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Prenatal green space exposure and child's cognition: mediation by cord blood IGF1 in the ENVIRONAGE birth cohort

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ABSTRACT

Background: Green space exposure has been linked to improved cognitive functioning over the life course. We examined whether newborn insulin-like growth factor 1 (IGF1) plays a part in this.

Methods: We measured cord blood plasma IGF1 in 317 mother–child pairs from the ENVIRONAGE birth cohort. Prenatal green space exposure was assessed within several radii (50–1000 m) around the maternal residence. Multivariable linear regression models were used to associate IGF1 levels with green space exposure. Cognitive functioning was assessed at follow-up at 4 to 6 years of age, using the Cambridge Neuropsychological Test Automated Battery (CANTAB), and converted to components by principal component analysis. Mediation analysis was conducted to examine the relationship between green space exposure and cognitive functioning, with IGF1 as a mediator.

Findings: Prenatal short vegetation (< 3 m in height) exposure associated with newborn IGF1 within 50, 100 and 1000 m ($P \leq 0.05$), and newborn IGF1 significantly predicted the neurocognitive domain of attention/psychomotor speed during childhood ($P < 0.01$). Newborn IGF1 significantly mediated the association between prenatal short vegetation exposure and the latencies of the Motor Screening task and the Big/Little Circle task: Per IQR increase in short vegetation within 50 m, the latencies decreased by 0.45 % (95 % CI: −0.986 to −0.047, P = 0.014) and 0.48 % (95 % CI: −1.164 to −0.016, P = 0.044) via IGF1.

Interpretation: Residential surrounding green space during pregnancy may be associated with long-lasting cognitive benefits for the child, mediated through higher cord blood IGF1 protein levels at birth.

1. Introduction

Residential green space, as defined by vegetated areas such as parks and forests, is associated with a multitude of benefits related to health, including cognitive performance (Bijnens et al., 2022, Dadvand et al., 2017, Dockx et al., 2022a, Nieuwenhuijsen and Khreis, 2017). These benefits span across age groups, from early childhood (Dadvand et al., 2017, Dockx et al., 2022a) to adulthood (Zhu et al., 2019). While the brain exhibits relative plasticity throughout life, early life exposure may be of particular importance due to the active development of the brain in this time period (Luque-Garcia et al., 2022, Miguel et al., 2019). Indeed, several birth cohort studies have linked green space exposure during pregnancy or early life to enhanced cognitive and neurodevelopmental outcomes (Asta et al., 2021, Bijnens et al., 2020, Dadvand et al., 2017, Dockx et al., 2022a, Liao et al., 2019).

Mechanisms possibly explaining the link between green space and health are the reduction of noise (Jimenez et al., 2021), air pollution (Asta et al., 2021, Liao et al., 2019), and stress (Hedblom et al., 2019), and encouragement of physical activity (Ward et al., 2016), and social activities (James et al., 2015), many of which also impact cognitive functioning (De Keijzer et al., 2016). However, the biological basis has been scarcely examined. Epigenetic changes, including DNA methylation in genes related to neurodevelopment and intelligence, have been associated with green space exposure (Alfano et al., 2023, Dockx et al., 2022b, Lee et al., 2021, Xu et al., 2021). Evidence also points to involvement of the dopaminergic system, such as altered blood

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methylation of the dopamine transporter (Lee et al., 2021) and a possible reduction in the risk of having too low serum dopamine levels (Egorov et al., 2017). Interestingly, this can be speculated to occur through modulation of the insulin-like growth factor 1 (IGF1), as research in a rat model has shown IGF1 to protect dopaminergic neurons (Ayadi et al., 2016, Ebert et al., 2008), which, in turn, may release IGF1 themselves (Akirov et al., 2018, Pristerà et al., 2019). IGF1 is a neurotrophic factor essential for brain development (Gubbi et al., 2018) and postnatal neuronal maturation (Wrigley et al., 2017). In the adult brain, IGF1 is not only associated with regions of active neurogenesis but is also promoting this (Nieto-Estevez et al., 2016).

Cross-sectional studies show that higher circulating IGF1 levels correlate with better cognitive performance in both children (Gunnell et al., 2005, Mäntyselkä et al., 2019) and older adults, where it may exert a protective effect against neurodegenerative conditions such as delirium (Li et al., 2018) and Alzheimer's Disease (Hu et al., 2016). Some studies have shown IGF1 to be susceptible to environmental exposures, with a few studies up to date examining prenatal exposures. Mothers who experienced childhood trauma (Lamadé et al., 2021) or were exposed to arsenic (Ahmed et al., 2013), were more likely to give birth to newborns with lower cord IGF1 levels. Occupational exposure to traffic-related air pollution has furthermore been associated with higher IGF1 levels in police officers, compared with police officers working indoors (Tomei et al., 2004). However, to our knowledge, the relationship between prenatal green space exposure and IGF1 levels has not yet been explored.

In this study, we hypothesize that higher exposure to residential green space during pregnancy is related to higher IGF1 levels at birth, which partially mediates the effect of green space exposure on cognition.

2. Methods

2.1. Study population

The Environmental Influence *on* Ageing in Early Life (ENVIR*ON*AGE) birth cohort was used as the study population (Janssen et al., 2017). The ENVIR*ON*AGE birth cohort is still ongoing, having recruited mother-newborn pairs since February 2010 in the province of Limburg (Belgium). Eligibility includes singleton birth, the ability to fill out questionnaires regarding the mother's lifestyle, physique, and residence characteristics. At birth, umbilical cord blood is collected. Mother-child pairs are invited for follow-up when the child is between 4 and 6 years of age, at Hasselt University (Diepenbeek, Belgium). The mothers fill out questionnaires about the socio-demographic and lifestyle characteristics of her and her child, and the child completes the cognitive measurements using the Cambridge Neuropsychological Test Automated Battery (CANTAB). Detailed study procedures can be found elsewhere (Janssen et al., 2017). Informed written consent is obtained for all participants both at birth and follow-up, with the child giving oral permission. The procedures have been approved by the ethical committees of Hasselt University and East-Limburg Hospital in Genk, Belgium. Ethical approval was obtained from Hasselt University (Diepenbeek, Belgium, reference no. B371201216090 and B371201524537) and is in line with the Helsinki Declaration (Janssen et al., 2017). This study fulfils the Strengthening the Reporting of Observational Studies in Epidemiology (STOBE) reporting guidelines.

Final sample size was $n = 317$ (supplementary eFig. 1). The mothers gave birth between February 2010 and June 2015, and cognitive measurements took place between 2014 and 2020.

2.2. Cord blood collection and IGF1 measurements

EDTA-coated BD Vacutainer® K2E plastic whole blood tubes were used for drawing umbilical cord blood immediately after delivery at the proximal (neonatal) end of the umbilical cord (BD, Franklin Lakes, NJ, USA). Plasma was obtained by centrifuging the samples for 15 m at 3200 rpm. The cord blood plasma samples were stored in Eppendorf tubes at −80 °C before being shipped to and analysed by East-Limburg Hospital in Genk, Belgium. IGF1 was measured by electrochemiluminescence immunoassays using the Modular E601 and −2 automatic analyzer (Roche, Basel, Switzerland) with the Elecsys IGF-1 assay. The limit of blank was 3.5 ng/mL and the detection limit was 7 ng/mL. The limit of quantitation, defined as having a coefficient of variation ≤ 20 %, was 15 ng/mL. The measuring range was 7 – 1600 ng/mL. The intra-assay coefficient of variation ranged from 1.0 % to 3.5 %, and the inter-assay coefficient of variation ranged from 2.5 to 4.6 %. Due to the cross-talk between IGF1 and insulin, insulin was also measured in cord blood plasma. Technicians were blinded to exposure status.

2.3. Residential green space exposure

The percentage of green space was calculated at a 50 m, 100 m, 500 m, and 1000 m radius around the maternal residential address during pregnancy based on the high-resolution (1×1 m) Green Map of Flanders from the year 2012 from the Agency for Geographic Information Flanders. These buffers cover the potential passive effects from living close by the green space, such as visual aesthetics, and probable uses of green spaces further away, such as walking or running (WHO, 2016). The Green Map of Flanders is based on flight orthophotos taken every three years during summer in Flanders, Belgium. The plane contains two cameras, one used to detect height and texture, and one used for colour and near-infrared measurements for vegetation detection and NDVI measurements. These photos are combined with the Digital Heightmodel Flanders (Digitale Hoogtemodel Vlaanderen) to assess the height of the vegetation. Landuse is classified based on existing maps for urbanicity and agriculture, together with patterns in the pixels, such as many green pixels together of a certain height suggesting a forest. This results in three main classes, being 'agriculture', 'urban' and 'rest', with each class being subdivided into 'water', 'green' and 'not green'. 'Green' is then further subclassified as 'low green' and 'high green', which, in this study, is renamed into 'short vegetation' and 'tall vegetation' for clarification. The kappa-statistic was 0.94 in the 2012 map, showing a high accuracy in the assignment of class. More information can be found at metadata.vlaanderen.be, Groenkaart Vlaanderen 2012 (in Dutch). "Total green" was constructed as the sum of the short and tall vegetation measurements. Residential green space exposure was determined using geocoded addresses and Geographical Information System (GIS) ArcGIS 10 software. As the percentage of green spaces are assumed to be relatively stable over the years, the 2012 map was chosen as a middle-ground between the children born in 2010 and 2015, as the next map was constructed in 2015.

2.4. Cognitive functioning and principal component analysis

At 4–6 years of age, cognitive functioning was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, UK), which is a computerized set of cognitive tests that can be used from 4 years of age (Luciana, 2003). In our study, we included the four tests Motor Screening, Big Little Circle, Spatial Span, and the Delayed Matching to Sampling, with the former two assessing attention and psychomotor speed, and the two latter assessing visual recognition and working memory of the child (Fig. 1). The child was given instructions by trained personnel using a standardized script and was explained that the tests could be stopped anytime, if the child so desired. If the child did not understand a task, it would be repeated once. A description of the tasks can be found in supplementary eMethods 1.

To examine the association between cord IGF1 and childhood cognition, principal component analysis (PCA) of the cognitive measures was conducted to reduce the risk of inflated Type I error from multiple testing (supplementary eMethods 2). Two components were used per PCA, explaining at least 70 % of the variance (supplementary eTable 1).

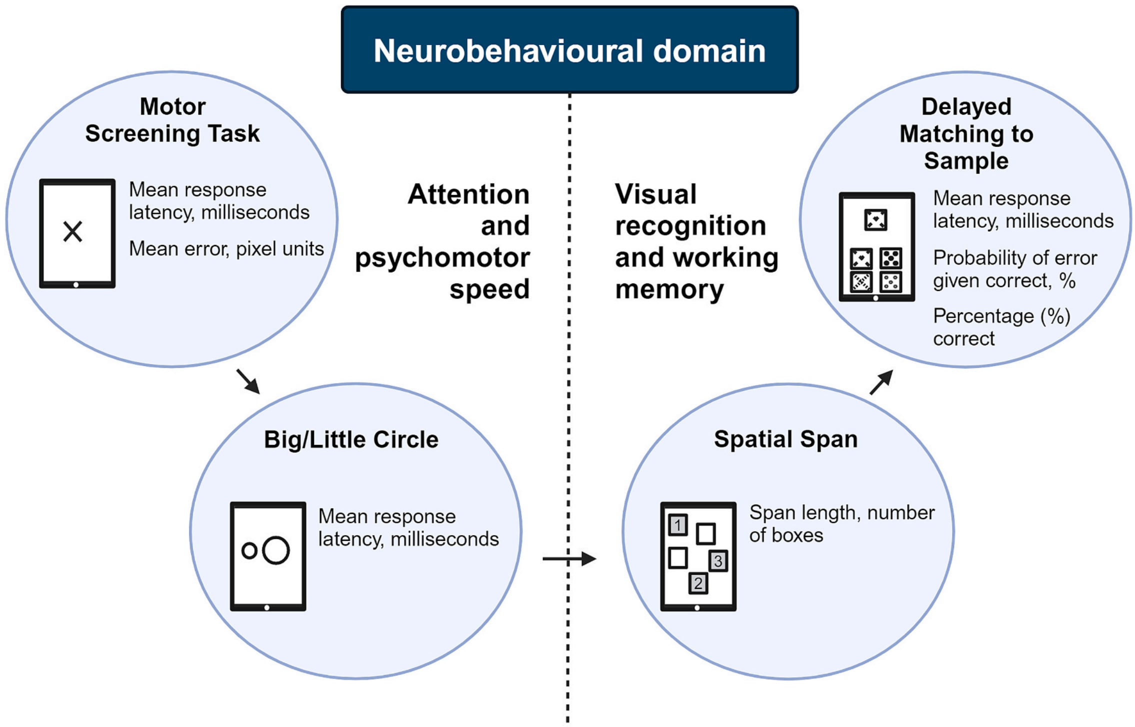

Fig. 1. Overview of the used CANTAB tests. Arrows designate the order of the tests. CANTAB, Cambridge Neuropsychological Test Automated Battery. For the best performance, both the latencies and probability of error given correct need to be low, and both *span length* and *percentage correct* need to be high.

2.5. Statistical analysis

Statistical analysis was done in R version 4.4.2 and RStudio, "Kousa Dogwood" release, version 2024.12.0.467 (RStudio: Integrated Development Environment for R, PBC, Boston, MA). Statistical significance was defined as a P-value ≤ 0.05 from 2-sided tests. Cord blood IGF1 was log10-transformed to comply with normality. Two segments of main analyses were conducted: 1) Analyses between residential green space exposure and cord blood IGF1, and 2) analyses between green space and cognition, with IGF1 as a mediator. Missing values were listwise deleted.

Linear regression models were used to associate cord blood IGF1 with residential, prenatal green space exposure. The model was adjusted for maternal age, education, parity, time spent at the residence at birth, and newborn sex, gestational age, birthweight, and cord blood plasma insulin levels (supplementary eMethods 3; supplementary eFig. 2). We adjusted for the technical storage time variable, defined as time between sample collection and measurement. Collinearity was checked by the variance inflation factor (VIF) test using the "car" package (Fox, 2019) and confounding was checked by removing the individual covariates, examining the change in effect estimate and standard error. Effect estimates are expressed as a percentage difference with 95 % CI in IGF1 levels per interquartile range (IQR) increment in residential green space. Sensitivity analyses were performed based on the directed acyclic graph (DAG) (supplementary eFig. 2). These include additional adjustment for pregnancy complications, BMI, prenatal air pollution and maternal alcohol consumption or smoking during pregnancy, alongside stratification by sex and season of delivery. Additionally, interaction terms were examined, and analyses re-conducted without participants who moved within the last trimester.

IGF1 was examined as a predictor of the principal components of cognition. As IGF1 was log10-transformed, estimates were expressed as the change in the principal component variable per 10 % increase in cord blood IGF1, with 10 % chosen to represent a relevant change within the observed distribution.

Mediation analysis between the green space buffers and the first cognitive domain of attention/psychomotor speed, with IGF1 as a mediator, was done using the *mediation* package in R (Tingley et al., 2014). For further information about the mediation procedure and choice of covariables for the mediator and outcome models, see supplementary eMethods 4 and supplementary eFig. 3. GraphPad Prism 8 was used to make graphs.

2.6. Roles of the funding source

The funder of this study did not influence the study design, data collection, analysis, interpretation, or writing of this article.

3. Results

3.1. Study population

At the time of birth, the mean age (SD) of the mothers was 29.9 (4.2) years with 66.9 % having at least gained a college degree (Table 1). The majority of mothers (54.6 %) were primiparous mothers and had a mean (SD) gestational age of 39.6 (1.4) weeks. 46.4 % of the newborns were boys. The mean weight (SD) of the newborn was 3398.9 (444) g. The mean IGF1 and insulin concentrations (SD) were 84.1 (29.8) ng/mL and 41.5 (34.0) ng/mL, respectively. The mean total green space exposure within 50–1000 m ranged from 46.6 – 52.3 % with IQR's from 20.9 to 26.5 (Table 2). The buffers were correlated with one another (supplementary eFig. 4).

At follow-up, the children had a mean (SD) age of 4.6 (0.4) years, with an average sleep duration of 11.0 (1.1) hours. The majority (55.8 %) of children watched TV or used tablets between one and two hours per day, with 8.8 % of children going above two hours.

3.2. Cord blood plasma IGF1 and prenatal green space

The determinants of cord blood plasma IGF1 can be viewed in supplementary eTable 2. After adjustment for covariables (maternal age, education, parity, years at residence, and newborn sex, gestational age, birthweight and cord blood insulin), prenatal short vegetation exposure

Table 1
Characteristics of the ENVIRONAGE mother–child pairs (n = 317).

Variables	No. (%) or mean (SD)
Mothers	
Age, years	29.9 (4.2)
Education	
None or low	19 (6.0)
Secondary education	86 (27.1)
College/university	212 (66.9)
First time mothers	173 (54.6)
BMI	24.2 (4.5)
Newborn	
Female	170 (53.6)
Birth weight, g	3398.9 (444.0)
Gestational age, weeks	39.6 (1.4)
Cold season of delivery*	173 (54.6)
IGF1, ng/mL	84.1 (29.8)
Insulin, ng/mL	41.5 (34.0)
$PM_{2.5}$, μg/m^3	14.0 (2.5)
Children	
Age at follow up, years	4.6 (0.4)
Sleep duration, h	11.0 (1.1)
Screen time	
Less than 1 h per day	112 (35.3)
Between 1 and 2 h per day	177 (55.8)
More than 2 h per day	28 (8.8)
Maternal education at follow up	
None or low	13 (4.1)
Secondary education	76 (24.0)
College/university	228 (71.9)

BMI was pre-pregnancy BMI, measured 7-9th gestational weeks. *: Delivery between 1st of October and 31st of March. IGF1, insulin-like growth factor 1; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; H, hours.

Table 2
An overview of the green space buffer characteristics in the ENVIRONAGE cohort.

Buffers	Mean (%)	IQR (%)	25th percentile (%)	Median (%)	75th percentile (%)
Total green					
50 m	46.6	24.2	34.5	46.8	58.7
100 m	48.5	21.5	38.4	47.9	59.9
500 m	51.6	20.9	40.5	53.4	61.4
1000 m	52.3	26.5	39.5	55.4	66.0
Short vegetation					
50 m	33.9	18.9	24.5	33.7	43.4
100 m	33.2	15.9	25.7	32.8	41.6
500 m	28.4	9.4	23.3	28.6	32.7
1000 m	24.5	8.4	19.9	24.3	28.4
Tall vegetation					
50 m	12.8	14.3	3.4	8.0	17.7
100 m	15.3	14.6	6.6	11.0	21.2
500 m	23.1	20.3	11.8	20.2	32.0
1000 m	27.8	25.1	15.2	26	40.3

Short vegetation was defined at all vegetation below 3 m in height. Tall vegetation was defined as all vegetation above 3 m in height. Total green was a summarisation of both short and tall green. ENVIRONAGE, Environmental Influence On Ageing in Early Life; IQR, interquartile range.

within all buffers (50 – 1000 m) were found to be significantly or borderline associated with cord blood IGF1 (Fig. 2; supplementary eTable 3). The strongest effect was observed within 50 m, with an IQR increment (18.9 %) in the short vegetation increasing cord blood IGF1 with 14.7 % (95 % CI: 2.60 to 28.24 %, P = 0.016). Tall vegetation and total green space did not associate with IGF1 (supplementary eTable 3).

Sensitivity analyses were conducted based on the DAG (supplementary eFig. 2). Models were further adjusted for pregnancy complications, particulate matter with a diameter of < 2.5 μm, BMI, or whether the mother smoked or consumed alcohol during pregnancy (supplementary eTable 4). The results remained largely the same (supplementary eTable 4). Removal of mothers who moved within the last trimester decreased the estimates and increased the p-values (supplementary eTable 5).

Stratifying based on sex and season of delivery (supplementary eTable 6) revealed that girls experienced significantly stronger effects across all buffers, with the strongest difference being visible with short vegetation within 100 m (per IQR (15.9 %) increase: girls: β = 21.71 %, 95 % CI: 4.66 to 41.52 %, P = 0.012; boys: β = −1.81 %, 95 % CI: −17.72 to 17.18 %, P = 0.840). Interestingly, the effect of season of delivery flipped, with 50 and 100 m buffers being only significant during warm seasons, whereas 500 and 1000 m were only significant during cold seasons (supplementary eTable 6). There were no significant interaction effects.

3.3. *Cord blood IGF1 and cognition at 4–6 years of age*

3.3.1. *Attention and psychomotor speed*

Principal components of the cognitive measures were done for the neurocognitive domain of attention/psychomotor speed and visual recognition/working memory. The two principal components of attention/psychomotor speed consisted of the Motor Screening Task and Big/Little circle task, and explained 50.0 % and additionally 33.4 % of the variance, respectively. See supplementary eTable 1 for the characteristics of the principal components.

Unadjusted linear regression models between cord blood IGF1 and the principal components of the neurocognitive domains showed a significant negative association between IGF1 and the first principal component of attention/psychomotor speed (β = −6.06 per 10 % increase in IGF1, 95 % CI: −9.52 to −2.61, P < 0.01). Higher cord blood IGF1 was inversely associated with principal component 1 (in other words, faster reaction speeds). The other principal component was not associated with IGF1 (per 10 % increase in IGF1: principal component 2 of attention/psychomotor speed: β = 0.33, 95 % CI: −2.55 to 3.21, P = 0.821).

When further adjusted for maternal education, child age, sex, screen time, and average sleep duration at the time of follow-up, the estimate between the first principal component of attention/psychomotor speed and IGF1 decreased, although the significance did not change (β = −2.18 per 10 % increase in IGF1, 95 % CI: −3.49 to −0.88, P < 0.01).

We found that IGF1 significantly and inconsistently mediated the association between short vegetation exposure within 50 and 100 m and the first principal component of attention/psychomotor speed (for an IQR increment: 50 m (IQR = 18.9 %): indirect effect = −0.03, 95 % CI: −0.07 to −0.004, P = 0.024; 100 m (IQR = 15.9 %): indirect effect = −0.03, 95 % CI: −0.06 to −0.001, P = 0.050) (Table 3). 500 m and 1000 m presented with borderline significant results (P = 0.072 and P = 0.070, respectively). Thereby, short vegetation decreased the latencies through IGF1. IGF1 was not found to mediate associations between tall vegetation exposure or total green space exposure and the first principal component of attention/psychomotor speed (P's > 0.05) (Table 3).

3.3.2. *Visual recognition and working memory*

The two principal components of visual recognition and working memory consisted of the tasks Spatial Span and Delayed Matching to Sample. The first principal component explained 46.7 % of the variance, and the second an additional 24.6 %. See supplementary eTable 1 for their characteristics. Unadjusted linear regressions between these principal components and cord blood IGF1 showed no associations (principal component 1: β = −0.98, 95 % CI: −4.90 to 2.95; principal component 2: β = 1.95, 95 % CI: −0.89 to 4.79).

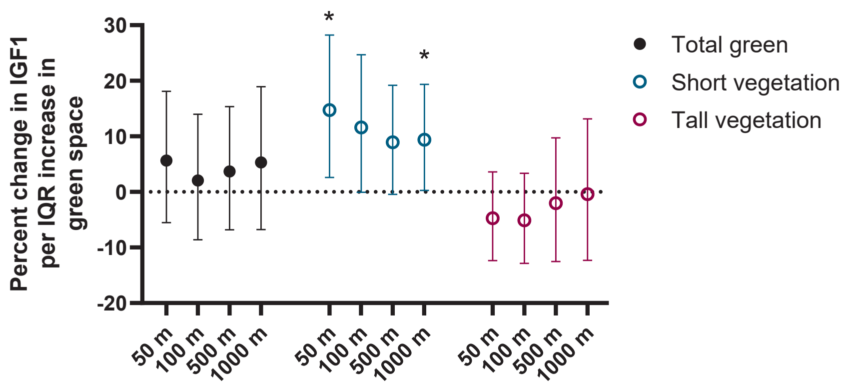

Fig. 2. Association of prenatal green space exposure in buffers from 50 to 1000 m with IGF1 in 317 ENVIRONAGE participants. Green space exposure was determined prenatally around the residence. Estimates were derived from linear regression models and are expressed as a ng/mL increase in IGF1 per IQR increase in prenatal green space exposure with 95 % CI bars. Short vegetation indicates vegetation < 3 m in height, whereas tall vegetation indicates vegetation > 3 m in height. Total green is a summarisation of both. The models contain the covariables maternal age, education, parity, time at residence, newborn sex, gestational age, weight, and insulin protein and were derived from linear regression models. CI, confidence interval; IGF1, insulin like growth factor 1; ENVIRONAGE, Environmental Influence On Ageing in Early Life. *: $P < 0.05$.

3.3.3. *Sensitivity analyses*

Sensitivity analyses revealed the results between IGF1 and the first principal component of attention/psychomotor speed to be robust (supplementary eTable 7). However, the p-value for short vegetation within 500 and 1000 m increased slightly after removal of unfocused children (supplementary eTable 7).

To better understand the underlying mediation effect of IGF1 observed between short vegetation and the first principal component of attention/psychomotor speed, we conducted additional mediation analyses on the individual CANTAB measures that made up this principal component (i.e. the Motor Screening Task (latency and probability of error) and the Big/Little Circle task (latency)). IGF1 mediated the associations between the latencies of the Motor Screening task and Big/Little Circle task and short vegetation exposure within 50 (P's = 0.014 and 0.044, respectively), 100 (P's = 0.066 and 0.060), 500 (P's = 0.080 and 0.088) and 1000 (P's = 0.058 and 0.058) m: For an IQR (18.4 %) increase in short vegetation within 50 m, the latency of the Motor Screening Task decreased by 0.45 % through IGF1 (95 % CI: −0.99 to −0.05 %, P = 0.014) (Fig. 3A). The same order of magnitude was observed for the Big/Little Circle task (indirect effect: −0.48 %, −1.16 to −0.02 %, P = 0.044) (Fig. 3B). Similar, albeit lower estimates, were noted across the other short vegetation buffers (Fig. 3, supplementary eTable 8. IGF1 did not mediate the effects between short vegetation exposure and the mean error of the Motor Screening task (P > 0.05) (supplementary eTable 8).

4. Discussion

Our longitudinal study is among the first to elucidate a potential biological mechanism linking prenatal green space exposure to improved cognitive outcomes in children, specifically highlighting the role of insulin-like growth factor 1 (IGF1).

The association between green spaces and health can be attributed to several mechanisms. Firstly, green spaces contribute to the reduction of noise and air pollution, two factors known for their role in cognition. Secondly, green spaces within close proximity might encourage physical activity and foster social interactions and community engagement, promoting mental and emotional well-being. Thirdly, the reduction in stress allows for mental and physical restoration. Despite these benefits, the biological mechanisms remain unclear.

In this study we found specifically short vegetation to have an association with IGF1, with IGF1 mediating the effect between this type of vegetation and attention/psychomotor speed. This could simply be due to the higher percentage of short vegetation compared to tall vegetation (for instance, the mean within 50 m: 33.9 % and 12.8 %, respectively), or due to a particular type of landscape having a larger impact due to e.g. ease of access or microbiome (Dockx et al., 2021). The microbiome has been found to be different between urban and rural landscapes (Flies et al., 2020), with Dockx et al., (2021) showing that short vegetation (< 3 m in height) increases the abundance of the fungal genera *Epicoccum* and *Psuedopithomyces*. While there are seemingly no studies on these genera and IGF1, both direct interactions through the skin, or indirect, through the gut-lung axis, are possible. This is strengthened by our sensitivity analysis showing a much higher impact of green space on IGF1 when the date of delivery is in a warm season, with differing aerial microbiome compositions (Núñez et al., 2021). Interestingly, we found this to change within 500 and 1000 m buffers, with a cold season of delivery having the biggest effect. Since these buffers are likely too large to have an impact on the indoor microbiome, these results may stem from colder months allowing for more intense exercise with lower temperatures. The use of green spaces, however it may change during the seasons, may in any case have de-stressing abilities. Previous studies in rats found prenatal stress to lower the IGF1 protein levels of the offspring (Basta-Kaim et al., 2014), while in humans, maternal trauma was found to negatively impact newborn IGF1 protein levels (Lamadé et al., 2021). The lowering of stress may therefore be the link between green space exposure and IGF1.

This is important, as low newborn IGF1 levels have previously been correlated with poor brain growth (Hellström et al., 2016) and poor cognitive outcomes in infants with infantile spasms (Riikonen et al., 2010). The reverse also applies, with high IGF1 levels in infants with infantile spasms having favourable cognitive outcomes (Riikonen et al., 2010). Additionally, IGF1 has in cross-sectional studies previously been found to be associated with cognition and IQ in 6 – 8 year olds, both based on Raven's Coloured Progressive Matrices (Mäntyselkä et al., 2019) and Wechsler Intelligence Scale for Children (Gunnell et al., 2005). Furthermore, IGF1 declines after reaching adulthood, and has been found to be associated with cognitive decline in the elderly, which can be reversed with an increase of IGF1 (Sonntag et al., 2013).

Other studies examining the potential biological mechanisms between green space exposure and cognition suggest that DNA methylation changes may play a role (Alfano et al., 2023, Dockx et al., 2022b, Lee et al., 2021, Vos et al., 2024, Xu et al., 2021). Lee et al., (2021) measured the association between prenatal green space exposure, DNA methylation at 2 years of age and the intelligence quotient (IQ) at 6 years of age in 59 individuals. 25 CpG sites were found to be significantly associated with green space, whereas one CpG site related to dopamine transport was also associated with IQ at 6 years of age. This is especially relevant due to dopamine neurons having been found to be able to release IGF1 (Akirov et al., 2018, Pristerà et al., 2019). Likewise, several

Table 3
Mediation analyses between prenatal green space exposure and the first principal component of attention/psychomotor speed, with cord blood IGF1 protein as mediator.

Green space buffer	Indirect effect (95 % CI)	Direct effect (95 % CI)	Total effect (95 % CI)
Total green space within 50 m	−0.013 (−0.04 to 0.012, P = 0.360)	0.068 (−0.118 to 0.245, P = 0.470)	0.055 (−0.132 to 0.227, P = 0.556)
Total green space within 100 m	−0.005 (−0.034 to 0.023, P = 0.730)	0.062 (−0.117 to 0.238, P = 0.530)	0.058 (−0.115 to 0.233, P = 0.550)
Total green space within 500 m	−0.008 (−0.039 to 0.017, P = 0.556)	0.127 (−0.022 to 0.287, P = 0.086)	0.118 (−0.029 to 0.28, P = 0.120)
Total green space within 1000 m	−0.012 (−0.042 to 0.019, P = 0.404)	0.133 (−0.05 to 0.301, P = 0.138)	0.121 (−0.062 to 0.296, P = 0.156)
Short vegetation within 50 m	**−0.032 (−0.072 to −0.004, P = 0.024)**	0.073 (−0.097 to 0.224, P = 0.376)	0.04 (−0.125 to 0.198, P = 0.654)
Short vegetation within 100 m	**−0.026 (−0.063 to −0.0005, P = 0.046)**	0.042 (−0.11 to 0.202, P = 0.650)	0.017 (−0.142 to 0.175, P = 0.900)
Short vegetation within 500 m	−0.020 (−0.046 to 0.002, P = 0.072)	0.092 (−0.029 to 0.215, P = 0.148)	0.072 (−0.044 to 0.202, P = 0.202)
Short vegetation within 1000 m	−0.021 (−0.048 to 0.002, P = 0.070)	0.059 (−0.049 to 0.182, P = 0.302)	0.038 (−0.073 to 0.161, P = 0.492)
Tall vegetation within 50 m	0.011 (−0.005 to 0.036, P = 0.188)	0.009 (−0.144 to 0.13, P = 0.962)	0.020 (−0.12 to 0.142, P = 0.796)
Tall vegetation within 100 m	0.012 (−0.008 to 0.039, P = 0.222)	0.027 (−0.11 to 0.154, P = 0.670)	0.039 (−0.093 to 0.158, P = 0.576)
Tall vegetation within 500 m	0.005 (−0.025 to 0.036, P = 0.734)	0.082 (−0.095 to 0.246, P = 0.4)	0.087 (−0.084 to 0.249, P = 0.382)
Tall vegetation within 1000 m	0.001 (−0.028 to 0.035, P = 0.974)	0.114 (−0.087 to 0.293, P = 0.308)	0.115 (−0.082 to 0.298, P = 0.302)

Results are expressed as the change in the principal component of attention and psychomotor speed per IQR increase in the green space buffer mediated by IGF1. The cognitive domain of attention and psychomotor speed were derived from a principal component analysis of the Motor Screening and Big/Little Circle tasks from CANTAB at 4–6 years of age. Short vegetation is defined as all vegetation below 3 m in height. Covariables used for the linear regression models between prenatal, residential green space exposure and cord blood IGF1 protein, as response variable, were storage time, maternal age, education and parity, and newborn sex, gestational age, weight, and insulin protein. Covariables used for the linear regression between prenatal, residential green space exposure and the cognitive domain, as response variable, were, at the time of follow up, maternal education and child sex, age, screen time, and sleep duration. CANTAB, Cambridge Neuropsychological Test Automated Battery. N = 317.

methylation studies have shown an involvement of the serotonin pathways in relation to green space (Alfano et al., 2023, Dockx et al., 2022b, Lee et al., 2021). The serotonin type 3 receptor has been found to regulate IGF1, and *vice versa*, that the neurogenesis of serotonin type 3 receptor-dependent neurons is mediated by IGF1 (Kondo et al., 2018). Additionally, IGF1 administration increases serotonin levels in the long term (Hoshaw et al., 2008) and exhibits long-term antidepressant activity outside the conventional selective serotonin reuptake inhibitor mechanisms (Kondo et al., 2018, Park et al., 2011). This is of interest due to the lower use of antidepressants in rural areas (Giovannini et al., 2020, Rigler et al., 2003), and may be of particular importance due to the potential long-term effects of IGF1.

This study has many strengths. First of all, the use of high-resolution green space indicators, with information on green space type, cause this study to give a good estimation of residential exposure, and allows a more in-depth analysis of the mechanism behind green space exposure, based on vegetation height. While misclassification may have occurred, the high kappa-statistic of 0.94 suggest a high reliability. While the map was made in 2012, the latest birth happened in 2015, and a risk of misclassification due to changes in the green space may therefore have occurred. However, green spaces are generally stable, and the use of two different maps may also cause bias. Additionally, the similarity of our results before and after the addition of several covariables and after several sensitivity analyses suggest our findings are robust. However, we do not have information regarding the use of green spaces nor the activities performed in there. The study population also has a higher percentage of people with a college degree, as compared to the population of Flanders (66 % and 50 % (Steunpunt.werk.be, 2023), respectively), making generalization less ideal. We do not know whether the cognitive benefits stem from prenatal or current green space exposure, as many of the children will likely live in the same environment as prenatally. Finally, we did not measure the autocrine IGF1 levels, as this would require an invasive procedure. However, endocrine IGF1 crosses the blood–brain barrier, and this therefore serves as an approximation of the brain IGF1 levels. IGF1 has furthermore a relatively short half-life. Despite the short half-life, IGF1 has been shown to have relatively robust levels, being used for detection of growth hormone deficiency and −excess, as it's not as responsive to sleep patterns, food intake or exercise as growth hormone (Ketha and Singh, 2015).

5. Conclusions

The higher IGF1 levels at birth observed in association to prenatal green space and its mediation role between green space and the neurocognitive domain of attention and psychomotor speed suggest that such environments may enhance neurodevelopmental processes.

From a public health perspective, these findings underscore the necessity of ensuring the presence of green spaces during pregnancy, not only for physical well-being but also for optimizing brain development in future generations. Future research is needed for confirming these associations, and determining whether the effect is through particular landscape structures, microbiota or other factors. By elucidating the IGF1 pathway, we provide a new potential mechanistic understanding and therefore a fundamental basis for establishing causation. The significance of this potential mechanistic evidence cannot be overstated, as it provides robust support for evidence-based policies that have far-reaching implications for urban planning and maternal health initiatives.

CRediT authorship contribution statement

Anna E. Soerensen: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Esmée M. Bijnens:** Writing – review & editing, Software, Investigation. **Yinthe Dockx:** Writing – review & editing, Investigation. **Dries S. Martens:** Writing – review & editing, Methodology. **Hanne Sleurs:** Writing – review & editing, Investigation. **Lore Verheyen:** Writing – review & editing, Investigation. **Michelle Plusquin:** Writing – review & editing, Conceptualization. **Tim S. Nawrot:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

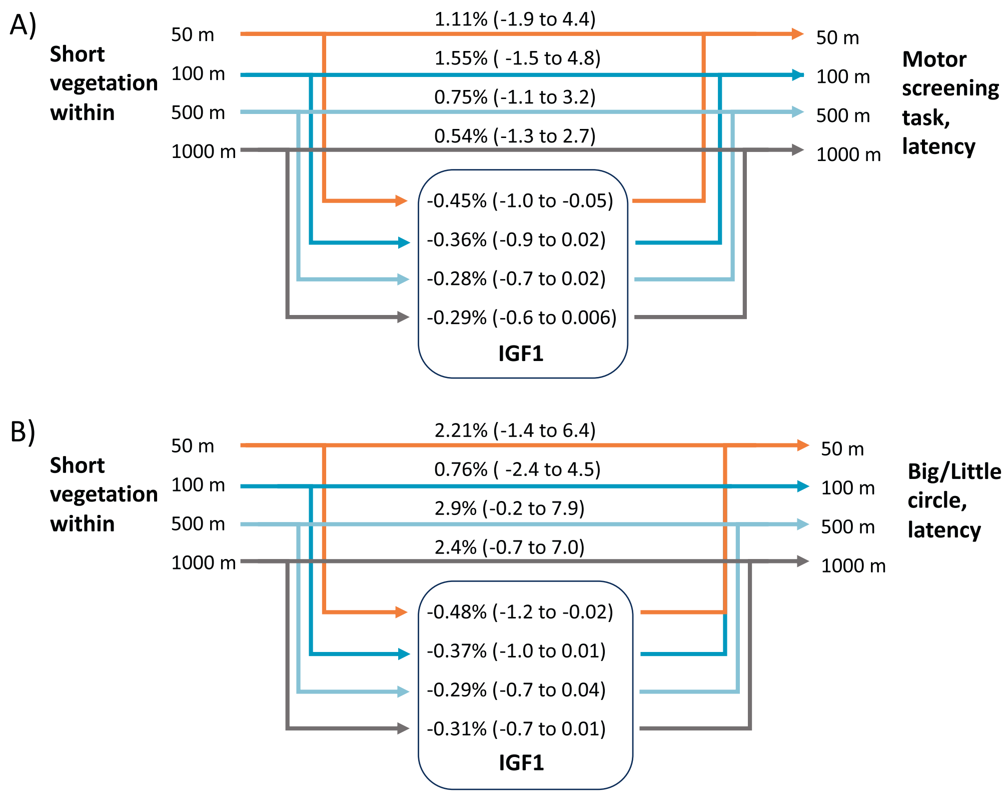

Fig. 3. IGF1 mediation analysis between prenatal, residential short vegetation exposure and cognitive measures in 317 ENVIRONAGE participants. Mediation analyses were done between short vegetation (vegetation < 3 m in height) and childhood cognitive measures from the Cambridge Neuropsychological Test Automated Battery (CANTAB), being the latency of A) the motor screening task, and B) the big/little circle task. Estimates are presented as percentages changes in the cognitive latencies mediated by IGF1, both the indirect effects, shown in the IGF1 box, and direct effects, with a 95 % confidence interval in brackets. All estimates are shown per IQR increase in the vegetation buffer. Negative values indicate a faster reaction speed, and positive values a slower reaction speed. Covariables used for the linear regression models between prenatal vegetation and newborn IGF1, as response variable, were storage time, maternal age, education, parity, time at residence, and newborn sex, gestational age, weight, and newborn insulin protein. Covariables used for the linear regression between prenatal vegetation and the cognitive measures as response variable, were maternal education and child sex, age, screen time, and sleep duration at the time of follow up. ENVIRONAGE, Environmental Influence On Ageing in Early Life.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109849.

Data availability

Data will be made available on request.

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