with 5000 permutations and threshold-free cluster enhancement (TFCE) [141] to address the multiple comparison correction. We investigated the association between MBMI and microstructural properties of neonatal brain. Neonates' sex and postnatal age in days were statistically controlled for in the general linear model. In Study III, MD maps masked with hippocampus and amygdala labels were used in the analysis. In Study IV, both FA and MD values within the TBSS skeleton were used in the analysis. Only the voxels reaching $p < .05$ level after TFCE correction were deemed statistically significant.

5 Results

5.1 Study I: Multimodal Neonatal Template and Atlas Collection

5.1.1 High-resolution multimodal neonatal brain templates for structural and diffusion MRI and atlas labels

The FBN template created includes T1- and T2-weighted templates and FA and MD average maps (Figure 5). The FBN atlases include gross anatomical, symmetric and asymmetric labels that were created by a vigorous process including the manual segmentation of the 21 sub-templates (Figure 6). The agreement across atlas labels quantified with GCI had a range of values between 0.71 to 92 (Table 4). A GCI value typically ranges from 0 to 1, where a value closer to 1 indicates a high level of conformity.

Table 4. Manual segmentation accuracy assessed using the Generalized Conformity Index (GCI).

Region of interest	GCI
Caudate	0.81
Putamen	0.81
Globus pallidus	0.71
Thalamus	0.86
Hippocampus	0.75
Amygdala	0.71
White matter	0.83
Cortex	0.80
Cerebrospinal fluid	0.80
Brainstem	0.86
Cerebellum	0.92

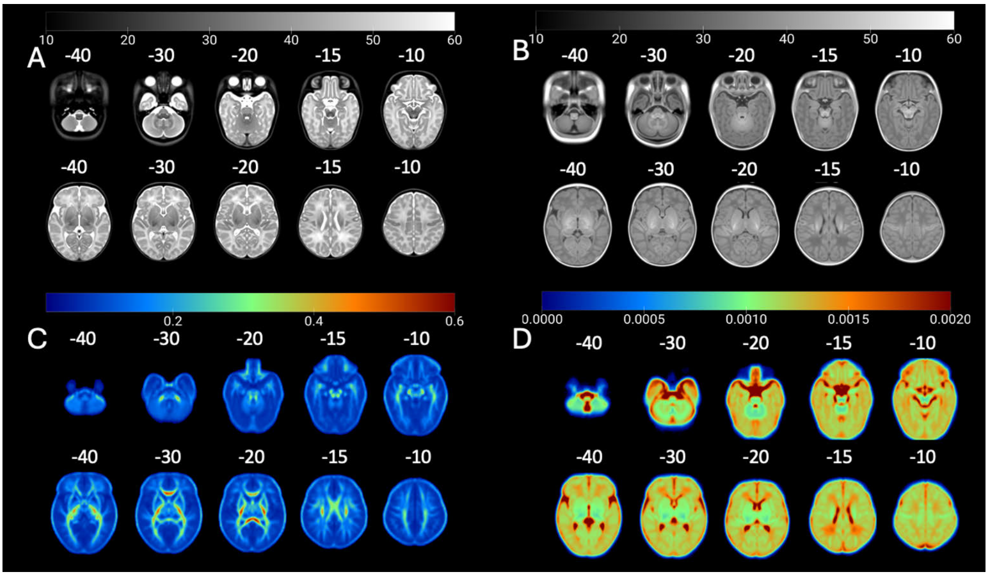

Figure 5. The FinnBrain Neonate (FBN-125) templates include A) T2-weighted, B) T1-weighted, C) diffusion tensor imaging (DTI)-derived fractional anisotropy, and D) mean diffusivity maps. In these templates, the intensity represents signal intensity for A and B, while for C and D, it corresponds to DTI tensor scalar values (unitless for C and measured in mm²/s for D). Each axial slice is labelled with its corresponding *z*-coordinate in the adult MNI template space, visualized using MRIcroGL software. This figure is from Tuulari et al. 2025 Communications Biology.

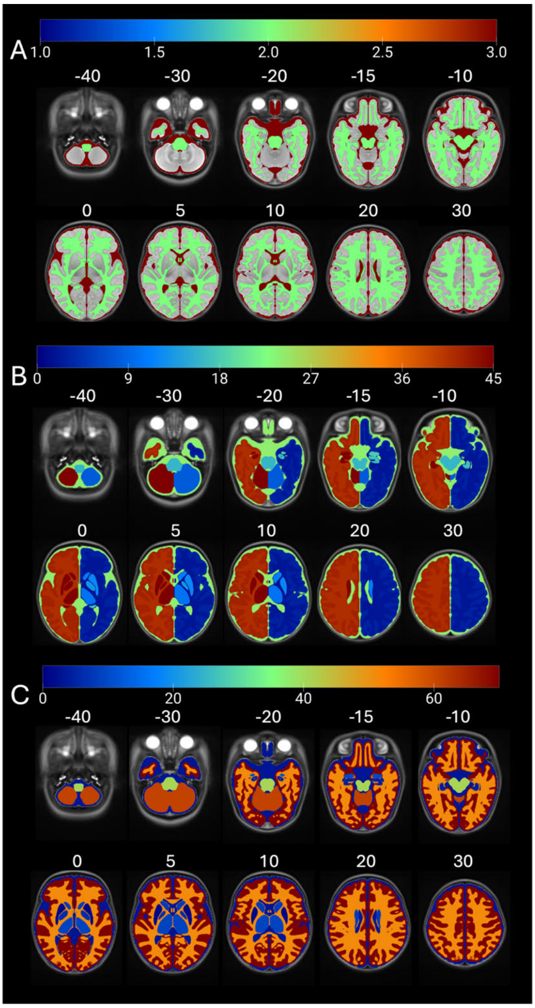

Figure 6. The anatomical labels for the FBN-125 templates include A) gross anatomical labels of grey and white matter, along with cerebrospinal fluid, B) asymmetric labels in FreeSurfer lookup table (LUT)-compliant form, and C) symmetric labels. In these templates, color scales represent anatomical label numbers, with clear anatomical definition of subcortical nuclei, particularly the thalamus. Each axial slice is labelled with its corresponding z-coordinate in the adult MNI template space, visualized using MRIcroGL software. This figure is from Tuulari et al. 2025 Communications Biology.

5.1.2 Transforming Neonatal Functional MRI Data to Adult Standard Spaces and Surface-based Approach

We generated standard transformations from the FBN-125 template to the adult MNI template space and applied these transformations to transfer the statistical maps of neonatal brain activations in response to social touch to adult MNI space [126]. The registrations demonstrated high accuracy (Figure 7).

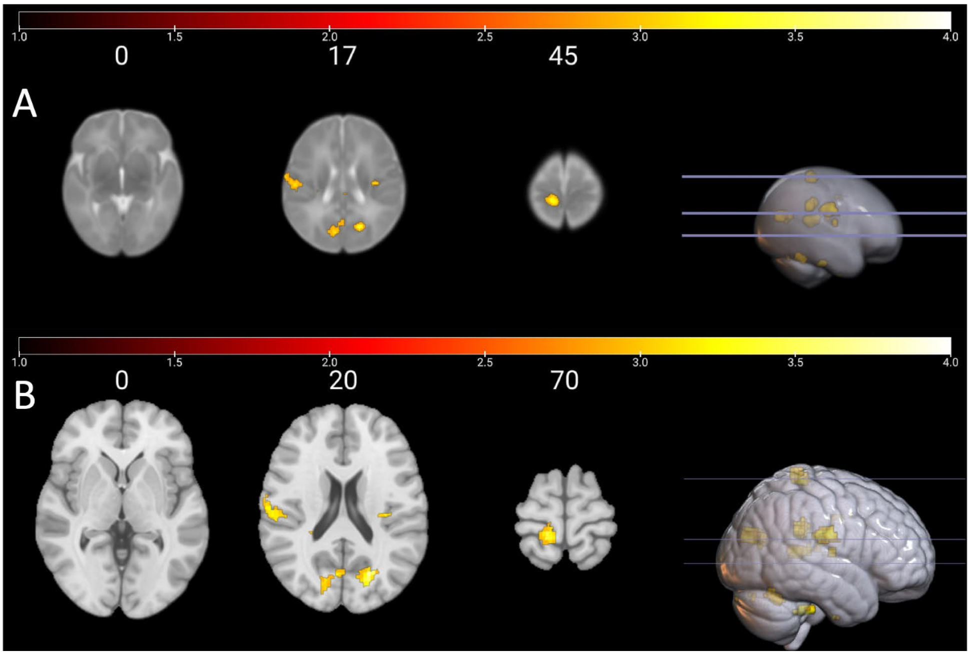

Figure 7. Visualization of the main effect of brushing versus rest conditions in neonates. A) Statistical maps displayed in the UNC neonate atlas template space. B) The same contrast mapped to adult MNI space (*mni_icbm152_t1_tal_nlin_sym_09a*) following transformations from UNC to FBN-125 neonate template space and subsequent standard transformations from FBN-125 to adult MNI space. Color bars represent T values from thresholded clusters ($p < 0.005$, FDR-corrected for multiple comparisons, $N = 18$). Adult MNI space z-coordinates are indicated above each axial slice. Different coordinate selections were used in UNC and MNI template spaces to visualize the same regions of interest in both images. This figure is from Tuulari et al. 2025 Communications Biology.

We applied a surface-based approach utilizing the recon-all-clinical, recon-all and ciftify pipelines of FreeSurfer to our averaged T2-weighted image (Figure 8). The standard surface transforms offer potential benefits for surface-based applications. They enable further analyses by facilitating the projection of statistical result maps, regions of interest, or other patterns from the standard Human Connectome Project (HCP) surface space to the FBN-125 surface space. Additionally, these transforms allow for the alignment of individual surface files to the FBN-125 surface space, which can then be mapped back to the HCP standard surface space. However, it is important to note that volumetric segmentations show variable agreement with joint label fusion segmentation labels.

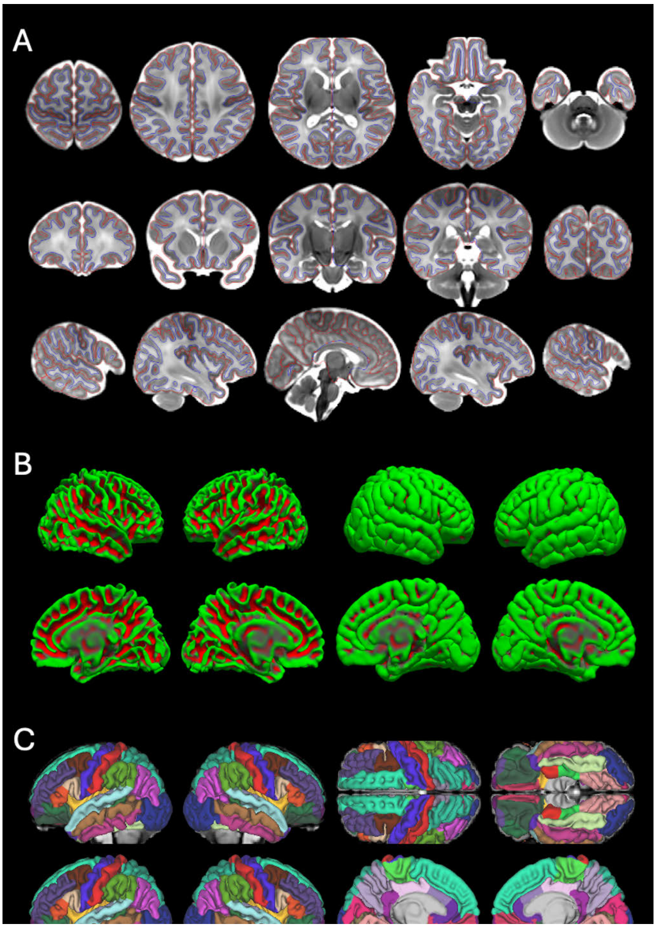

Figure 8. The cortical surface representations include A) white and pial surfaces outlined in blue and red, respectively, overlaid on the T2-weighted average image across axial, coronal, and sagittal slices; B) a 3D visualization of the white and pial surfaces for both hemispheres (left hemisphere on the left, right hemisphere on the right), with gyri marked in green and sulci in red; and C) the Desikan-Killiany parcellation displayed on a synthetic T1-weighted image. This figure is from Tuulari et al. 2025 Communications Biology.

5.2 Study II: Maternal Pre-pregnancy BMI and Striatal Microstructure in Neonates

A positive association was observed between MBMI and the mean MD in the left caudate nucleus (beta = 2.59 ± 0.919 ($\times 10^{-6}$), t = 2.813, p = 0.006, $R^2_{partial}$ = 0.07) (Figure 9). MBMI did not show any associations with mean MD in other ROIs (lentiform nuclei or the right caudate nucleus). The associations were confirmed with the sensitivity analyses. To eliminate the possible confounding effect of GDM, the cases with GDM were removed from the dataset (remaining n = 100). The same linear regression analysis was repeated with the subsample and the results remained the same; MBMI was still significantly associated with the mean MD in the left caudate nucleus (beta = 3.04 ± 1.013 ($\times 10^{-6}$), t = 2.997, p = 0.004, $R^2_{partial}$ = 0.07) but not with other striatal brain regions.

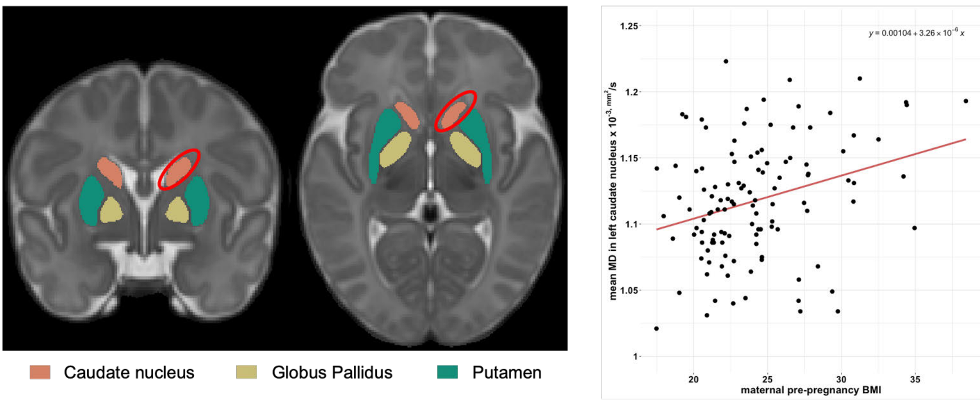

Figure 9. In the left panel, the bilateral regions of interest used in the study; caudate nucleus, putamen and globus pallidus are presented on a T2-weighted sample average brain image in radiological convention. In the right panel, a scatterplot showing the associations between maternal pre-pregnancy BMI and the mean MD in caudate nucleus.

5.3 Study III: Maternal Pre-pregnancy BMI and Hippocampal Microstructure in Neonates

5.3.1 ROI Analysis

A positive association was observed between MBMI and the mean MD in the right hippocampus (beta = 4.084 ± 1.341 ($\times 10^{-6}$), t = 3.045, p = 0.00287, $R^2_{partial}$ = 0.073) (**Figure 10**). The positive association between MBMI and the left hippocampus mean MD (beta = 3.670 ± 1.475 ($\times 10^{-6}$), t = 2.489, p = 0.0142, $R^2_{partial}$ = 0.05) did not survive the FDR correction. The association was confirmed with the sensitivity analyses. There were no associations between MBMI and amygdala.

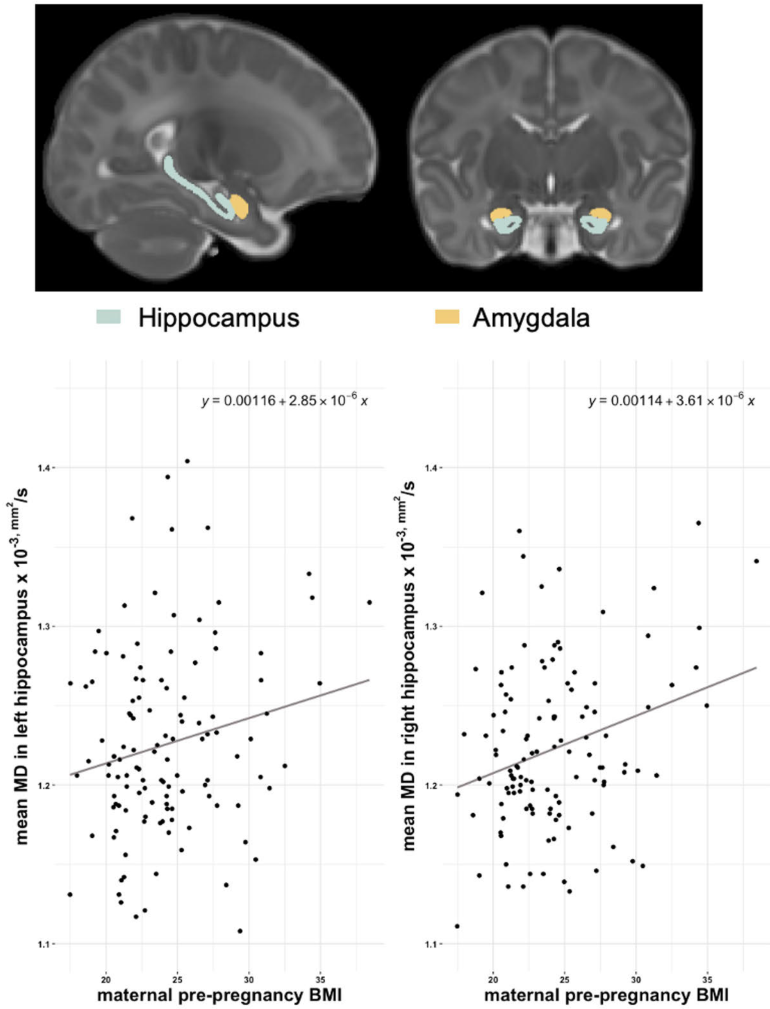

Figure 10. The bilateral regions of interest used in the study; hippocampus and amygdala are presented on a T2-weighted sample average brain image (top). A scatterplot showing the associations between maternal pre-pregnancy BMI and the mean MD in bilateral hippocampi (bottomconvention. In the right panel, a scatterplot showing the associations between maternal pre-pregnancy BMI and the mean MD in caudate nucleus

5.3.2 Voxel-wise Analysis

Voxelwise permutation tests, adjusted for infant's sex and age from birth in days, yielded significant voxels in the posterior right hippocampus and anterior left hippocampus (Figure 11). No significant voxels were detected in the amygdalae.

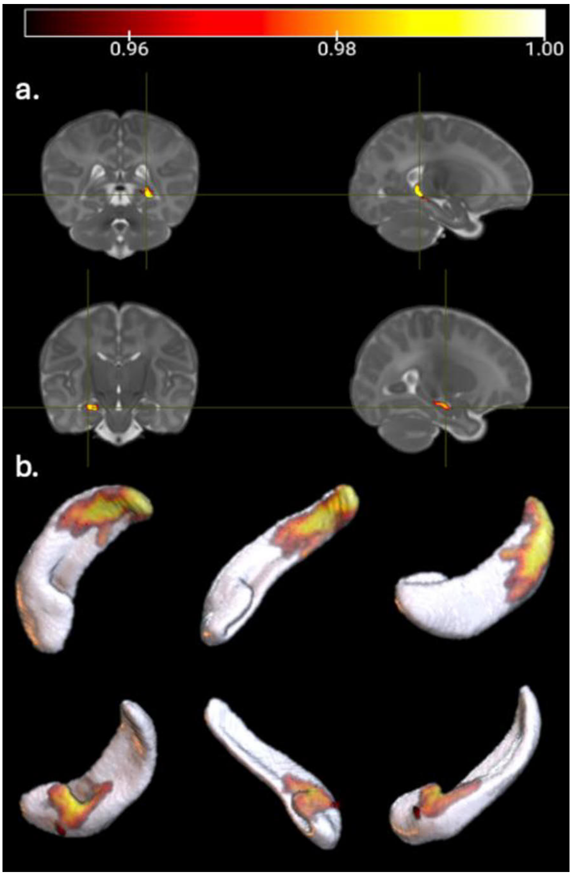

Figure 11. Positive associations between maternal pre-pregnancy body mass index and neonate hippocampus mean diffusivity analyzed using voxel-wise permutation testing, adjusted for infant sex and age at birth (in days), are shown on (a) a T2-weighted average whole-brain image of the study population and (b) a 3D rendering of the segmented right (top) and left (bottom) hippocampi. Voxels significant at $p < .05$ after threshold-free cluster enhancement correction for multiple comparisons are displayed. The colour bar represents $1 - p$ values. Figure (a) follows neurological convention (right hippocampus at the top, left hippocampus at the bottom)

5.4 Study IV: Maternal Pre-pregnancy BMI and White-Matter Integrity in Neonates

We found a positive association between MBMI and MD in voxelwise permutation tests, adjusted for infant sex and age in days from birth in the leftmost parts of the body of corpus callosum (BCC) (Figure 12). No significant associations found between the FA values and MBMI.

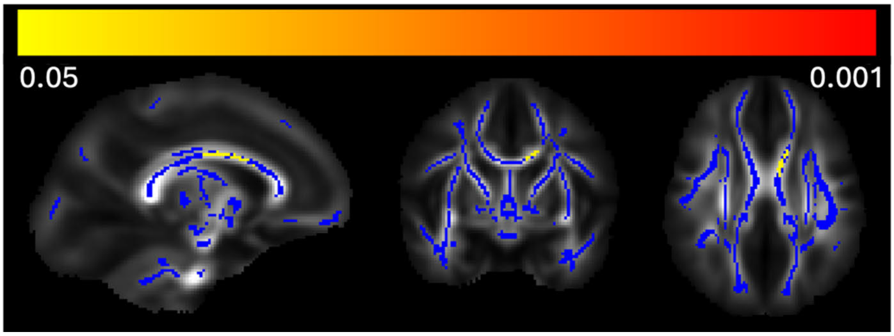

Figure 12. Positive associations between maternal pre-pregnancy body mass index and neonatal white matter mean diffusivity analyzed with a voxel-wise general linear model adjusted for infant sex and age from birth in days, presented on the data-specific mean FA template and skeleton (blue). Voxels that are significant (p <.05) after threshold-free cluster enhancement (TFCE) correction for multiple comparisons with 5000 permutations are shown in the figure. The figure is in radiological convention (right hemisphere on the left and left hemisphere on the right.

6 Discussion

6.1 The Significance of Creating a Multimodal Neonate Template

The creation of the FBN-125 neonatal template and atlas collection represents a significant step forward in standardizing neonatal neuroimaging analyses. Existing neonatal atlases and templates are often limited by age range, small sample sizes and lack of multimodal imaging data. One of the most important contributions of our work is filling this gap by providing multimodal templates incorporating both structural and diffusion MRI created based on 2–6 weeks old neonates.
Moreover, the preexisting templates suffer from insufficient integration with standard adult neuroimaging spaces. We offer a template that is compatible with adult MNI space, facilitating direct comparisons between neonatal and adult imaging data by enabling researcher to map statistical results and regions of interest from FBN-125 to adult MNI templates. This is crucial for longitudinal and developmental neuroscience research, as it allows for more precise spatial normalization and cross-study comparisons. The ability to map neonatal data onto an adult standard space can enhance meta-analytic approaches and improve the reproducibility of findings in neonatal neuroimaging studies.

Another key aspect of our work is the anatomically precise manual segmentation of subcortical structures. Many existing neonatal atlases subdivide the thalamus into myelinated and unmyelinated parts, whereas our approach provides a more biologically relevant segmentation that better reflects the anatomy of infants within the first two months of life. This improves the accuracy of region-of-interest analyses and contributes to better-defined neuroanatomical maps that can be used across studies.

6.2 Interpretation of Diffusion M RI Metrics in Relation to Maternal Weight Status

MD is a measure of the average overall movement of water molecules and is affected by the cumulative barriers, such as cellular structures and membranes, within a specific biological environment or tissue [142]. Consequently, lower MD values typically suggest higher tissue density and / or organization, whereas higher MD values suggest lower tissue density [143]. In pediatric DTI, it is expected that MD will decrease as the brain matures due to the growing presence of restrictive components [144]. Hence, the increase in MD values as the MBMI gets higher might suggest a disruption or slowing down the pace of infant neurodevelopment.

6.3 Associations between Maternal Pre-Pregnancy BMI and Microstructural Properties of Neonatal Brain

In Study II, we showed a positive association between MBMI and MD in left caudate nucleus. Reward sensitivity plays a crucial role in weight gain, serving as a behavioral driver of excess caloric intake [145]. Heightened sensitivity to food-related rewards has been consistently associated with excessive weight gain [75]. Notably, adolescents at high risk due to parental obesity have repeatedly demonstrated increased activation of the caudate nucleus in response to high-sugar foods compared to their low-risk counterparts [146,147]. This finding suggests that the caudate activation seen in high-risk group, at least in part, may be due to the *in utero* exposure to maternal obesity. Interestingly, in a deep learning study utilizing anatomical scans from nearly 18,000 adult participants, researchers developed a convolutional neural network capable of predicting BMI with high accuracy [148]. Notably, their findings revealed that it was the left caudate nucleus, rather than the right, that played a dominant role in BMI prediction, highlighting the relationship between caudate nucleus and obesity.

In Study III, we showed a positive association between MBMI and MD in hippocampal MD using two different approaches an ROI-based analysis and a voxel-based analysis which provided further anatomical precision. Individual differences in sensitivity and/or responsivity to food reward often translates as excessive eating and preference towards more palatable and high caloric food [149] which means an immediate positive reward of eating is followed by a negative consequence of excessive weight gain and this creates a conflict. Evidence from gambling research suggests that in these conflicting cases when the behavior might lead to a negative consequence, hippocampus is responsible for controlling the behavior to avoid the negative consequence [150]. Indeed, an interesting study of Parcet et al. showed the association reduced hippocampal volume with the interaction between high reward sensitivity and high BMI and therefore, proposed that a dysfunctional hippocampus might contribute to overweight [151]. Moreover, Kanoski and Grill, drawing from both clinical and preclinical research, determined that the hippocampus regulates eating behavior by integrating external and internal contexts, as well as mnemonic and cognitive information [152]. Our study provides valuable insights into how *in utero* exposure to high MBMI may contribute to atypical hippocampal microstructure, subsequently in long term may be observed as individual differences in engaging with eating behavior.

Neonatal hippocampal development is known to be sensitive to intrauterine exposures to maternal factors such as maternal stress and anxiety [153,154], MBMI appears to be one of these factors as well. The associations between MBMI and hippocampal microstructure are particularly compelling when considered alongside findings linking MBMI to cognitive abilities and the vital role of hippocampus in learning and memory. Several studies have reported negative associations between MBMI and cognitive outcomes in children: for instance, MBMI has been linked to lower academic success at ages 6, 10 and 14 years [155] . A Canadian birth cohort study showed negative associations between MBMI and cognitive development at age three [156] and a systematic review of 10 studies reported that 90% of the articles found similar associations between maternal obesity and lower cognitive functioning in children [157] . Negative cognitive outcomes in children who were born to mothers with obesity raises the possibility that MBMI-related microstructural changes contribute to these outcomes.

The amygdala begins to develop as early as 7-8 week of gestation and is known to be sensitive to prenatal factors [158–161]; including maternal stress[162] and gestational malnutrition [163]. Surprisingly, there were no significant associations MBMI and amygdala MD. Though it is, worth noting that 2 mm isotropic voxel size combined with small size of amygdala as a structure might contribute to the null finding.

In Study IV, we showed a positive association with MBMI and MD values in the body of the left corpus callosum. Location wise our findings align with previous research that has reported a negative association between FA values and maternal fat mass percentage in the BCC among other white matter tracts [110]. However, unlike Ou et al., we did not find significant associations between MBMI and FA values. This discrepancy may be attributed to several factors such as the relatively low number of participants with overweight/obesity compared to those with normal weight, or differences in data acquisition or processing pipelines. For instance, the number of diffusion encoding directions used in this study was greater than what had been used in the previous study, making our analysis more sensitive. Interestingly, lower white matter integrity in BCC has been implicated in studies conducted with adults with obesity [164,165]. Overall, these findings contribute to a growing body of evidence linking maternal weight status to early brain development, emphasizing the importance of further research to unravel the long-term implications of these early microstructural differences.

6.4 Strengths and Limitations of the Studies

In this dissertation, the sample had lack of diversity in geographical regions and participant backgrounds. While this provides a well-defined reference population, it may hinder the generalizability of the findings, as it may not capture the potential variability in other populations.

6.4.1 Study I

The biggest strength of Study I is the creation of a multimodal, anatomically precise, and MNI-compatible neonatal neuroimaging resource. This atlas and template collection fills a critical gap in the field by providing standardized spatial transformations and diffusion MRI templates, enhancing the reproducibility and rigor of neonatal neuroimaging research. By establishing a robust foundation for future studies, this resource allows researchers to conduct more consistent and comparable analyses, ultimately advancing our understanding of early brain development.

The open-access nature of this resource encourages the scientific community to build upon it, fostering collaboration and further methodological advancements. The limitation of this study is that the dataset lacked substantial longitudinal follow-up, limiting its applicability for studying early postnatal brain maturation. Future research should aim to integrate this template with longitudinal datasets and extend its utility to diverse populations.

6.4.2 Studies II, III, and IV

Studies II, III, and IV provide a comprehensive microstructural analysis of the neonatal brain, incorporating both white matter and subcortical structures, including the striatum, amygdala, and hippocampus. The consistent associations found across multiple measures strengthen the reliability of the findings, suggesting that maternal obesity may have region specific and widespread effects on brain development. By highlighting not only the physical health risks but also the potential cognitive and emotional consequences of maternal obesity, these studies underscore the importance of early interventions to mitigate potential adverse outcomes.

Another key strength of Studies II, III, and IV is that they contribute to a relatively underexplored area of research. The relationship between maternal obesity and neonatal brain microstructure remains insufficiently studied, making these findings particularly valuable. Additionally, compared to previous research in the field, the sample sizes in these studies are significantly larger, increasing the statistical power and robustness of the results. The use of strong and well-validated analysis pipelines further enhances the reliability of the findings, reducing the likelihood of methodological biases and increasing confidence in the observed associations.

The study samples included a limited number of participants with GDM and lacked data on mothers' prior diabetes status. A larger sample of mothers with GDM, along with records of their preexisting diabetes, could have enabled a more comprehensive investigation into how *in utero* exposure to diabetes interacts with BMI to influence neonatal brain development. Incorporating body fat mass percentage alongside BMI could provide a more comprehensive representation of maternal pre-pregnancy weight status.

Diffusion-weighted MRI acquisition lacked reverse phase-encoding data used for correction of susceptibility-induced distortions [166]. Therefore, these distortions were not corrected in our studies, mainly limiting the accuracy of alignment between the DW and T1-weighted MR data in studies II and III. However, these distortions typically affect subcortical regions less than cortical regions. In future studies, the use of multiple diffusion-weighting values would enable a more thorough investigation of brain microstructure.

6.5 Clinical Relevance and Future

Studying the association between MBMI and neonatal brain development has significant clinical implications for early identification, prevention, and intervention aimed at optimizing fetal neurodevelopment and reducing the intergenerational burden of obesity.

The observed microstructural alterations in the neonatal caudate nucleus highlight the need for further research into their role in early weight gain trajectories, while hippocampal microstructural changes may serve as early biomarkers of later cognitive outcomes. Additionally, the association between maternal BMI and altered MD values in the body of the left corpus callosum suggests potential disruptions in interhemispheric connectivity, which may have broader implications for neurodevelopment. Notably, we observed lateralized effects, raising the question of whether these asymmetries reflect a direct influence of MBMI or due to normal developmental asymmetry. Future research should aim to disentangle these possibilities to better understand the mechanisms driving these differences. Investigating these findings in larger cohorts, as well as exploring the potential moderating effects of postnatal environmental factors, will be crucial for a comprehensive understanding of these associations. Future research should prioritize longitudinal studies to track the developmental trajectories of these brain alterations from infancy through childhood and adolescence. Large-scale, multisite neuroimaging projects could provide valuable frameworks for assessing the long-term impact of prenatal factors on neurodevelopment. Integrating advanced neuroimaging methods with behavioral and metabolic assessments will allow for a more holistic understanding of how MBMI influences brain-behavior relationships over time.

Future research should, also, focus on enhancing neonatal brain templates by incorporating higher-resolution imaging and advanced segmentation methods to mitigate partial volume effects and improve structural delineation. Given the dynamic changes in tissue contrast during early brain development, longitudinal studies covering the transition from neonatal to early childhood stages are needed to refine developmental atlases. Expanding datasets to include preterm and diverse populations would enhance template generalizability. Additionally, integrating surface-based approaches for functional parcellation, similar to those used in adult neuroimaging, could provide a more comprehensive understanding of neonatal brain organization. Collaboration with large-scale projects such as the Developing HCP and Baby HCP will be crucial for advancing standardized neonatal-to-adult transformations, facilitating cross-age comparisons, and improving developmental neuroimaging research.

7 Conclusions

Study I
We created a collection of multimodal templates and cortical and subcortical atlases that addresses critical gaps in the field by providing a multimodal, anatomically precise, and MNI-compatible resource for neonatal neuroimaging. By standardizing spatial transformations and improving the availability of diffusion MRI-based templates, our work lays the foundation for more rigorous and reproducible neonatal neuroimaging studies. We encourage the scientific community to utilize and build upon this resource to further advance our understanding of early brain development.

Study II
The results of this study indicated a positive association between maternal pre-pregnancy weight status and the average MD values in the left caudate nucleus. Since higher MD is typically associated with reduced tissue density, these findings suggest that prenatal exposure to maternal obesity may hinder the growth or maturation of tissue density in the infant's left caudate nucleus. Further research is needed to determine the prognostic significance of early caudate nucleus development and the weight trajectories of children born to mothers with obesity.

Study III
The results of this study demonstrated a positive association between maternal pre-pregnancy BMI and MD values in the neonatal bilateral hippocampi. These results emphasize the role of the intrauterine environment, particularly maternal weight status, in shaping early neurodevelopment. Future research is needed to explore the long-term effects of prenatal exposure to elevated maternal BMI and its interactions with various lifestyle factors on cognitive and emotional well-being of the children.

Study IV
The findings of this study demonstrated a positive association between maternal pre-pregnancy BMI and MD in the leftmost parts of the body of corpus callosum,

suggesting that maternal obesity may influence white matter maturation in neonates. Longitudinal research is needed to determine whether this association persists throughout childhood and whether it plays a role in shaping long-term cognitive outcomes. Additionally, large-scale studies are essential to assess the potential need for targeted interventions aimed at promoting maternal and child health.

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Aylin Rosberg

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