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Outdoor Light at Night and Children’s Body Mass: A Cross-Sectional Analysis in the Fr1da Study

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Abstract:	Background Emerging evidence supports an association between light at night (LAN) exposure with obesity or overweight in adults. However, effects of LAN exposure during childhood have yet to be further investigated. Objective In this study, we aimed to determine whether LAN exposure is associated with body mass in young children. Research design and method We used data from the Fr1da cohort study which screened children for early-stage islet autoimmunity in Bavaria, Germany from February 2015 to March 2019. A total of 62,212 children aged <11 years with complete residential information was included in the analysis. Self-reported weight and height were used to calculate age- and sex-specific body mass index (BMI) z-scores. LAN exposure was based on remotely sensed images from Visible Infrared Imaging Radiometer Suite and assigned to the children’s residencies. We used generalized additive models to estimate the associations between LAN exposure and BMI adjusting for potential confounders. Results We observed an increase in BMI z-scores of 34.0% (95% confidence interval (CI): 25.4-42.6) per 10 nW/cm2/sr increment in LAN exposure at baseline (2015) and of 32.6% (24.3-41.0) for LAN exposure one year prior to screening, both adjusted for age and sex. Similar associations were observed after adjustment for socioeconomic status and urbanization degree. Conclusion Our findings suggest that outdoor light exposure may be a risk factor for weight gain during childhood.
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Submission of manuscript: "Outdoor Light at Night and Children's Body Mass: A Cross-Sectional Analysis in the Fr1da Study"

02 January 2023

Dear Editor,

Enclosed please find our manuscript entitled "**Outdoor Light at Night and Children's Body Mass: A Cross-Sectional Analysis in the Fr1da Study"** for your consideration of publication in *Science of Total Environment*.

The global prevalence of childhood obesity and overweight has increased worldwide (Abarca-Gómez L et al., The Lancet, 2017). Epidemiological studies have shown a substantial increase in industrial and developed societies (Ogden CL, JAMA, 2008). This threatens the health of a generation of children because being obese or overweight during childhood is associated with a variety of negative health consequences in later life (Daniels S, International journal of obesity, 2009). Even though a sedentary lifestyle and increased calorie intake are considered as initial causes, the effect of environmental stressors is not fully understood.

In this epidemiological study based on data from the Fr1da children cohort conducted in Bavaria, Germany in 2015-2019 (JAMA 2020), we investigated the effect of residential exposure to light at night (LAN) on children's body mass. Our results provided evidence that increased exposure to outdoor LAN was significantly associated with higher body mass in children. This suggests that outdoor light exposure may be a risk factor for weight gain and may draw attention to investigating environmental light as a potential obesogenic factor during human development. We believe that the

Fr1da cohort is unique as it comprises an unselected public health cohort from a specific region (Bavaria, Germany) looking for environmental risk factors.

We declare that this work is original and has not been published elsewhere, nor is it currently under consideration at another journal. We have no conflict of interest to disclose.

Please refer any questions to mahnaz.badpa@helmholtz-muenchen.de.

Thank you for your assistance with this manuscript, and look forward to hearing from you.

Sincerely Yours,
Mahnaz Badpa

Outdoor Light at Night and Children's Body Mass: A Cross-Sectional Analysis in the Fr1da Study

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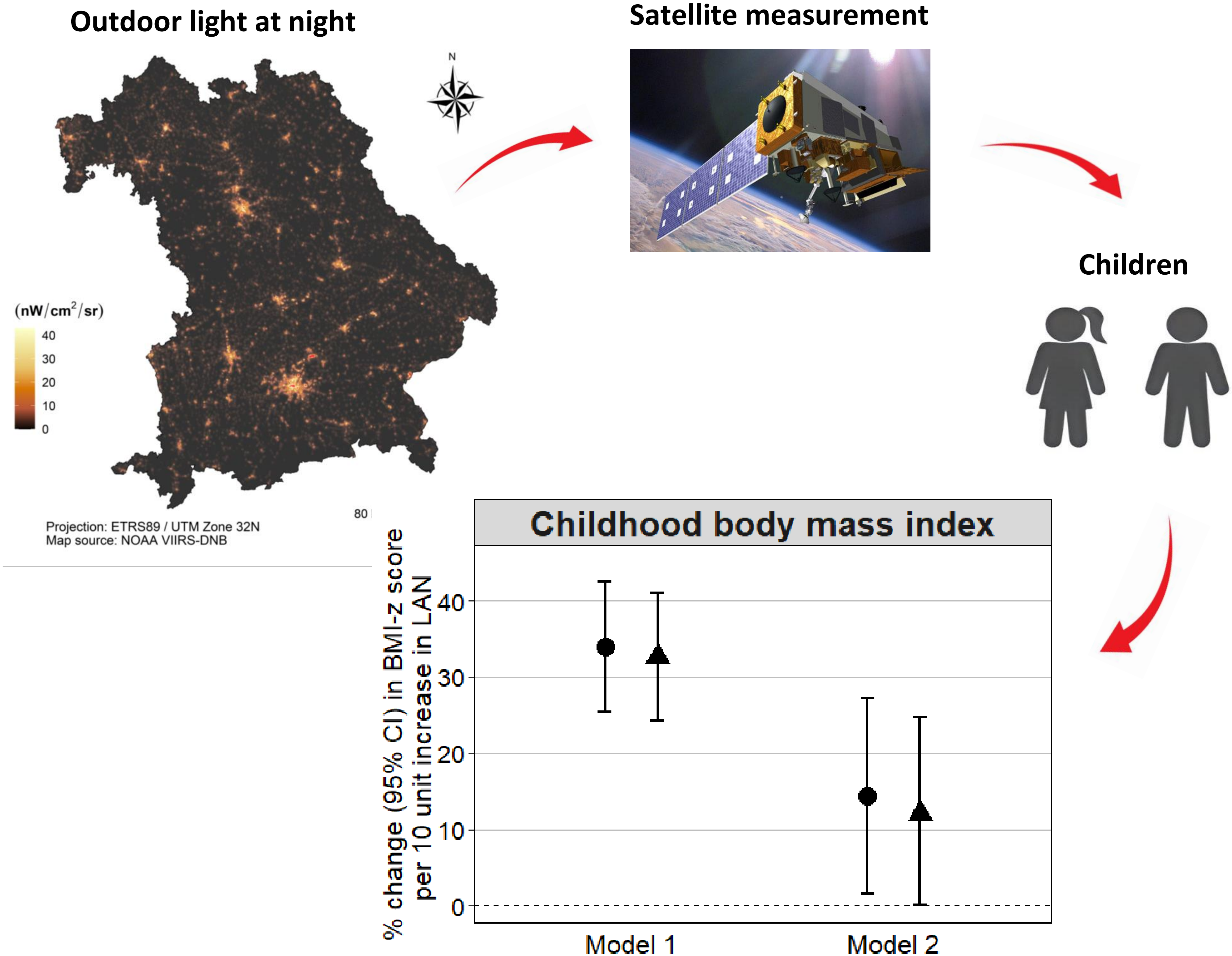
Graphical Abstract



Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex, percentage of low-income households, and urbanization degree

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Highlights

- A large population-based cohort of children is investigated.
- Address-level exposure to outdoor artificial light at night is included.
- Night-time light significantly increased children’s body mass index.
- Further long-term studies are need to confirm these results.

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Abstract

Background: Emerging evidence supports an association between light at night (LAN) exposure with obesity or overweight in adults. However, effects of LAN exposure during childhood have yet to be further investigated.

Objective: In this study, we aimed to determine whether LAN exposure is associated with body mass in young children.

Research design and method: We used data from the Fr1da cohort study which screened children for early-stage islet autoimmunity in Bavaria, Germany from February 2015 to March 2019. A total of 62,212 children aged <11 years with complete residential information was included in the analysis. Self-reported weight and height were used to calculate age- and sex-specific body mass index (BMI) z-scores. LAN exposure was based on remotely sensed images from Visible Infrared Imaging Radiometer Suite and assigned to the children's residencies. We used generalized additive models to estimate the associations between LAN exposure and BMI adjusting for potential confounders.

Results: We observed an increase in BMI z-scores of 34.0% (95% confidence interval (CI): 25.4-42.6) per 10 nW/cm^2/sr increment in LAN exposure at baseline (2015) and of 32.6% (24.3-41.0) for LAN exposure one year prior to screening, both adjusted for age and sex. Similar associations were observed after adjustment for socioeconomic status and urbanization degree.

Conclusion: Our findings suggest that outdoor light exposure may be a risk factor for weight gain during childhood.

Keywords: Long-term exposure, light at night, outdoor light exposure, body mass index.

1. Introduction

Over the past few decades, the global prevalence of childhood obesity and overweight has increased substantially[1-3]. For example, from 1970 to 2006, the prevalence rates in U.S. children and adolescents more than doubled[4, 5]. Similar increasing patterns are reported in Australia, China and the United Kingdom[6]. In fact, according to global pooling studies, almost all countries have prevalent obesity/overweight during childhood and adulthood[7-9]. This threatens the health of a generation of children because being overweight or obese during childhood is associated with a variety of negative health consequences in later life, such as cardiovascular diseases, gastrointestinal conditions, cancers, metabolic complications, and diabetes [10-13].

Obesity is a multifactorial disorder affected by interacting genetic and non-genetic factors[11], with a result of an imbalance between energy intake and expenditure[14, 15]. While a sedentary lifestyle and calorie intake are considered as initial causes, attempts to alleviate their detrimental impacts have not led to significant changes in the prevalence of obesity. It implies the influence of additional factors that may play a role in the etiology of obesity [16, 17]. Artificial light exposure is among the suspected factors.

In modern societies, urbanization and infrastructure development have led to higher exposure to artificial lights, emitted by residential areas, road illumination and economic activities[18]. The widespread use of electrical lighting has beneficial effects on the quality of human life and suits contemporary lifestyles [14, 19]. However, benefits have been accompanied by adverse health impacts, mainly through disrupting circadian processes driving physiological mechanisms including metabolism[20], sleep-wake cycles[21], and body mass[22]. For example, several epidemiological studies showed a negative association between light at night (LAN) exposure and obesity [23-25] and diabetes[26]. In the U. S., the increasing trends in LAN exposure paralleled the increase in obesity rates [27]. Night-shift workers with disrupted sleeping and eating phases were more likely to be obese compared with day-shift workers [28, 29]. LAN exposure was further associated with the risk of hormone-dependent types of cancer such as breast and prostate cancer in the U.S.[30], Spain[31], and worldwide[32].

However, although childhood plays a critical role in the establishment of lifelong adiposity trajectories[33], most previous studies focused on adults and little is known about the LAN impacts on children's health. Therefore, the present study investigated the association between exposure to outdoor LAN with BMI in children in Bavaria, Germany, using data from the Fr1da study, a large cohort of Bavarian children.

2. Methods

2.1. Study population and design

The present study was based on data from the Fr1da cohort in Bavaria, Germany. From February 2015 until March 2019, more than 90,000 children were recruited in this population-based screening for early-stage type 1 diabetes (having ≥2 pancreatic islet autoantibodies). Inclusion criteria were residing in Bavaria and having no previous diagnosis of diabetes. Recruitment was offered by primary care pediatricians during medical check-up visits and written informed consent was obtained from the parents or legal guardians. Information on participants' residential addresses at the screening time and individual characteristics including age, sex, weight, and height were collected with self-administered questionnaires at the visit. The study design is described in detail elsewhere.[34] We included 62,630 Fr1da participants aged < 11 years with valid residential information in our analysis (Figure 1). We also repeated the main analyses using Fr1da PLUS data (n=32,806), the second phase of Fr1da conducted between October 2019 and March 2021 in the same area (Supplemental Figure S1). The study protocol was approved by the institutional review board at Technical University Munich.

2.2. Outcome definition

Height and weight were used to calculate BMI (BMI= weight (kg)/height (m^2)). Age- and sex-specific BMI z-scores were then calculated using the World Health Organization Child Growth Standards[35] through the following formula:

$$\text{BMI z-score: } [(\text{BMI}/\text{M})\text{L} - 1]/(\text{L}\times\text{S}).$$

where M= median, L= Box-Cox power transformation, and S= coefficient of variation. Missing BMI z-scores (n= 12,574) were imputed using regression predictions for deterministic imputation. Participants with a BMI z-scores > 5 or < −5 were excluded (n=79), followig the Fr1da base paper[36].

2.3. LAN exposure

Population-based studies [32, 37, 38] investigating LAN exposure primarily used data derived from the U.S. Defense Meteorological Satellite Program (DMSP) images[39]. However, the application of the DMSP data in epidemiological research may cause exposure misclassification, mainly due to their poor spatial resolution (~5 km^2 at nadir). In 2011, a new instrument namely Visible Infrared Imaging Radiometer Suite (VIIRS)[40, 41] was launched jointly by National Aeronautics and Space Administration (NASA) and National Oceanic and Atmospheric Administration to collect high-quality radiometric data with worldwide coverage [39]. The new instrument has several improvements, such as a higher spatial resolution (~ 750 m^2 at nadir), a finer radiometric quantization (14 bit), a lower light imaging detection limit (~ 2×10^{-11} W cm^{-2} sr^{-1}), a wider dynamic range, radiometric calibration, and having no saturation. Moreover, the VIIRS overpass time is after midnight (around 1:30 a.m.), whereas the DMSP overpass time was early evening (around 7:30 p.m.).[42] A recent study in Israel[43] compared DMSP and VIIRS data to investigate the association between light pollution and breast cancer incidence and reported the VIIRS data being a significantly stronger predictor.

We used monthly and yearly average raster grids from 2014 to 2019 with the coverage of 180° W, 75° N, 180° E, and 65° S and the spatial resolution of ~300m x 400m and assigned them to the residential address of the study participants. The address geocoding procedure has been described in our previous paper[44]. Exposure to LAN was assessed 1) at baseline (2015), and 2) within one year prior to screening (by averaging the monthly mean values from the month of screening to the 12th month beforehand). We excluded outliers defined as LAN values more than the 3rd quartile + 3*interquartile range (n=339) (Figure 1).

2.4. Confounders

Individual-level covariates included screening age (continuous) and sex (female or male). Percentage of households with low income provided by WiGeoGIS[45] maps at 1x1 km² spatial resolution for 2014 was used as a measure of neighborhood socioeconomic status (SES). Level of urbanization of residence was derived from the Eurostat[46] maps for 2018 comprising three categories: 1=cities (highly urbanized areas), 2=towns and suburbs (intermediate urbanized areas) and, 3=rural areas (low-urbanized areas).

2.5. Statistical analysis

To evaluate the association between LAN exposure and changes in BMI z-scores we used generalized additive models adjusting for confounding factors. We included LAN as a linear term and adjusted for age and sex (model 1) and additionally for the percentage of low-income households and urbanization degree (model 2). Effect estimates are presented as percent change with 95% confidence intervals (CIs) per 10 nW/cm^2/sr increase in LAN. To examine the exposure-response curve, we included LAN as a thin-plate spline and plotted the respective curves.

Since the Fr1da PLUS screening took place mostly during the Covid-19 pandemic, we generated two pandemic-related variables and further added them to the validation analysis: 1) a binary lockdown variable indicating whether the child was screened during severe lockdown periods (yes vs. no); 2) a monthly time trend starting from the first month of screening and added as a linear term.

In sensitivity analyses we 1) investigated whether the associations were similar in preschool ages by restricting the dataset to children aged 1.75 to 5.99 years; 2) checked the confounding role of other SES factors by replacing urbanization degree with population density (low/medium density: ≤400 vs. high density: >400 persons/km^2); 3) repeated all analyses using the dataset excluding imputed BMI z-scores.

All statistical analyses were performed using R 4.0.2 for Windows with the “mgcv” package and spatial analysis tools in the “raster”, “rgdal”, and “sp” packages. A p value <0.05 was considered statistically significant.

3. Results

3.1. Descriptive statistics

A total of 62,212 participants was included in our analyses. The mean age was 3.33±1.28 years, 48.3% were female and the mean BMI z-scores was 0.12±1.03. The mean LAN exposure was 7.93±7.78 nW/cm^2/sr at baseline and slightly higher with 8.31±7.97 nW/cm^2/sr within one year prior to screening (Table 1).

3.2. Regression models

Per 10 nW/cm^2/sr increment in LAN, BMI z-scores significantly increased by 33.99% (95% CI: 25.42-42.56) at baseline and by 32.63% (24.27-40.99) within one year before screening (model 1). Similar associations were observed when additionally controlling for low-income households and urbanization degree but in smaller magnitude (model 2). When stratified by sex, the effects were much more pronounced in males than in females (Table 2).

The inclusion of LAN as smooth function indicated linear relationships between both exposure variables and BMI z-scores (Supplemental Figure S2).

In sensitivity analyses, associations remained stable when we restricted the dataset to preschool-aged children. Controlling for population density instead of urbanization degree resulted in slightly higher estimates. Lower estimates were seen after the exclusion of imputed BMI z-scores, but only for the model 1 adjustment set (Figure 2, Supplemental Table S1).

The validation analysis also confirmed positive and statistically significant associations, although the estimates were attenuated. Associations remained robust when further adjusting for the pandemic-related variables (Figure 2, Supplemental Table S2).

4. Discussion

Despite the growing body of evidence on the adverse effects of light pollution on human health, the planet has been more exposed to LAN over recent years [47]. In this large cohort of young children, we explored the association of outdoor LAN levels at baseline and one year prior to screening with BMI z-scores. Our results provide epidemiological evidence that exposure to LAN is significantly associated with higher BMI after controlling for demographic and SES factors.

Despite the limited studies conducted, our findings were consistent with previous studies in children, adults, and animals, meaning that variation in light exposure may affect body mass [17, 48, 49]. In a recent Chinese study among over 47,000 children and adolescents aged 6–18 years, participants exposed to higher outdoor LAN levels had larger BMI z-scores (β= 0.26, 95% CI: 0.18–0.33 per unit increase in LAN) and higher odds of being overweight or obese (the third quartile vs. the lowest quartile: overweight + obesity: OR= 1.40, 95% CI: 1.25–1.56; obesity: OR= 1.46, 95% CI: 1.29–1.65,)[50]. A Korean cross-sectional study among 10,040 adults found a positive association between outdoor artificial LAN and obesity, after adjustment for various confounders (OR= 1.20; 95% CI= 1.06-1.36)[25]. A large-scale ecological study looking at data from more than 80 countries around the world reported a positive association between outdoor LAN exposure with overweight and obesity in adult women and men (B= 0.002–0.009, t= 2.739–2.877, $P<0.01$ and B= 0.003–0.043, t= 1.972–2.658, $P<0.1$, respectively), after adjusting for per capita GDP, level of urbanization, birth rate and regional differences in overweight and obesity prevalence[14]. A meta-analysis of 12 studies reported that higher LAN exposure was associated with 13% (summary odds ratio (SOR)= 1.13; 95% CI: 1.10–1.16) and 22% (SOR= 1.22, 95% CI; 1.07–1.38) higher odds of overweight and obesity, respectively[51].

Consistent results were reported for the association of LAN with BMI and the risk of overweight/obesity in shift workers. For example, a meta-analysis including 28 studies revealed higher odds of obesity/overweight for night shift workers (OR= 1.23; 95% CI= 1.17-1.29)[52]. However, the results may not be generalized to the general population because the levels of LAN exposure in shift workers are substantially higher than in the general population.

Even though this is an epidemiological study looking into the links between LAN exposure and BMI and the findings do not directly attribute a causal relationship, the results are in line with results from previous laboratory experiments[53]. Fronken et al.[49] reported changes in the circadian clock in mice exposed to dim LAN temporally altered feeding behavior and increased weight gain. Arbel et al.[54] showed that after a 6-week period and under similar locomotor activity and calorie intake conditions, mice fed only during the 12-h light phase gained significantly more weight than mice fed only during the 12-h dark phase (32 ± 1.5 g and 26 ± 1.7 g in the case and control groups, respectively; $p < 0.05$).

Several pathways have been suggested through which artificial light pollution could potentially affect human health. For example, it is hypothesised that LAN can alter the circadian rhythm. Circadian cycles regulate almost all organisms to synchronize their physiologic process with daily changes in the environment [55]. Disruption of the 24-h light-dark cycle may cause both external and internal desynchrony, impair metabolic functions and result in a variety of disorders such as obesity and diabetes[56, 57].

Circadian misalignment induced by LAN exposure can also affect sleep duration. Studies showed short sleep duration was associated with obesity in all age groups[58] and children[59]. A review by Cho et al. reported negative health effects of exposure to bright light while sleeping in children and adolescents[60]. Sleep deprivation and desynchronized sleep-wake cycles may affect metabolism and lead to higher risks of obesity[51]. In addition, it can induce behavioural changes such as dietary patterns and physical activity which might be potential mediators in the LAN-obesity relationship[61]. Studies in humans have shown that phase-delayed feeding patterns are associated with altered metabolism and increased BMI[62].

Another pathway could be through suppression of nocturnal melatonin, a pineal hormone which is primarily known for its critical regulating role in circadian rhythms, sleep onset and immune system[63]. Melatonin secretion is low during the daytime but high in the dark. Exposure to light during evening and night can delay or suppress normal melatonin secretion which can result in several diseases in humans, including different types of cancer, metabolic syndrome, and weight gain[64]. An experimental study reported significantly lower melatonin concentrations by exposure to light in both children and adults[65]. The study also showed melatonin suppression by light was particularly pronounced in children, suggesting that melatonin is more sensitive to light during childhood.

Strengths and Limitations

Our study has several strengths. First, to the best of our knowledge, this study is the first epidemiological evidence of the associations between outdoor LAN in pre-pubertal children. Second, This study is based on a large sample size which enabled us to investigate the associations in a statistically precise manner. Third, participants were geographically distributed across the study area which ensured large exposure contrasts. Fourth, we used the VIIRS nighttime light radiance data that have significant improvements in many aspects over the DMPS data which were mainly used in previous epidemiological studies. Fifth, along with the evidence from other cross-sectional and laboratory studies, the association found between outdoor LAN and childhood body mass in our study may help change governmental policy and public health strategies to reduce outdoor LAN. Finally, we also performed validation and sensitivity analyses and the results were similar to the main results, indicating the robustness of our findings.

Our results may be subjected to several limitations. First, we used satellite data to estimate individual LAN exposure, while outdoor LAN values may not precisely reflect individual LAN exposure as indoor LAN from electronic lamps, television, smartphones and computer screens can also affect individual exposure levels. However, the objective of this study was to investigate outdoor light pollution in order to determine whether it is associated with children's health, especially BMI level, which was found to be significantly associated. In addition, compared to indoor LAN, outdoor LAN exposure is more likely to be reduced by effective government regulations to limit outdoor artificial light pollution. Second, it has previously been shown that the health effects of LAN are related not only to the intensity of light per se, but also to the exposure conditions such as the duration and biological time of the exposure [60]. These data were not available in our study. The lack of residential history is another limitation. The residential addresses at the screening time were used as a proxy measure for exposure to LAN. Relocation and changes in light pattern might have led to exposure misclassification and biased risk estimates. However, we believe misclassification bias due to mobility changes during childhood to be relatively small because of low mobility rates. A German study reported that 73.3% of the study children lived almost half of their life at the registration address or nearby[66]. Moreover, the BMI variable used in this study was based on self-reported information on children’s weight and height, which is prone to misclassification. Finally, because Fr1da was designed to investigate the early stages of pancreatic islet autoimmunity, the collected data are insufficient for an in-depth study. For example, we could not determine potential contributors including indoor lighting and lifestyle-related factors.

5. Conclusion

Our results show that increased exposure to outdoor LAN was associated with higher body mass in children. This may draw attention to investigating environmental light as a potential obesogenic factor during human development, suggesting that lowering artificial LAN levels and returning to natural light patterns might be useful interventions for pediatric obesity prevention. Continued research on the impact of indoor and outdoor LAN and their independent and combined effects on human health as well as further interventional studies are needed.

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Authors' contributions

All authors contributed to the study design and conceptualization. The underlying data were verified and analyzed by MB, KW, and AS, and all authors interpreted the findings. The manuscript was drafted by MB with support from KW, AS, and AGZ. All authors read and critically revised the manuscript and approved the final version. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AGZ led the project and had final responsibility for the decision to submit for publication.

Conflict of interest statements

None declared.

Role of funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Ethics committee approval

The Fr1da study was approved by the institutional review board at Technical University Munich

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Table Captions

Table 1. Descriptive statistics of the study participants

Table 1. Percent changes (95% CIs) in BMI z-score per 10 nW/cm^2/sr increase in LAN

Table 2. Descriptive statistics of the study participants

Study variables	Fr1da (N=62,212)		
	Mean ± SD / N (%)	**Min**	**Max**
Age (years)	3.33 ± 1.28	1.00	10.97
Sex (female)	29,690 (48.3)		
BMI z-score (n miss=1,034)	0.12 ± 1.03	-4.93	4.97
Households with low income (<1,250 €) (%)	20.71 ± 22.31	0.00	100.00
Urbanization degree			
cities	21,130 (34.0)		
towns and suburbs	23,549 (37.8)		
rural areas	17,533 (28.2)		
LAN (nW/cm^2/sr)			
Baseline exposure	7.93 ± 7.78	0.00	42.91
One-year exposure	8.31 ± 7.97	0.15	42.99

SD: Standard deviation; **Min**: Minimum; **Max**: Maximum; **BMI z-score**: Age- and sex-specific BMI; **N miss**: Number of missing observations; **LAN**: Light at night; **nW/cm^2/sr**: nanoWatts per square centimetre per steradian; **Baseline exposure**: Exposure in the study base year (2015); **One-year exposure**: Exposure within one year prior to screening.

Table 3. Percent changes (95% CIs) in BMI z-score per 10 nW/cm^2/sr increase in LAN

LAN (nW/cm^2/sr)	Model 1[a]	Pvalue	Model 2[b]	Pvalue
Total				
Baseline exposure	34.0 (25.4 - 42.6)	<0.001	14.4 (1.6 - 27.2)	0.03
One-year exposure	32.6 (24.3 - 41.0)	<0.001	12.1 (0.0 - 24.8)	0.04
Female				
Baseline exposure	18.9 (9.1 - 28.7)	<0.001	3.3 (-11.1 - 17.6)	0.66
One-year exposure	19.5 (9.9 - 29.0)	<0.001	4.8 (-9.4 - 19.0)	0.51
Male				
Baseline exposure	55.6 (40.2 - 71.0)	<0.001	31.2 (8.6 - 53.8)	0.01
One-year exposure	51.6 (36.5 - 66.6)	<0.001	23.7 (1.3 - 46.2)	0.04

LAN: Light at night; **nW/cm^2/sr**: nanoWatts per square centimeter per steradian; **Baseline exposure**: Exposure in the study base year (2015); **One-year exposure**: Exposure within one year prior to screening.

[a] Model 1 shows the estimates after adjusting for age and sex.

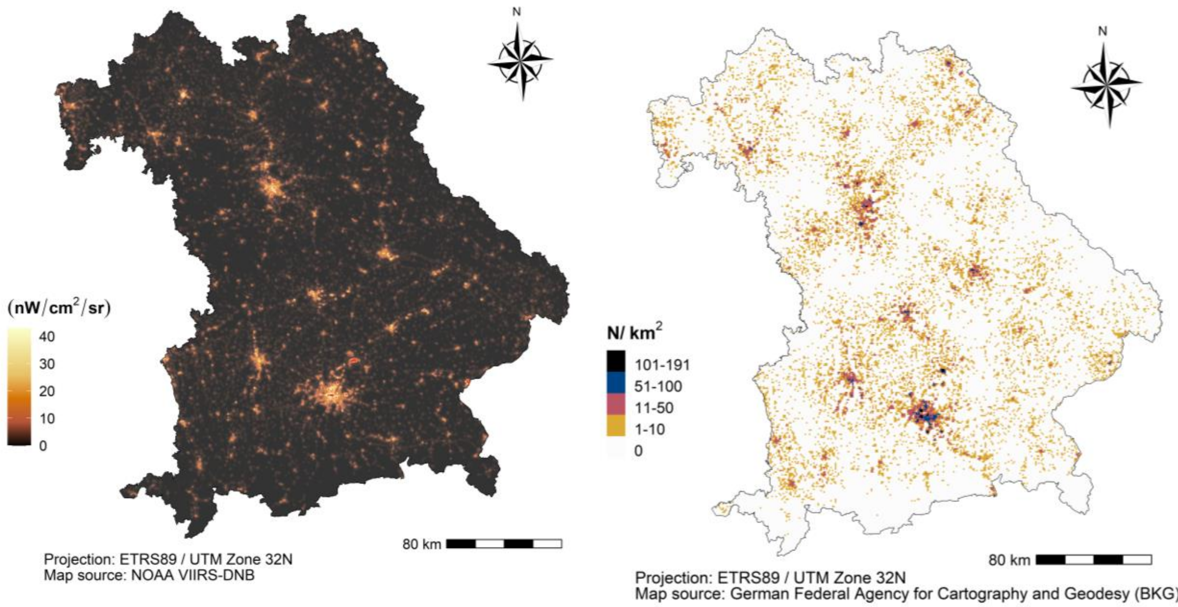
[b] Model 2 shows the estimates after adjusting for age and sex, percentage of low-income households, and urbanization degree.

Figure Captions

Figure 1. Spatial distribution of LAN exposure and participants of the Fr1da cohort in Bavaria, Germany.

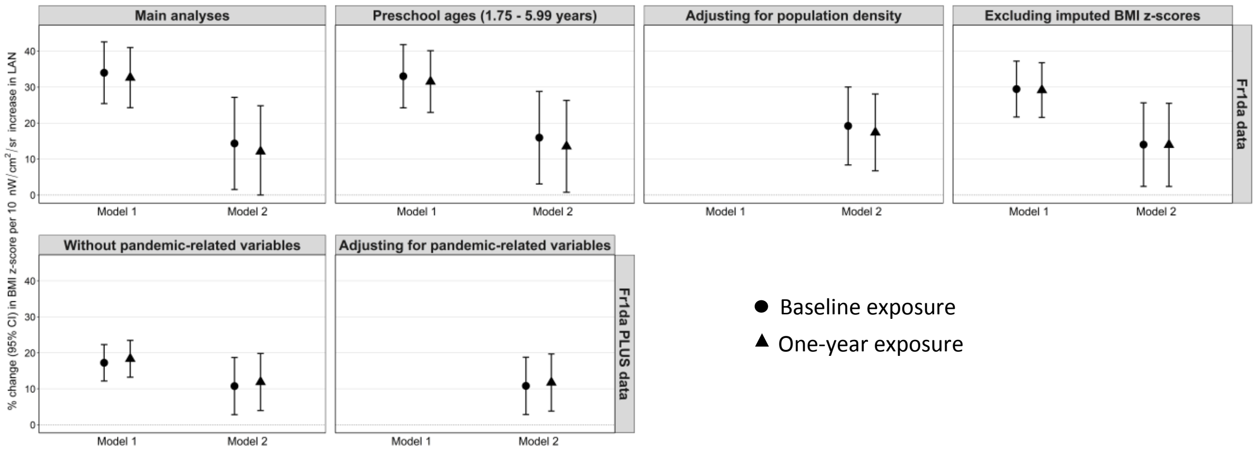
Figure 2. Sensitivity and validation analyses: Association between LAN exposure and BMI z-scores.

Figure 1. Spatial distribution of LAN exposure and participants of the Fr1da cohort in Bavaria, Germany. The left panel shows the levels of LAN exposure at baseline (2015). The right panel shows the spatial distribution of the participants (n = 62,212).



LAN: Light at night; **nW/cm²/sr**: nanoWatts per square centimeter per steradian.
Note: The red grids on the left panel represent the outliers.

Figure 2. Sensitivity and validation analyses: Association between LAN exposure and BMI z-scores.



LAN: Light at night; **nW/cm^2/sr**: nanoWatts per square centimetre per steradian; **Baseline exposure**: Exposure in the study base year (2015 for Fr1da and 2019 for Fr1da PLUS); **One-year exposure**: Exposure within one year prior to screening.

Model 1 shows the estimates after adjusting for age and sex.

Model 2 shows the estimates after adjusting for age and sex, percentage of low-income households, and urbanization degree.

Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Authors' contributions

All authors contributed to the study design and conceptualization. The underlying data were verified and analyzed by MB, KW, and AS, and all authors interpreted the findings. The manuscript was drafted by MB with support from KW, AS, and AGZ. All authors read and critically revised the manuscript and approved the final version. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AGZ led the project. MB, KW, and AS had final responsibility for the decision to submit for publication.