Exposure to light at night (LAN) and risk of obesity: a systematic review and meta-analysis of observational studies

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Summary

Background: There is emerging evidence of the association between light at night (LAN) exposure and weight gain.

Objective: We aim to conduct a systematic review and meta-analysis of observational studies on the association between LAN exposure and risk of obesity in human subjects.

Methods: Peer-reviewed observational studies were systematically searched from MEDLINE (EBSCO), Academic Search Complete (EBSCO), CINAHL Plus (EBSCO) and PubMed up to 24 December 2019. Random-effects models were developed to estimate the associations between LAN exposure and weight-related outcomes of overweight and obesity as measured by body mass index (BMI), waist circumference, waist-hip-ratio and waist-to-height-ratio. The I^2 statistic was used to assess the degree of heterogeneity across studies. The National Toxicology Program's Office of Health Assessment and Translation (OHAT) risk of bias rating tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline were respectively employed to assess the risk of bias and to appraise the quality of the generated evidence.

Results: A total of 12 studies (three with longitudinal and nine of cross-sectional design) published between 2003-2019 were included for systematic review, while seven of them fulfilling the inclusion/exclusion criteria were included in the meta-analysis. A higher LAN

exposure was significantly associated with 13% higher odds of overweight (BMI≥25 kg/m^2) (Summary Odds Ratio; SOR: 1.13, 95% CI: 1.10-1.16) with low heterogeneity (I^2 = 27.27%), and 22% higher odds of obesity (BMI≥30 kg/m^2) (SOR: 1.22, 95% CI: 1.07-1.38) with substantial heterogeneity (I^2 = 85.96%). Stratifying analyses by the levels of measurement of LAN exposures (macro-, meso- and micro-levels) and time of LAN measurement (including before and while sleeping) consistently produced robust estimates, with higher exposure to LAN being positively associated with poorer weight outcomes. Assessment of risk of bias identified substantial detection bias for exposure, with over half of the pooled studies employing subjective LAN measures. The overall evidence of the association between LAN exposure and risk of obesity was rated as 'moderate' as per the GRADE guideline.

Conclusions: Exposure to LAN was reported to be a significant risk factor for overweight and obesity. Prospectively designed future studies with objectively measured multi-level LAN exposures and weight outcomes are required.

Keywords: Light at night, meta-analysis, body mass index, obesity.

Abbreviations: 95% CI: 95% confidence interval; BMI: body mass index; LAN: light at night; WC: Waist circumference; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio.

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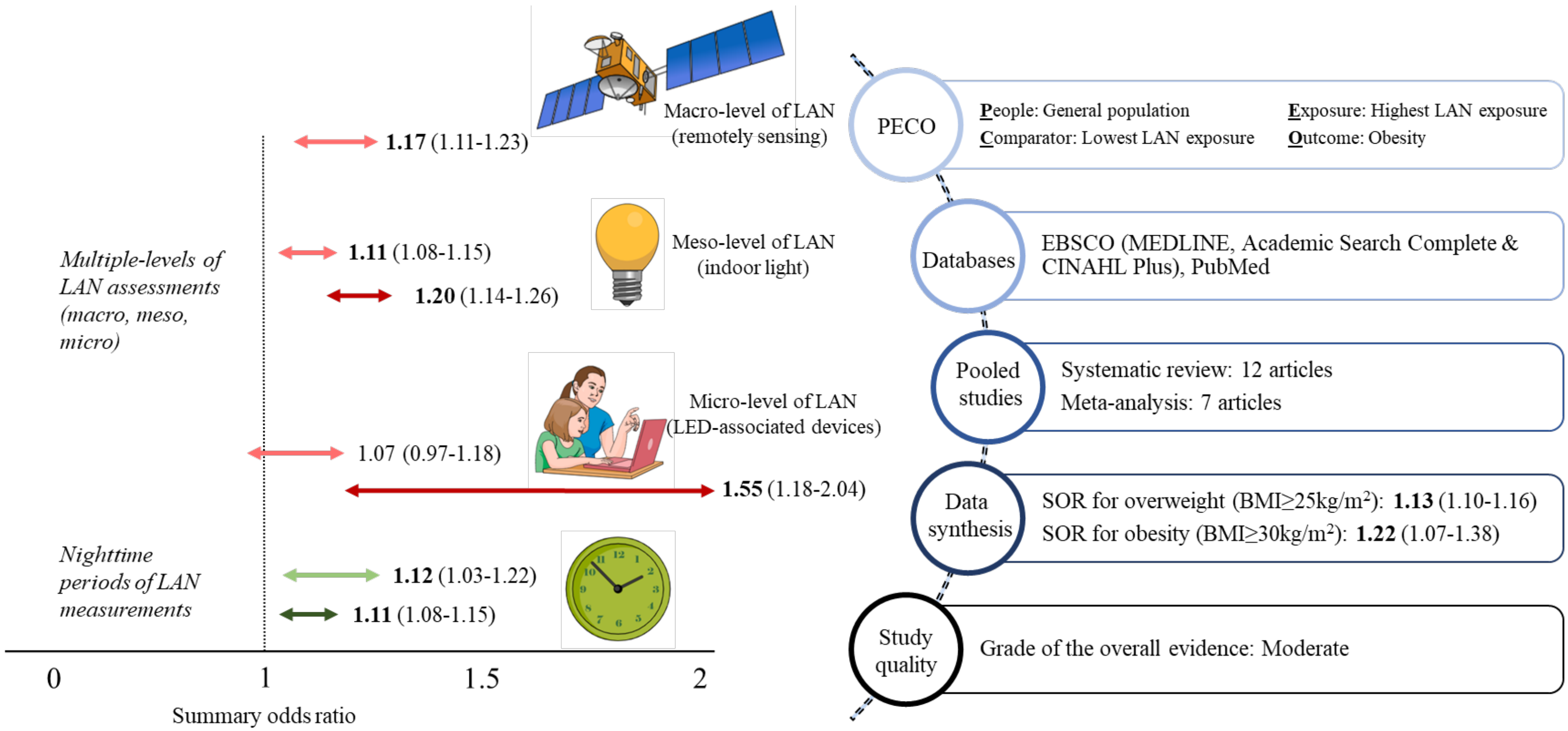
Supplementary 2: Study Profile

Graphical Abstract



Note. BMI, body mass index; LAN, light at night; LED, light-emitting diode; SOR: summary odds ratio.
↔ / ↔ : confidence interval of summary odds ratio for overweight (≥25kg/m^2)/obesity(≥30kg/m^2).
↔ / ↔ : confidence interval of summary odds ratio for overweight (≥25kg/m^2) before sleep/while sleeping.

1. Introduction

Obesity has emerged as a global epidemic and a public health challenge (Bluher, 2019; NCD-RisC, 2017; Swinburn et al., 2014). It is one of the top five risk factors of mortality and disability-adjusted-life-years (Stanaway et al., 2018), being associated with higher risks for type 2 diabetes (Tobias et al., 2014), cardiovascular diseases (Mandviwala et al., 2016), and cancers (Bhaskaran et al., 2014; Arnold et al., 2016), and incurring significant healthcare expenditures (Kent et al., 2017). It has been widely acknowledged that the socio-economic status, diet, lifestyle and built environmental correlates of sedentary behaviors associated with contemporary urban living constitute primary risk factors of adiposity (Katzmarzyk et al., 2015).

The etiology of obesity is believed to be a result of sedentary behaviour and imbalance energy uptake and expenditure. An important pathway affecting metabolism is the link between perturbations in the circadian clock and resulting neuro-endocrinal and metabolic alterations, leading to obesity (Laermans and Depoortere, 2016). Urban light pollution, being a major circadian disruptor, constitutes one of the emerging risk factors of obesity. It has been estimated that there has been 6% increment in artificial light at night (LAN) each year globally and its implications on worldwide obesity prevalence have been acknowledged (Hölker et al., 2010; Fonken and Nelson, 2014). Deviations from the natural diurnal photoperiods owing to urban lifestyles have the potential to cause perturbations in our sleep-wake cycles, altering intracellular circadian clocks including alterations in the molecular mechanisms within adipocyte and adipose accumulation (Bray and Young, 2007; Bonmati-Carrion et al., 2014). LAN has also been hypothesized to suppress endogenously-produced melatonin synthesis associated with weight gain, thereby contributing to obesity (Salgado-Delgado et al., 2011; Reiter et al., 2012). Beyond the exposures to artificial light both at a macro-/neighbourhood-scale (on the street) and at a meso-level (within the indoor home-environment following the dusk), the proliferation of light-emitted devices in the recent years, facilitated by the rapid technological advancements, has also constituted new source of micro-level stimulus disrupting individuals' circadian rhythm and energy homeostasis (Feillet, 2010; Chang et al., 2015).

Direct evidence of association between LAN exposure and weight gain has first emerged from laboratory-based animal experimental studies (Reiter et al., 2012). Independent of caloric intake and physical output, mice kept under bright and dim LAN conditions were found to have

significant weight gain and diminished glucose tolerance as compared to the control-counterparts kept under natural light conditions (Fonken et al., 2010; Fonken et al., 2013). However, human epidemiological studies have been limited, thus far indirectly employing night shift work as a surrogate for LAN exposure in most instances with the assumption that night shift workers are principally exposed to a higher degree of LAN (Sun et al., 2018). Only recently, with the ubiquity of macro-level LAN exposures in urban areas in conjunction with micro-level exposures from electronic devices associated with urban lifestyles, there has been evidence on the links between LAN exposures and chronic diseases (Stevens, 2009; Cho et al., 2015; Lai et al. 2020). We therefore conducted the first systematic review and meta-analysis to address the primary question: 'among the general population, what is the association of the highest LAN exposure compared to the lowest LAN exposure on risk of obesity as evident from observational studies?', a crucial Population-Exposure-Comparator-Outcome-Study Design (PECOS) statement guiding the present review (Wikoff and Miller, 2018) (*Appendix A*).

2. Methods

2.1 Study protocol and registration number

We followed the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement (Shamseer et al., 2015) (*Appendix B*) and our study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42019152249).

2.2 Information sources and search strategies

We searched for study keywords as identified by PECOS statement with further modifications and supplementations based on prior literature and online materials (*Appendix D*) in MEDLINE (EBSCO), Academic Search Complete (EBSCO), CINAHL Plus (EBSCO) and PubMed. A two-stage search strategy was employed; firstly, keywords in relation to LAN and body weight were searched, while, in the second stage, keywords in relation to light-emitted device use, body weight and nighttime were used. The search terms adopted in the two-stage strategy are illustrated in *Appendix C*. The search engines were decided based on prior articles analyzing the attributes of search engines (*Appendix E*). All searches were limited to title or abstract, and for studies involving human participants up to 24 December 2019. After excluding duplicates, all

articles retrieved were reviewed based on title and abstract, followed by a more exhaustive full-text review. An additional screening was employed across the reference lists included in all the selected studies and other related review articles. A manual search in Google Scholar was subsequently conducted.

2.3 Study eligibility criteria for systematic review

In the present systematic review, per the inclusion criteria, studies were included for which: (a) the exposure was LAN or light-emitted device use at night; (b) the outcome variable contained one or more of body weight-related risk (e.g., overweight and obesity measured by body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and diabetes or type 2 diabetes); and were (c) observational in design (e.g., cross-sectional and longitudinal study); (d) included human subjects; (e) peer-reviewed journal articles; and (f) in English language. Studies were excluded from the systematic review if they were: (a) reviews or commentaries, (b) laboratory-based studies; (c) non-human studies; (d) ecological in design with the absence of adjustments of individual-level covariates; and (e) studies without proper specification for nighttime light exposure.

2.4 Data accuracy and expertise

Two researchers (KYL and CS) with the expertise in environmental epidemiology independently assessed the articles being included, extracted all estimates and conducted the risk of bias assessments. Discrepancies were resolved by discussions and consensus. All the authors (KYL, CS, MN, JG and CW) contributed to data interpretations and remodifying the draft based on mutual agreement.

2.5 Data items

A list of data items (*Appendix F*) were extracted for each of the individual studies selected for the systematic review and were input into a predefined table in Excel. A summary table comprising the study's lead author, year of publication, geographical setting, sample size, sex, age, definition of outcome, definition of LAN and exposure classification of each study were also provided.

2.6 Statistical pooling and data synthesis

2.6.1 Identifying heterogeneity

The heterogeneity statistic (I^2) was employed to examine the consistency of the cumulative evidence between the studies. I^2 (%) calculated as, 100%*(Q - df)/Q, is used to identify the degree of heterogeneity and consistency across studies (Higgins et al., 2003). Q represents Cochran's heterogeneity statistic and df is the degree of freedom. An I^2 of 0% is indicative of null heterogeneity, while 50% and 75% are synonymous with moderate and high levels of heterogeneity respectively (see *Appendix G* for the complete guideline for interpretations).

2.6.2 Statistical pooling

Odds ratio (OR) or relative risk (RR) with 95% confidence interval, or effect coefficient (β) with standard error (SE) were abstracted. Only studies with the provisions of commonly defined cut-off points (e.g., BMI ≥25 kg/m^2) for weight-related outcomes as well as relevant estimates were included for meta-analysis. In each selected study, the model adjusting for the highest number of confounding variables was selected if multiple-adjusted models were provided. In cases where different levels of LAN intensities or frequencies of light-emitted device usage were provided, the estimate contrasting the highest in reference to the lowest category was extracted. Estimates were inversed before analysis when the highest (or brightest) LAN category was taken as the referent. Under circumstances where more than one light source was provided the effect estimate for combined LAN exposure was chosen. If results from both cross-sectional and prospective studies were reported, data generated from the prospective analysis was selected.

2.6.3 Highest versus lowest meta-analysis

The 'metafor' package within RStudio was used for meta-analysis (Viechtbauer, 2010). Random-effects models allowing difference in effect size across studies, were employed to calculate the summary ORs (summary odds ratios, SORs) if a minimum of two estimates were available. The World Health Organization's (2018) standard definitions of overweight (BMI≥25 kg/m^2) and obesity (BMI≥30 kg/m^2) were employed to conduct the overall analysis. Forest plots were used to visualize the included studies and main findings of the overall pooled analysis. The

confidence interval of each effect estimate were represented by a horizontal line, while a black box and the diamond denotes the OR of individual studies and the SOR respectively.

2.6.4 Sub-group analysis

The SORs for various weight-related outcomes measured by BMI, WC, WHR and WHtR were stratified by different levels of measurements of LAN exposures (macro-, meso- and micro-levels), and nighttime periods at which it was measured, if a minimum of two estimates were available.

2.6.5 Sensitivity analysis

Five sensitivity tests were conducted to further examine the strength of the overall risk for overweight (BMI≥25 kg/m^2) and obesity (BMI≥30 kg/m^2) by repeated the analysis after: (a) excluding the study with the highest effect estimate; (b) excluding the study with the highest study weight; (c) stratifying by sex (Park et al., 2019; Abay and Amare, 2018; McFadden et al., 2014) to avoid combining these estimates with those recruiting both male and female participants; (d) stratifying by two age groups given the data available (≥15 and <15 years); and (e) including only cross-sectional study results. Given the limited number of studies, (c) could not be performed to assess the strength of the overall risk for obesity.

2.7 Risk of bias in individual studies

The risk of bias in individual studies was assessed by adopting the Office of Health Assessment and Translation (OHAT) risk of bias rating tool (Rooney et al., 2014), being previously employed in review articles examining the associations between environmental exposures (including air pollution) and cardiovascular diseases (Achilleos et al., 2017; Wikoff et al., 2017) (Appendix H). A total of seven risk of bias domains including (1) selection bias, (2) confounding bias, (3) attrition/exclusion bias, (4) detection bias for exposure, (5) detection bias for outcome, (6) selective reporting bias and (7) other bias, specific to underlying study design; cross-sectional and cohort (or longitudinal) studies were assessed. Each risk of bias domain in individual studies was graded as: ‘definitely low’, ‘probably low’, ‘probably high’ or ‘definitely high’. The domain was rated as ‘not reported’ when inadequate information was provided. A summary table

comprising answer formats (or symbols) representing the varying levels of risk of bias has been presented to visualize the results (*Appendix I*).

2.8 Confidence in the body of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline was employed to assess confidence in the body of evidence generated (Guyatt et al., 2008) (*Appendix J*). As per the GRADE procedure, the body of evidence in each study is assigned with a grade based on their study design in the first instance, and subsequently rated up or down based on assessment with respect to a total of eight criteria. An initial grade of 'moderate' is generally assigned to human observational studies in the field of environmental health, given it is often not feasible or unethical to design randomized control experiments for negative exposures/interventions (Woodruff and Sutton, 2014). We examined five of the GRADE criteria including (1) risk of bias, (2) indirectness, (3) inconsistency, (4) imprecision and (5) publication bias for potential downgrading, whereas additional three, including (6) large magnitude of effect, (7) dose response and (8) residual confounding were assessed for potential upgrading. A grade of -1 or -2 was assigned to each dimension for downgrading, while a grade of +1 or +2 was rated for upgrading. A score of 0 was given if the criteria for upgrading or downgrading were not met. A subsequent rate of either 'high', 'moderate', 'low' or 'very low' was assigned to the body of evidence on the basis of the reviewers' judgement arrived at via thorough discussions.

Publication bias was examined by using a funnel plot of logarithms of OR versus the inverse of their standard deviation (1/SE). Due to the small number of publications included in this meta-analysis, Egger's linear regression test (Egger et al., 1997) for funnel plot asymmetry was also used to examine publication bias. A p-value<0.1 is regarded as evidence of asymmetry. The test for publication bias was conducted independently for the two major outcomes including the overall risks for overweight and obesity.

3. Results

3.1 Study selection

Adopting a two-stage search strategy, 1873 and 2967 articles were retrieved from the first and the second stages respectively (Figure 1). In the former, exclusions were made on account of

duplication (n = 583), non-English publications (n = 5) and not meeting the criteria on assessments of title and abstract (n=1263), leaving 22 articles. Of these remaining, 15 were further excluded after full text assessment on account of laboratory-based experimental design (n = 1), ecological study design (n = 3) and inclusion of non-human subjects (n = 11), yielding a total of seven studies from the first stage. For the later stage, exclusions owing to duplication (n = 1443), being in non-English language (n = 14), and non-fulfillment of inclusion criteria based on assessments of title and abstract (n=1495) meant 15 articles remained for full assessment. Of these, 12 were further excluded due to its absence of time of exposure assessment, yielding a total of three articles from the second search. Two extra articles (Abay and Amare, 2018; Giammattei et al., 2003) were included based on an additional screening, as specified before. A total of 12 studies were included for systematic review.

3.2 Systematic review

Table 1 presents a summary of the main characteristics of the 12 studies examining the associations between LAN exposures and obesity. In order to visualize the temporality of diurnal LAN exposure measurements (with respect to how 'light' and 'night' were defined across the studies pooled), a brief summary has been illustrated in Table 2.

Two cross-sectional studies comprising 42,112 participants and conducted in South Korea (Koo et al., 2016) and Nigeria (Abay and Amare, 2018) measured outdoor LAN at a macro-level within residential catchment or at a street level by using remotely-sensed satellite data. Both the studies employed satellite data derived from US Defense Meteorological Satellite Program's (DMSP's) Operational Linescan System (OLS), and LAN values were assigned to the participants' residential addresses for data available for or nearest to the survey years. In Koo et al. (2016)'s study, both sex aged 39 to 70 were included, while only women aged 15 to 49 were recruited in Abay and Amare (2018)'s study.

Three longitudinal studies (Obayashi et al., 2020; Park et al., 2019; Obayashi et al., 2016) and three cross-sectional studies (McFadden et al., 2014; Obayashi et al., 2013; Calamaro et al., 2012) had assessed LAN at meso-level in terms of exposures in the bedroom. The follow-up durations of the three longitudinal studies were 5.7 (mean) (Park et al., 2019), 3.5 (median)

(Obayashi et al., 2020) and 1.75 years (median) (Obayashi et al., 2016) respectively. Two of the studies were conducted in the US (Park et al., 2019; Calamaro et al., 2012), three in Japan (Obayashi et al., 2020; Obayashi et al., 2016; Obayashi et al., 2013), and one in the UK (McFadden et al., 2014). Except the three Japanese studies employing the same cohort data of sample sizes ranging from 528 to 766, the remaining three studies comprised a total of 157,690 samples ranging from 625 to 113,343. Two studies included women-only participants (Park et al., 2019; McFadden et al., 2014), three older adults (Obayashi et al., 2020; Obayashi et al., 2016; Obayashi et al., 2013) and one included only children (Calamaro et al., 2012). Three studies used objective exposure measure, employing light-meter to measure bedroom LAN (Obayashi et al., 2020; Obayashi et al., 2016; Obayashi et al., 2013), whereas the remaining three adopted questionnaire-based self-reported LAN exposures (Park et al., 2019; McFadden et al., 2014; Calamaro et al., 2012). All the six studies measured LAN while sleeping, while one additionally measured LAN in 4 hours before bedtime, the first hour after bedtime as well as the last hour before rising (Obayashi et al., 2016).

The remaining four cross-sectional studies (Dube et al., 2017; Arora et al., 2013; Chahal et al., 2013; Giammattei et al., 2003) had investigated the associations between nighttime use of light-emitting devices as a marker of micro-level light-emitting diodes (LED)-associated LAN and weight-related outcomes among subjects aged 18 or below, comprising a total of 6749 subjects of both sex. One of the studies measured the self-reported frequency of light-emitted device use in an hour before sleep (Dube et al., 2017), one during bedtime (Arora et al., 2013) and one after the time the subjects were expected to sleep (Chahal et al., 2013). The remaining one asked if the participants had ≥2 hours of television watching per night (Giammattei et al., 2003). Two of the studies were conducted in Canada (Dube et al., 2017; Chahal et al., 2013), one each in the US (Giammattei et al., 2003) and UK (Arora et al., 2013).

Except for the most recent study examining diabetes mellitus (Obayashi et al., 2020), all the included studies employed BMI to define subjects' adiposity status. Eight of the studies assessed BMI objectively (Abay and Amare, 2018; Dube et al., 2017; Koo et al., 2016; Obayashi et al., 2016; Obayashi et al., 2013; Arora et al., 2013; Chahal et al., 2013; Giammattei et al., 2003), while in another, the authors employed subjective measure (Calamaro et al., 2012). One study

adopted self-report of participant-measured weight and height to determine prevalent and incident obesity respectively (Park et al., 2019), while another employed measured data reported by subjects (McFadden et al., 2014). Cut-off points for BMI at 25kg/m^2 and/or 30kg/m^2 were used in seven studies (Park et al., 2019; Abay and Amare, 2018; Dube et al., 2017; Koo et al., 2016; McFadden et al., 2014; Obayashi et al., 2013; Chahal et al., 2013), and four employed BMI z-score (Arora et al., 2013; Calamaro et al., 2012), and one each employed BMI change (Obayashi et al., 2016) and BMI at the 85th percentile (Giammattei et al., 2003). WC (Park et al., 2019; McFadden et al., 2014; Obayashi et al., 2013), WHtR (Park et al., 2019; Obayashi et al., 2016; McFadden et al., 2014) and WHR (Park et al., 2019; McFadden et al., 2014) were also employed as objectively-measured alternate weight-related outcomes with defined cut-off points. Two studies employed blood samples to identify diabetes mellitus and/or dyslipidemia (Obayashi et al., 2020; Obayashi et al., 2013).

3.3 Meta-analysis

3.3.1 Highest versus lowest analysis and sub-group analysis

A total of seven studies with defined cut-off points for weight-related outcomes and with sufficient relevant data were included in the meta-analysis (Park et al., 2019; Abay and Amare, 2018; Dube et al., 2017; Koo et al., 2016; McFadden et al., 2014; Obayashi et al., 2013; Chahal et al., 2013). Subjects in the highest LAN exposure category were associated with a 13% higher odds of being overweight (BMI≥25 kg/m^2) in reference to those in the lowest (SOR: 1.13, 95% CI: 1.10-1.16) (Figure 2) with a low level of heterogeneity (I^2 = 27.27%). Subjects in the highest exposure category had 22% higher odds of obesity (BMI≥30 kg/m^2) (SOR: 1.22, 95% CI: 1.07-1.38 in reference to the lowest exposure category) (Figure 3) with evidence of substantial heterogeneity (I^2 = 85.96%).

Table 3 presents the SORs for different weight-related outcomes across the three levels of LAN exposures (macro-, meso- and micro-levels) and two nighttime periods of measurements. A higher LAN exposure was significantly associated with a higher odds of overweight (BMI≥25 kg/m^2) (SOR: 1.17, 95% CI: 1.11-1.23) with null heterogeneity (I^2 = 0%) for LAN measured at macro-level (neighbourhood- and street-level). For measurements at a meso-level of bedroom lighting, a similar consistent positive association with weight outcomes was reported, being associated with higher odds of overweight (BMI≥25 kg/m^2) (SOR: 1.11, 95% CI: 1.08-1.15),

obesity (BMI≥30 kg/m^2) (SOR: 1.20, 95% CI: 1.14-1.26), WC≥88m (SOR: 1.11, 95% CI: 1.09-1.14), WHR≥0.85 (SOR: 1.07, 95% CI: 1.01-1.14) and WHtR (SOR: 1.11, 95% CI: 1.03-1.20), with moderate to substantial level of heterogeneity ($I^2 \geq 50\%$). For LAN measured at micro-level as LED-associated LAN, the results remained significant only in the case of obesity, being associated with 55% higher odds of obesity (SOR: 1.55, 95% CI: 1.18-2.04) with moderate heterogeneity ($I^2 < 40\%$). Stratifying our analyses by nighttime period of exposures indicated that a higher LAN exposure was associated with 12% (95% CI: 1.03-1.22) and 11% (95% CI: 1.08-1.15) higher odds of overweight for LAN measured before sleep and while sleeping respectively. A moderate level of heterogeneity was observed in cases of LAN exposure measured while sleeping (I^2 = 58.50%).

3.3.2 Sensitivity analysis

The results of our sensitivity tests remained consistent with the main finding, with LAN exposure being associated with an increased odds of overweight subsequent to exclusion of the study with the highest estimate (SOR: 1.12, 95% CI: 1.09-1.16) and the highest weight (SOR: 1.14, 95% CI: 1.10-1.19) from our pooled analyses (*Appendix K*). A higher LAN exposure was also associated with an elevated odds of overweight in studies involving both sexes (SOR: 1.14, 95% CI: 1.04-1.26) and female only (SOR: 1.13, 95% CI: 1.09-1.16). However, a moderate level of heterogeneity was evident in the test that excluded the three women cohort studies (I^2 = 54.70%). Consistently, an increased LAN exposure was also significantly associated with a higher odds of obesity after excluding the study with the highest estimate (SOR: 1.16, 95% CI: 1.06-1.27) and that with the highest weight (SOR: 1.22, 95% CI: 1.16-1.28). A substantial heterogeneity was evident in the test that excluded the highest weight (I^2 = 85.54%). Stratifying by age, a higher LAN exposure was associated with a higher odds of overweight only among subjects aged 15 years or above (SOR: 1.14, 95% CI: 1.09-1.19), while a higher odds of obesity among subjects aged below 15 (SOR: 1.55, 95% CI: 1.18-2.04) with moderate levels of heterogeneity. The significant association between LAN exposure and obesity was also evident with the inclusion of only cross-sectional studies (SOR: 1.19, 95% CI: 1.02-1.39) with a substantial heterogeneity (I^2 = 91.58%). Sensitivity analysis with only prospective studies couldn't be performed on account of limited number of studies with comparable weight outcomes.

3.4 Assessments for risk of bias in individual studies

The risk of bias assessment has been summarized in *Appendix L* with detailed evidence of judgement criteria for each study illustrated in *Appendices M* and *N* for longitudinal and cross-sectional studies respectively. Detection bias for exposure was graded as 'definitely high' in seven of 12 (58.33%) studies, given these studies employed only subjectively measured LAN. Detection bias for outcome was also rated as 'definitely/probably high' in two out of nine cross-sectional studies (22.22%) employing self-reported height and weight, or measured data reported by subjects. Selection and exclusion biases were both rated as 'not reported' in a study (Abay and Amare, 2018) with the absence of sufficient explanations of the selected samples as well as exclusion criteria. A 'probably low' level of risk of bias was reported in the other domains with respect to confounding, selective reporting and other bias across the studies pooled.

3.5 Confidence in the body of evidence

The assessment results of confidence in the body of evidence are shown in *Appendix O*. An initial grade of 'moderate' was assigned to the body of evidence based on their study design as observational studies. Confidence of the cumulative evidence was weakened due to the serious detection bias for exposures employing only subjective LAN measures as well as clues of biases with respect to selection, exclusion and outcome in several studies. A judgement of downgrading was not permitted in the risk of bias domains relative to indirectness, inconsistency, imprecision and publication. Large effect magnitude, dose-response relationship and confounding effect were also not evident in the included studies, so upgrading was not applicable. The overall evidence of the association between LAN exposure and risk of obesity was judged to be 'moderate' on the basis of thorough assessment of the grading criteria.

4 Discussion

We present the first systematic review and meta-analysis of observational studies reporting associations between LAN exposure and weight-related outcomes of overweight, obesity, WC, WHR, and WHtR in human subjects. Overall, our pooled analyses found that a higher LAN exposure was consistently associated with 13% and 22% higher odds of overweight (BMI≥25 kg/m^2) and obesity (BMI≥30 kg/m^2) respectively, the associations remaining robust across all the sensitivity tests. The positive associations with the various weight-related outcomes also

remained consistent across the three levels at which LAN exposures were measured (i.e., macro-, meso- and micro-levels of LAN exposure) and the time periods of its assessment (i.e., before sleep and while sleeping). Our overall positive finding is consistent with a large-scale ecological study involving more than 80 countries worldwide which reported a positive correlation between LAN exposure measured by remote sensing technology and overweight and obesity, adjusting for per capita GDP, level of urbanization, birth rate, food consumption and regional differences in overweight/obesity prevalence (Rybnikova et al., 2016).

Our OHAT risk of bias assessments reported a 'definitely high' risk of detection bias for exposure with over half of the studies employing only subjective LAN exposures. This exemplifies the need for a nuanced approach to measuring LAN exposures including simultaneous LAN assessment at micro-, meso- and macro-levels. Bias with respect to selection, exclusion and outcome were also evident in some of the included studies. The body of evidence was subsequently rated as 'moderate' as per the GRADE guidelines, indicating the need for well-designed longitudinal studies with more rigorous and objective measures of LAN as well as the outcome in the field.

4.1 Macro-level of exposure

Two of the included cross-sectional studies (Abay and Amare, 2018; Koo et al., 2016) have employed LAN metrics at a neighbourhood- and street-level derived from remotely sensed data; nonetheless their cross-sectional design impeded causal inference. The marked absence of large-scale longitudinal studies suggests future work should explore linking accumulated LAN values derived from satellite data collected at multiple time points to the participants' residential addresses to study impacts of LAN exposures and its changes upon individual weight changes over time. Such designs are expected to supplement existing evidence with more robust examination of potential causal associations between LAN exposures and different weight-related outcomes.

The application of remotely sensed satellite data for measuring macro-level LAN must be considered with due caution, given the risk of measurement error and exposure misclassification. The use of DMSP-derived data for LAN measurements in epidemiological research have been criticized owing to their poor spatial resolution of approximately 5 km (Miller et al., 2013; Kyba,

2016). There is a need for finer resolution nightlight dataset for greater precision as has been evidenced in a recent ecological study in Israel, with higher resolution data (day night band of Visible Infrared Imaging Radiometer Suite, VIIRS) being reported as a stronger predictor for breast cancer rates than the traditional low resolution DMSP (Rybnikova and Portnov, 2017). Images taken by astronauts from the International Space Station with very high spatial resolution of around 10-100 m are also recommended, despite their incapacity to be calibrated into photometric units (Zhang et al., 2015). Temporal congruence is another important area for future work, given the natural variations in nocturnal melatonin secretions, with a maximal secretion occurring in the second half of the night (Ackermann et al., 2012). The time at which a satellite data/photo employed for LAN measurements was taken should be specified, as has been reported in just one of the studies (Koo et al., 2016).

4.2 Meso-level of exposure

Two of the Japanese studies (Obayashi et al., 2013; Obayashi et al., 2016) employed light-meters to objectively measure indoor bedroom LAN (at the meso-level), while the remaining three adopted questionnaire-based self-reported LAN measures (Park et al., 2019; McFadden et al., 2014; Calamaro et al., 2012). Light-meter derived LAN measures are novel as they are time-stamped and the Japanese studies had assessed nighttime LAN within 4 hours before bedtime and the last hour before rising up (Obayashi et al., 2016). That the two Japanese studies were limited to older population who are commonly prone to suffer from ganglion cell loss or changes in eye lens density associated with LAN absorptions and resulting melatonin suppressions (Semo et al., 2003; Herljevic et al., 2005) suggests that future research should also focus on a more representative population including younger age-groups. Given the potential likelihood for information bias (recall bias and associated measurement error) associated with questionnaire-based LAN measurement, future studies should validate survey-based data with objectively-measured LAN, such as by using a portable light meter to ensure validity and thereby avoid exposure misclassifications (Kyba and Spitschan, 2018).

4.3 Micro-level of exposure

Our pooled analyses reported that participants in the highest category of LAN exposures attributed to technological devices were associated with higher odds of obesity in reference to

those in the lowest exposure category. Direct association between duration of mobile phone usage and degree of melatonin suppression has been established. A previous study reported that exposure to mobile phone radiations for 30 minutes did not vary melatonin secretion (Wood et al., 2006), while another reported a 23% melatonin suppression associated with an hour of exposure to light-emitted devices at night (Figueiro and Overington, 2016). The global penetration rate of LED devices has been estimated to increase dramatically from <1% in 2010 to over 60% in 2020 (Statista, 2019). Given only a small number of cross-sectional studies thus far, the potential causal effect from nighttime light-emitting device usage to circadian dysfunction and associated induced adiposity warrants further research.

Additionally, all the pooled studies measuring LAN exposures at micro-level adopted self-reported measurement of nighttime light-emitted device usage, and are consequently prone to recall bias and under-estimating the effects. Other instruments such as a personal dosimeter can be used for objectively measuring individual's micro-level LAN exposure attributed to usage of light-emitted devices through measuring the value of electric field strength for selected frequencies close to body (Thomas et al., 2008).

All studies of micro-level exposure to LAN thus far, included subjects aged 18 or below, given the effect of LAN upon melatonin suppression is particularly pronounced in children as compared to adults (Higuchi et al., 2014; Nagare et al., 2019). Importantly, rapid weight gain in childhood interacts with an individual's entire life span (Johnson et al., 2006). Future studies should thus focus on multiple population sub-groups; adolescents given the effectiveness of early preventive intervention in offsetting risks of obesity in adulthood as well as their adult counterpart who are more likely to be at risk of LAN exposures via their work and work-related lifestyles and the potential for circadian desynchronization and obesity risks.

4.4 Measurements of outcome

Future studies should be designed to examine links between LAN exposures and incidence of obesity relying on anthropometry conducted at multiple time-points and matched assessment of LAN exposures for greater reliability. Apart from anthropometry, the use of biomarkers of adiposity has the potential to provide more useful information, especially in directly associating physiological changes attributed to adiposity with exposures. The Japanese study conducted by

Obayashi et al. (2013, 2020) had been the first to employ blood biomarkers of glucose and lipid metabolism to examine the effect of LAN on diabetes mellitus, but was limited to older adults. Future longitudinal studies of general population should employ appropriate biomarkers of adiposity (Musaad and Haynes, 2007) for a better understanding of the physiological pathways from LAN exposure to obesity.

4.5 Residual confounding

Observational studies are inherently associated with residual confounding. To address this, future studies on the links between LAN exposure and adiposity should adjust for all key determinants for weight gain, including diet and markers of sedentary behaviour for robust effect estimates. Additionally, differential light exposures attributed to natural seasonal alterations, with lower exposure to daily ambient light during winters has been evidenced to significantly increase the sensitivity of melatonin suppression, relative to summer times (Higuchi et al., 2007). Studies should thus account for seasonal alternations during the analysis. Other potential modifying factors including wearing of eye mask whilst sleeping, consumption of melatonin supplements and nightshift work should also be accounted for.

4.6 Potential mechanisms

Retinal exposure to light under normal day-light conditions entrained through the photoreceptor Retinal Ganglion Cells (ipRGC) are relayed to the master circadian, the clock suprachiasmatic nuclei (SCN) present within the anterior hypothalamus and subsequently to the peripheral clocks and cellular oscillators located throughout the body, which are all responsible for circadian rhythm. The SCN and the peripheral clock thus ensures rhythmicity in the production of metabolically relevant hormones including melatonin, leptin and insulin (Feillet, 2010; LeGates et al., 2014). Perturbations in day-light conditions and increased exposure to LAN acts as a chrono-disrupter, desynchronizing sleep-wake cycles affecting individual’s activities, endocrinology and metabolism, leading to a higher risk for obesity (Stevens et al., 2007; Plano et al., 2017). Specifically, perturbations in the peripheral circadian clock within the adipose tissue causes alterations in its metabolism and disturbs the energy balance (Bray and Young, 2007; Laermans and Depoortere, 2016). The effects are further exacerbated by lifestyle and dietary habits including consumption of high fat food, changes in dietary patterns; disruption of *Per 1*

and Per 2 clock genes causes high fat diet induced inflammation (Xu et al., 2014). Of importance is also lifestyle related to shiftwork responsible for circadian desynchrony and sleep deprivation which have been directly associated with adiposity (Patel and Hu, 2008, McHill et al., 2017). Another pathway is via suppression of nocturnal melatonin, a known antiobesogen attributed to LAN-induced circadian desynchrony (Ríos-Lugo et al., 2010; Touitou et al., 2017). Melatonin has important metabolic functions including mobilization of insulin signaling pathways, maintaining energy balance by regulating energy flows as well as energy expenditures; its suppression being associated with insulin resistance, glucose intolerance and sleep disturbance, all risk factors of adiposity (Cipolla-Neto et al., 2014). Recent studies have suggested that melatonin may also burn calories through stimulating the aggregated activities of brown adipose tissue (BAT) by converting excessive energy into heat (Tan et al., 2011; Reiter et al., 2012).

4.7 Strengths and limitations at the review-level

We employed an exhaustive search strategy to examine evidence of associations between LAN exposure and weight-related outcomes with comprehensive consideration over the supplementary impact induced by technological products. We excluded ecological studies to overcome the distortion of estimates which did not adjust for individual-level confounders, thereby increasing robustness of the pooled effect estimates. The OHAT risk of bias rating tool was employed to systematically identify the underlying risk of bias associated with multiple domains of each included study, while the GRADE guideline was used to scientifically appraise the overall quality of the generated evidence. Due to limitations of available data, further stratified meta-analysis by socio-economic status as well as dose-response meta-analysis estimating the incremental risks for obesity across the LAN exposure profiles could not be conducted.

5 Conclusions

LAN is a technological development that contributes directly to the economic and social productivity, thereby enhancing wealth and welfare of our cities. Nonetheless, like most features of the cities that enrich human civilization, LAN also poses risks to population health. We present the first systematic review and meta-analysis of the association between LAN exposure

and obesity in human subjects, reporting a higher LAN exposure was associated with 13% and 22% higher odds of overweight and obesity respectively. Evidence of the associations of LAN exposures with weight-related outcomes were also found across the three levels of LAN exposures and two nighttime measurement periods. At the same time, caution should be taken while interpreting the study findings, given our OHAT risk of bias assessment identified a substantial detection bias for exposure attributed to subjective measurement of LAN, and the overall body of evidence generated was graded as 'moderate'. Further large-scale prospective cohort studies with objectively measured and time-matched exposures and outcomes across various geographical settings and population sub-groups are warranted to add to the accumulating evidence-base for reducing the health burdens associated with obesity. Controls over excessive outdoor night light that have been part of the byelaws of major cities of high income countries, being important not only for controlling nuisance but, also for public health. Further, the evidence suggests that private night light is as much a public health issue as outdoor night light. These evidences are likely to contribute towards more effective policy interventions to control light pollution from artificial lighting in our cities with an objective of minimizing/offsetting health risks.

Declaration of interest

No conflict of interest

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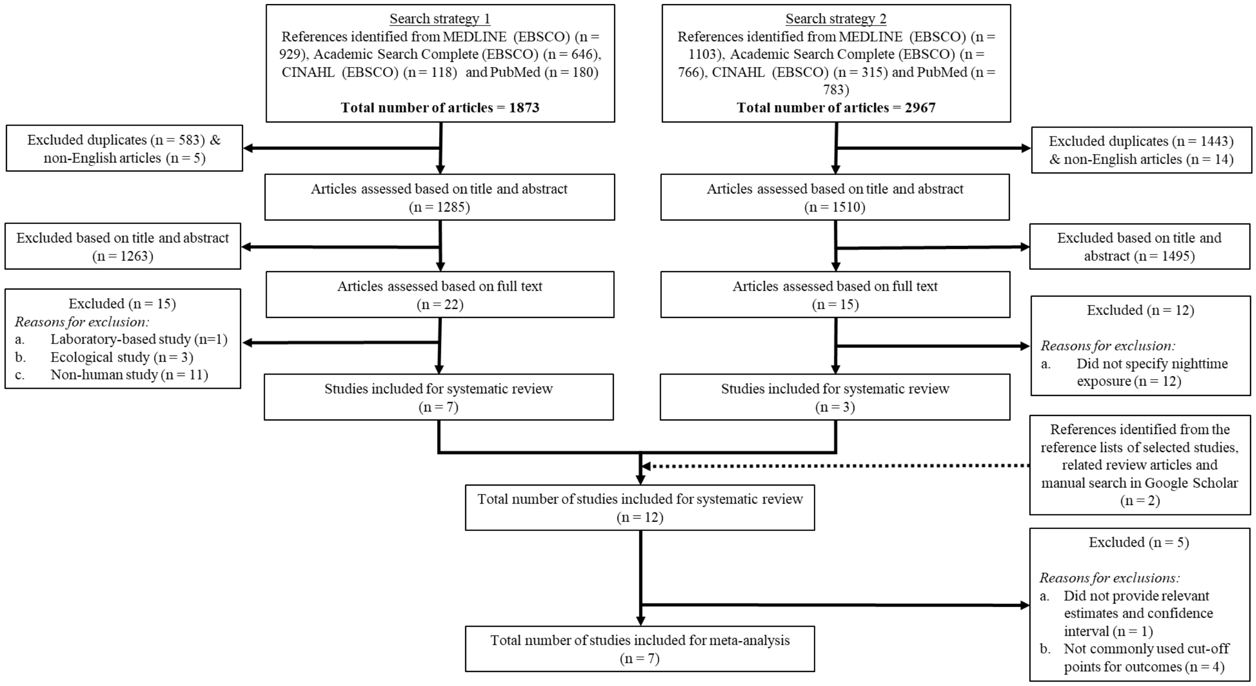

Figure 1. Flow chart of the search strategies and study selection process.

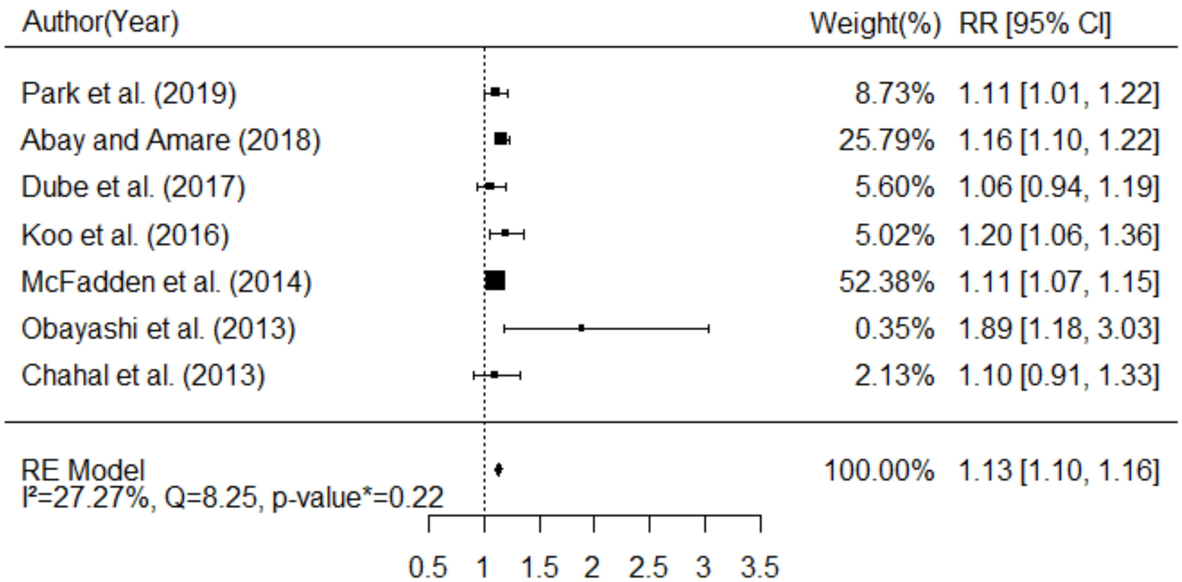

Figure 2. Forest plot of the seven studies on the association between LAN exposure and overweight (body mass index≥25kg/m^2).
Note. OR: odds ratio

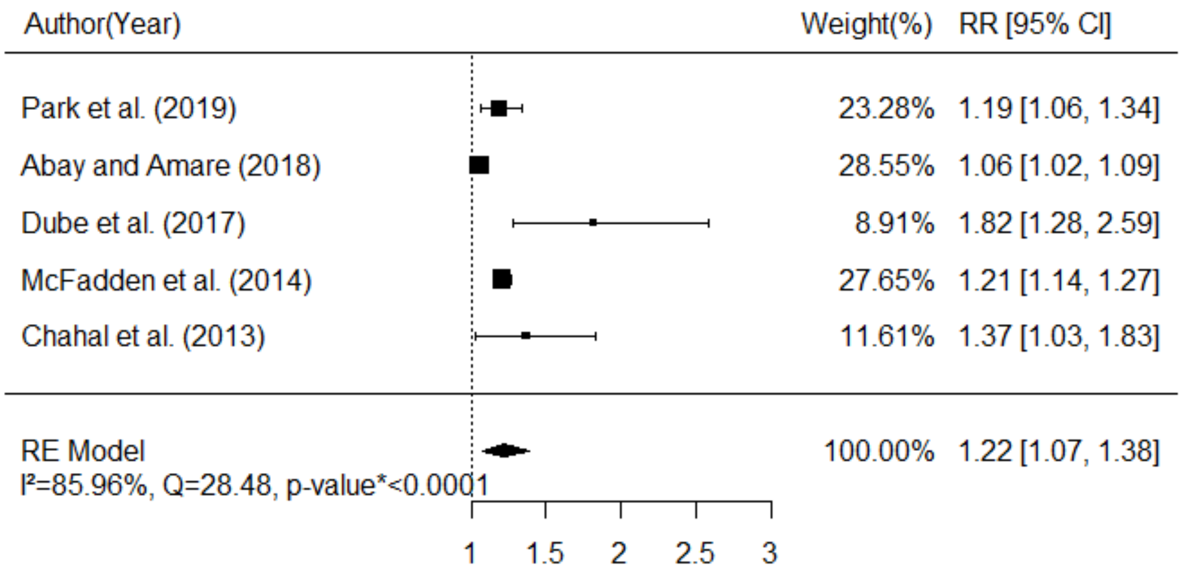

Figure 3. Forest plot of the five studies on the association between LAN exposure and obesity (body mass index≥30kg/m^2).

Note: *p-value for heterogeneity; OR: odds ratio.

Table 1. Summary of main characteristics of the 12 studies included examining the association between LAN and risk of obesity.

Author (year)	Setting	No. of subjects	Sex & Age	Outcome	Definition of LAN	Exposure classification	
Obayashi et al. (2020)[a]	Japan	678	Both; ≥60	Diabetes mellitus (based on medical history, current diabetes treatment, or HbA1c level ≥6.5%)	The average portable light meter measured light intensity recorded between bedtimes and rise times over two consecutive nights	Dark average <5 lux LAN average ≥5 lux	Ref. 3.17 (1.32-7.63)
Park et al. (2019)[a]	US & Puerto Rico	43722	Female; 35-74	Overweight (BMI≥25), Obesity (BMI≥30), WC, WHR, WHtR	Self-reported types of LAN that were usually present while sleeping at enrollment	Outcome: Overweight No ALAN exposure Small nightlight in room Light outside room Light/television in room	RR (95% CI) Ref. 1.11 (1.00-1.22) 1.08 (0.97-1.20) 1.22 (1.06-1.40)
Abay and Amare (2018)[b]	Nigeria	33586	Female; 15-49	Overweight (BMI≥25), obesity (BMI≥30)	Nightlight intensity measured at the cluster level and for various time periods (data sourced from the DMSP)	Outcome: Overweight Night light (0-50th percentile) Night light (50-75th percentile) Night light (75-90th percentile) Night light (above 90th percentile)	Estimate (SE) Ref. 0.022 (0.017) 0.080 (0.019) 0.147 (0.028)
Dube et al. (2017)[b]	Alberta, Canada	2334	Both; Grade 5 (aged 10-11)	Overweight (BMI≥25), obesity (BMI≥30)	Self-reported (by children) frequency of bedroom use of electronic entertainment and communication devices during an hour before sleep at night	Outcome: Overweight No access and no use Access but never used Access and frequently used	OR (95% CI) Ref. 0.92 (0.80, 1.05) 1.06 (0.94, 1.19)
Koo et al. (2016)[b]	South Korea	8526	Both; 39-70	Obesity (BMI≥25)	Yearly average nightlight data from 2001 and 2002 derived from the DMSP	Outcome: Obesity Low outdoor ALAN (DN45-63) Higher outdoor ALAN (DN45-63)	OR (95% CI) Ref. 1.20 (1.06, 1.36)
Obayashi et al. (2016)[a]	Japan	766	Both; ≥60	WHtR change, BMI change	Light exposures measured by a portable light meter during the evening, nighttime, in the first (1 hour after bedtime) and last hour of the night (1 hour before rising time) for two consecutive days	Outcome: BMI change mean <3 lux mean ≥3 lux mean <10 lux mean ≥10 lux	β (95%CI) Ref. 0.405 (0.011, 0.799) Ref. 0.391 (-0.143, 0.932)

(Continued)

(Continued)

Author (year)	Setting	No. of subjects	Sex & Age	Outcome	Definition of LAN	Exposure classification	
McFadden et al. (2014)[b]	UK	113343	Female; 16-103	Overweight (BMI≥25), Obesity (BMI≥30), WC, WHR, WHtR	Self-reported lightness of the room subjects slept in at night	<u>Outcome: Overweight</u> Lightest level Middle level Darkest level	OR (95% CI) Ref. 0.97 (0.94, 1.00) 0.90 (0.87, 0.94)
Obayashi et al. (2013)[b]	Japan	528	Both; ≥60	Obesity (BMI≥25), WC, diabetes (antidiabetic medications, or FPG ≥ 126 mg/dl and HbA1c ≥6.5%), dyslipidemia	Nightlight exposures measured by a portable photometer during the bed-in-time to bed-out-time by a self-reported sleep diary	<u>Outcome: odds of being obese</u> (BMI≥25kg/m^2) Dim group (<3 lux) LAN group (≥3 lux)	 OR (95% CI) Ref. 1.89 (1.18-3.04)
Arora et al. (2013)[b]	UK Midlands region	632	Both; 11-18	BMI z-score	Self-reported (by young people) technology use (computer use, mobile telephones, TV viewing, video gaming) at bedtime	Use of specific technologies at bedtime Computer use Mobile telephone TV viewing Video gaming	Beta (SE) 0.26 (0.08) 0.01 (0.09) 0.31 (0.08) 0.40 (0.08)
Chahal et al. (2013)[b]	Alberta, Canada	3398	Both; grade 5 (aged 10-11)	Overweight (BMI 25-<30), obesity (BMI ≥30)	Self-reported (by children) nighttime use of electronic entertainment and communication devices after the time the subjects were normally expected to go to sleep	<u>Outcome: overweight</u> Watch TV or movies Play computer games or video games Use of Internet Chat online or on social network Use a phone to chat or test	OR (95% CI) 1.12 (0.93, 1.34) 1.05 (0.87, 1.27) 1.01 (0.85, 1.21) 0.98 (0.82, 1.17) 0.86 (0.68, 1.10)
Calamaro et al. (2012)[b]	US	625	Both; 6-10	BMI z score change	Self-reported (by caregiver) the presence of a nightlight in the child's bedroom	No data shown; A nightlight was not associated with a change in the BMI z scores in adjusted models (p > .10)	
Giammattei et al. (2003)[b]	Santa Barbara County, US	385	Both; Grade 6-7 (aged 11-13)	BMI at or above the 85th percentile	Self-reported (by children) television watching on an average school night	 <2h of television per night ≥ 2h of television per night	OR (95% CI) Ref 1.24 (0.95, 1.63)

Note: [a]Longitudinal study; [b]Cross-sectional study; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; DMSP: Defense Meteorological Satellite Program; DN, digital number; OR: odds ratio; RR: relative risk; Ref.: Reference group.

Table 2. Summary of the temporality of diurnal ALAN exposure measurements in the 12 observational studies of the associations between LAN exposure and weight-related.

	Dusk	Sleep	Rising
Macro-level of LAN exposure (nightlight at the area or street level)			
1. Abay and Amare (2018)			
2. Koo et al. (2016)	20:30-22:00		
Meso-level of LAN exposure (nightlight within an indoor setting)			
3. Obayashi et al. (2020)		while sleeping	
4. Park et al. (2019)		while sleeping	
5. Obayashi et al. (2016)	in 4 hours before sleep	while sleeping#	
6. McFadden et al. (2014)		while sleeping	
7. Obayashi et al. (2013)		while sleeping	
8. Calamaro et al. (2011)		while sleeping	
Micro-level of LAN exposure (nighttime use of light-emitted devices)			
9. Dube et al. (2017)	in 1 hour before sleep		
10. Arora et al. (2013)	bedtime		
11. Chahal et al. (2012)	after the time the subjects were expected to sleep		
12. Giammattei et al. (2003)	nighttime		

#Additionally explored nighttime light in 1 hour after bedtime and 1 hour before rising.

Table 3. Summary of odds ratios for different weight-related outcomes in association with LAN exposure by level of LAN exposure and nighttime periods.

	Number of study	Summary odds ratio (95%CI)	Test of heterogeneity		
			Q	p-value	I^2 (%)
Overall					
Overweight (BMI≥25 kg/m^2) (1)	7	1.13 (1.10-1.16)	8.25	0.22	27.27
Obesity (BMI≥30 kg/m^2) (2)	5	1.22 (1.07-1.38)	28.48	<0.0001	85.96
Level of LAN exposure					
Macro-level of LAN exposure					
Overweight (BMI≥25 kg/m^2) (3)	2	1.17 (1.11-1.23)	0.26	0.61	0
Meso-level of LAN exposure					
Overweight (BMI≥25 kg/m^2) (4)	3	1.11 (1.08-1.15)	4.82	0.09	58.50
Obesity (BMI≥30 kg/m^2) (5)	2	1.20 (1.14-1.26)	0.04	0.85	0
WC (≥88m) (6)	2	1.11 (1.09-1.14)	0.36	0.55	0
WHR (≥0.85) (7)	2	1.07 (1.01-1.14)	4.64	0.03	78.45
WHtR (high)* (8)	2	1.11 (1.03-1.20)	9.00	0.003	88.89
Micro-level of LAN exposure					
Overweight (BMI≥25 kg/m^2) (9)	2	1.07 (0.97-1.18)	0.10	0.75	0
Obesity (BMI≥30 kg/m^2) (10)	2	1.55 (1.18-2.04)	1.50	0.22	33.28
Nighttime periods					
Before sleep					
Overweight (BMI≥25 kg/m^2) (11)	3	1.12 (1.03-1.22)	2.05	0.36	2.41
While sleeping					
Overweight (BMI≥25 kg/m^2) (12)	3	1.11 (1.08-1.15)	4.82	0.09	58.50

*Not*e: WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio.
*In Park et al.'s (2019) study, high waist-to-height ratio was determined by ≥0.5, whereas in McFadden et al. (2014)'s study, high waist-to-height ratio was determined by ≥0.5 if aged <40 years, ≥0.55 if aged <50 years, and ≥0.6 if aged ≥50 years.

(1) Park et al. (2019), Abay and Amare (2018), Dube et al. (2017), Koo et al. (2016), McFadden et al. (2014), Obayashi et al. (2013), Chahal et al. (2013).
(2) Park et al. (2019), Abay and Amare (2018), Dube et al. (2017), McFadden et al. (2014), Chahal et al. (2013).
(3) Abay and Amare (2018), Koo et al. (2016).
(4) Park et al. (2019), McFadden et al. (2014), Obayashi et al. (2013).
(5) Park et al. (2019), McFadden et al. (2014).
(6) Park et al. (2019), McFadden et al. (2014).
(7) Park et al. (2019), McFadden et al. (2014).
(8) Park et al. (2019), McFadden et al. (2014).
(9) Dube et al. (2017), Chahal et al. (2013).
(10) Dube et al. (2017), Chahal et al. (2013).
(11) Dube et al. (2017), Koo et al. (2016), Chahal et al. (2013).
(12) Park et al. (2019), McFadden et al. (2014), Obayashi et al. (2013).