Adverse impact of nocturnal transportation noise on glucose regulation in healthy young adults: Effect of different noise scenarios

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ARTICLE INFO

ABSTRACT

Background: Epidemiological evidence indicates an association between transportation noise exposure and a higher risk of developing type 2 diabetes. Sleep disturbances are thought to be one of the mechanisms as it is well established that a few nights of short or poor sleep impair glucose tolerance and insulin sensitivity in healthy good sleepers.

Objectives: The present study aimed to determine the extent to which exposure to nocturnal transportation noise affects glucose metabolism, and whether it is related to noise-induced sleep alterations.

Methods: Twenty-one young healthy volunteers (nine women) participated in a six-day laboratory study starting with a noise-free baseline night, then four nights sleeping with randomly-presented transportation noise scenarios (three road and one railway noise scenario) with identical average sound level of 45 dB but differing in eventfulness and ending with a noise-free recovery night. Sleep was measured by polysomnography. Glucose tolerance and insulin sensitivity were measured after the baseline, the last noise night and the recovery nights with an oral glucose tolerance test using Matsuda and Stumvoll insulin sensitivity indexes. Eleven participants were assigned a less eventful noise scenario during the last noise night (LE-group), while the other ten had a more eventful noise scenario (ME-group). Baseline metabolic and sleep variables between the two intervention groups were compared using a non-parametric Mann-Whitney U test while mixed models were used for repeated measure analysis.

Results: All participants had increased glucose$_{AUC}$ (mean ± SE, 14 ± 2%, $p < 0.0001$) and insulin$_{AUC}$ (55 ± 10%, $p < 0.0001$) after the last noise night compared to the baseline night. 2 h-glucose level tended to increase only in the ME-group between baseline (5.1 ± 0.22 mmol·L^{-1}) and the last noise night (6.1 ± 0.39 mmol·L^{-1}, condition: $p = 0.001$, interaction: $p = 0.08$). Insulin sensitivity assessed with Matsuda and Stumvoll indexes respectively decreased by 7 ± 8% ($p = 0.001$) and 9 ± 2% ($p < 0.0001$) after four nights with transportation noise. Only participants in the LE-group showed beneficial effects of the noise-free recovery night on glucose regulation (relative change to baseline: glucose$_{AUC}$: 1 ± 2%, $p = 1.0$ for LE-group

and 18 ± 4%, p < 0.0001 for ME-group; Stumvoll index: 3.2 ± 2.6%, p = 1.0 for LE-group and 11 ± 2.5%, p = 0.002 for ME-group). Sleep was mildly impaired with increased sleep latency of 8 ± 2 min (< 0.0001) and more cortical arousals per hour of sleep (1.8 ± 0.6 arousals/h, p = 0.01) during the last noise night compared to baseline. No significant associations between sleep measures and glucose tolerance and insulin sensitivity were found.

Conclusion: In line with epidemiological findings, sleeping four nights with transportation noise impaired glucose tolerance and insulin sensitivity. Based on the presented sound exposure, the eventfulness of the noise scenarios seems to play an important role for noise-induced alterations in glucose regulation. However, we could not confirm our hypothesis that transportation noise impairs glucose regulation via deterioration in sleep quality and quantity. Therefore, other factors, such as stress-related pathways, may need to be considered as potential triggers for noise-evoked glucose intolerance in future research.

1. Introduction

Exposure to transportation noise is a major public health issue ranking among the top environmental risk factors for health in Europe (Hanninen et al., 2014; Vienneau et al., 2015). Long-term exposure to transportation noise has been associated with increased risk for cardiovascular diseases (Selander et al., 2009; Van Kempen and Babisch, 2012; Héritier et al., 2017; Vienneau et al., 2015; Foraster et al., 2017) and type 2 diabetes (T2D) (Clark et al., 2017; Eze et al., 2017; Sorensen et al., 2013; Eze et al., 2017; Kempen et al., 2018). However, the underlying mechanism linking noise exposure and development of T2D remains unclear (Liu et al., 2016; Cui et al., 2016), and the dose-response is poorly understood with adverse effects observed below the WHO recommended threshold (Héritier et al., 2017; Hurtley, 2009).

Both epidemiological and field studies attributed a key role to sleep in the regulation of glucose homeostasis and incident T2D. Short sleep duration and poor sleep quality were found to impair glucose regulation (Anothaisintawee et al., 2016). Several experimental studies confirmed the importance of sleep duration on glucose regulation (Spiegel et al., 1999; Reutrakul and Van Cauter, 2014). Donga et al. (2010), for example found that one night with a 4-h sleep restriction resulted in a marked decrease in insulin sensitivity and glucose tolerance. Sleep quality, and more precisely the amount of deep sleep and the severity of sleep fragmentation, also seems crucial for glucose regulation (Reutrakul and Van Cauter, 2014). Sleep fragmentation as a consequence of selective (Herzog et al., 2013; Tasali et al., 2008) and nonselective (Stamatakis and Punjabi, 2010) auditory slow wave sleep (SWS) suppression, without reducing total sleep duration, was found to initiate glucose intolerance and insulin resistance. The underlying mechanisms include increased brain energy metabolism (Maquet, 1995) and increased sympathetic activity during slow wave sleep (Tasali et al., 2008; Brandenberger et al., 2001). As several studies reported impaired sleep quality due to nocturnal transportation noise exposure (Basner and McGuire, 2018), we hypothesized that transportation noise impairs glucose regulation by its deleterious effects on sleep.

To date, environmental noise effects on health are typically evaluated using the average energetic dose over longer time periods expressed, for example, as the LAeq (i.e., A-weighted equivalent continuous sound pressure level) (Theakston, 2011). However, such measures have limited explanatory power for predicting specific noise effects such as annoyance or sleep disturbances (Griefahn et al., 2006). Acoustical characteristics of noise events, such as the distribution of maximum sound pressure level and the slope of rise of the level, explain some physiological reactions including awakenings and increased heart rate better than the LAeq (Griefahn et al., 2006; Basner et al., 2011; Brink et al., 2008; Marks et al., 2008). Thus, Wunderli et al. proposed, the intermittency ratio (IR), an integral measure of the energy contribution of distinct noise events on the total sound exposure, which reflects the "eventfulness" of a noise situation. For example, passing trains yield a higher IR than a highway, which produces rather continuous noise (Wunderli et al., 2015). A recent study from Héritier and colleagues indicated that a moderate IR at night (2nd-4th quintile) was

more relevant than continuous noise (quintile 1) or highly variable noise (quintile 5) for increased risk of all cardiovascular and ischemic heart diseases (Héritier et al., 2017).

The goal of the present laboratory study was to determine if short-term (a few nights) nocturnal transportation noise exposure affects glucose regulation in healthy adults. Furthermore, we tested if the eventfulness of transportation noise is related to effects on glucose metabolism as well as sleep alterations, and whether the latter confers changes in glucose regulation. Additionally, we tested for laboratory stay effects on glucose regulation by applying the same protocol to a control group sleeping only under noise-free conditions.

2. Material and methods

2.1. Study participants

Participants were recruited between July 2014 and August 2016 through advertisements on university websites, in newspapers and in public buildings in Switzerland, Germany and France. They were screened for medical, psychological and sleep disorders through questionnaires, a medical examination and a full polysomnography during an adaptation night in the laboratory. Exclusion criteria were > 15 periodic leg movements per hour and an apnea-hypopnea index > 10. Participants underwent blood tests to ensure that haematology and fasting glucose levels were within normal range, as well as a hearing test to guarantee normal hearing threshold according to age and gender. Participants habitually slept 7 to 9 h per night and indicated good subjective sleep quality (Pittsburgh Sleep Quality Index (Buysse et al., 1989), PSQI ≤ 5) and no daytime sleepiness (Epworth Sleepiness Scale (Johns, 1991), ESS ≤ 10). To control for potential circadian phase misalignment, we excluded extreme chronotypes (Munich Chronotype Questionnaire (Roenneberg et al., 2003), MCTQ < 2 or MCTQ ≥ 7), shift workers, and did not permit trans-meridian flights within the month preceding study participation. Noise sensitivity was assessed using the short version of the German *Lärmempfindlichkeitsfragebogen* (LEF-K) (Zimmer and Ellermeier, 1998) and the *Noise Sensitivity Questionnaire* (NoiSeQ) (Schutte et al., 2007). Although it was not part of the selection criteria, noise sensitivity did not differ between study volunteers and only 3 out of the 21 participants, and none of the control group, reported living in a rather noisy environment. All participants were non-smokers and medication-free (including drugs and hormonal contraceptives). Women were tested for pregnancy prior to study admission; none were excluded on this basis. For all but two women, the entire lab protocol was conducted between day 0 and 11 after menses onset, i.e. during the follicular phase. The two remaining women started the study during the late luteal phase and were subsequently excluded from the analysis. One additional woman could not be included in this analysis because of difficulties with blood collection during the oral glucose tolerance test (OGTT). Thus, 21 participants (nine women) out of 286 (184 women), were included in the present analyses. A control group of six young men, matched in age and BMI to the intervention group, was also studied. All participants gave written

informed consent. The study protocol, screening questionnaires and consent forms were approved by the local ethics committee (EKNZ/ Ethikkommission Nordwest- und Zentralschweiz, Switzerland), conformed to the Declaration of Helsinki and were performed in accordance with international ethical standards.

2.2. Methods

2.2.1. Pre-study condition

To maintain a regular sleep-wake rhythm, one week prior to study begin in the laboratory participants were asked to maintain their habitual bedtimes within ± 30 min, spend 8 h in bed and not take naps. Compliance was assessed via actigraphy (Actiwatch L, Cambridge Neurotechnologies, Cambridge, UK). Participants were asked to avoid stimulating nutriments (coffee, tea, chocolate) and alcohol, to eat as usual without extreme fatty meals and to avoid extreme physical activities in order to match the laboratory conditions as best as possible.

2.2.2. Laboratory study conditions

Participants spent six consecutive days and nights (Fig. 1) in the laboratory in individual windowless and sound proof bedrooms (12.5 m^2, http://www.chronobiology.ch/wp-content/uploads/2013/05/room_single_5_web.jpg). The reverberation time of the bedrooms was 0.6 s and the background noise level was below 20 dB(A). Light intensity during the day was kept constant at 150 lx and room temperature was set at 22 °C. Participants had an 8-h sleep opportunity per night scheduled at their habitual bedtimes.

2.2.3. Noise exposure characteristics

The sound stimuli were created by sampling portions of real-world field sound recordings. Thereby, outdoor sound recordings of single vehicle pass-by events were mixed and played back on a loudspeaker installed in the bedrooms. The spectral effect of sound transmission through a tilted window was simulated using a digital filter. Fig. 1 illustrates the study protocol. All participants started and ended the study week respectively with a noise-free baseline (BL) and recovery (RC) night during which a very low volume ambient sound scenario (Scenario 0) was applied to reproduce a tilted window situation (Fig. 1). It consisted of cricket chirps and distant traffic, with a LAeq of 30 dB at the ear of the sleeper. In between, participants were exposed from lights OFF to lights ON to four different noise scenarios (A, B, C and D), which were incompletely counterbalanced between noise nights NN2 to NN5: less eventful (LE) noise scenarios (A and B) alternated with more eventful (ME) noise scenarios (C and D). All noise scenarios had an identical hourly LAeq of 45 dB at the ear of the sleeper, which corresponds to an outdoor level of approximately 60 dB for a tilted window (Locher et al., 2018). Scenario A corresponded to a 4-lane highway, scenario B to a 2-lane country road, scenario C to a 1-lane urban road, and scenario D to a railway noise situation with five (four freight and one regional trains) different train pass-bys (see Table A in Appendix A for more information). The noise scenarios differed with respect to median sound level (LA50) and IR, two noise characteristics that negatively correlate with each other and that describe the eventfulness of the noise scenario (Table 1). LA50 is the noise level exceeded during 50% of the time. The noise scenarios with a low difference between LAeq and LA50 (i.e. scenarios 0 and A) had a low IR because of the steady sound level. During the last noise night (NN5), eleven participants slept with a LE noise scenario (LE-group, Fig. 1a), while ten slept with a ME noise scenario (ME-group, Fig. 1b). The control group underwent exactly the same laboratory condition and was instructed the same way. While they thought they would be exposed to transportation noise, they actually slept all six nights with Scenario 0 (Fig. 1c). During the last morning of the study, participants were asked to retrospectively evaluate noise annoyance of each night on a scale of 0 to 100 with the question "How annoyed were you during the respective night (BL-NN5-RC) by the noise"? Retrospective recall had the benefit to allow comparison between the noise scenarios and avoid directing participant's attention too much to the noise exposure during the study. Further details of the noise characteristics are described in Rudzik et al. (2018).

2.2.4. Control of diet and physical activity

Daily caloric intake during the laboratory was individually estimated using the Mifflin equation (resting energy expenditure = $9.99 \times$ weight + $6.25 \times$ height $- 4.92 \times$ age + $166 \times$ sex $- 161 \times 1.3$ for the low activity factor) (Frankenfield et al., 2003; Mifflin et al., 1990) and was kept constant. Each meal included 35% lipids, 50% carbohydrates and 15% protein. Meal timing was adjusted to the participant's wake up time and no snacks were allowed. Participants were encouraged to walk through the windowless corridor to ensure some light physical activity. In the morning of BL, NN5 and RC, weight was measured upon awakening after the participants used the toilet.
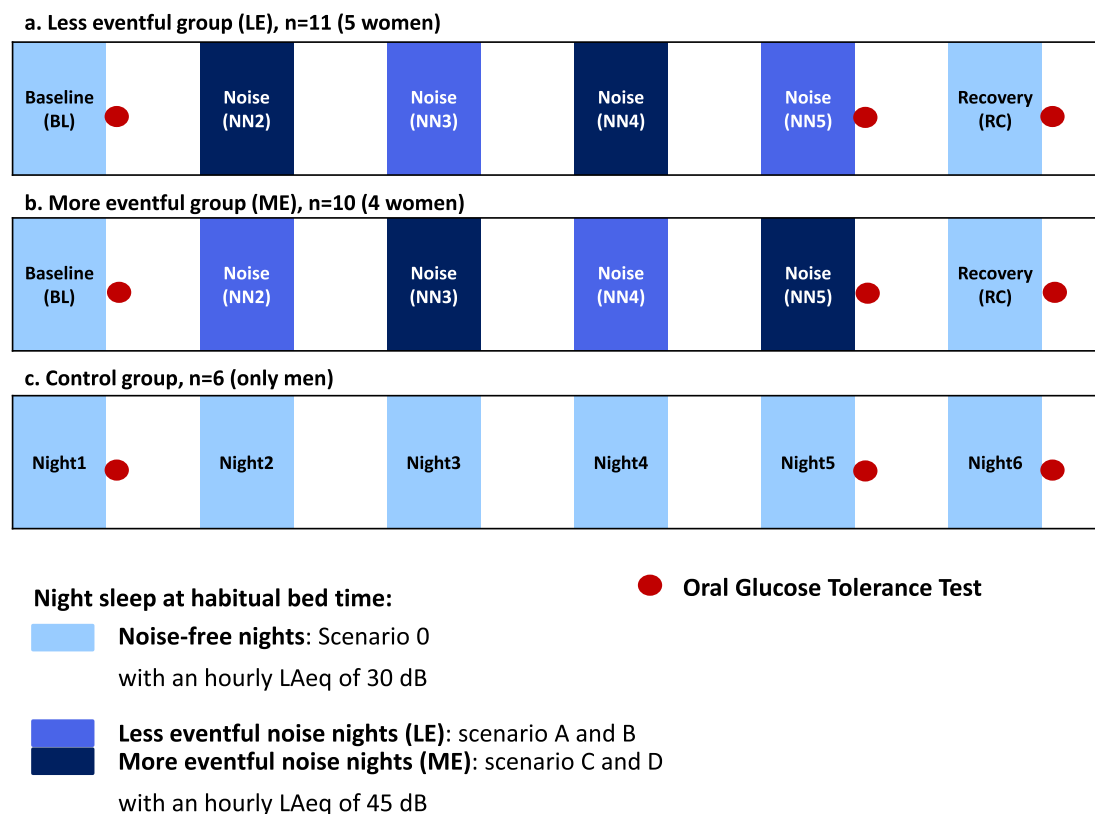
2.2.5. Glucose metabolism

Glucose metabolism was assessed via a two hour 75-g OGTT administered 1 h after awakening following BL, NN5 and RC, 30 min after inserting the venous catheter (Fig. 1). Two fasting ($t - 15$ and t0) and six post-load (time points: t10, t20, t30, t60, t90 and t120) blood samples were collected.

Assays. Blood was distributed in Na-fluoride tubes and immediately centrifuged for plasma glucose measurement. Serum insulin measurement was obtained from another tube after 30 min clotting at room temperature. Tubes were centrifuged at 4 °C for 10 min at 3500 rpm. All samples were then stored at -80 °C until assay. Plasma glucose was assayed via the hexokinase method (Glucose GOD-PAP test, Roche) with a limit of sensitivity of 0.11 mmol·L^{-1} and an intra-assay variation coefficient of 0.9%. Serum insulin was measured with an ELISA test (80-INSHU-E01.1; ALPCO) with a limit of sensitivity of 2.78 pmol·L^{-1} and an intra-assay variation coefficient of 6%.

Measures. Fasting glucose (G_0) and insulin (I_0) levels were calculated by averaging the values from blood samples at $t - 15$ and t0. Fasting insulin resistance was assessed using the HOMA-IR (($G_0 \times I_0$) / 22.5, (Matthews et al., 1985)). The area under the curve (AUC) for glucose and insulin was calculated using the trapezoidal rule. Glucose tolerance was assessed by calculating glucose$_{AUC}$ and via glucose concentration at t120 (G_{120}). Insulin sensitivity was estimated using the Matsuda index ($10,000 / \sqrt{G0 \times I0 \times \text{mean G} \times \text{mean I}}$ (Matsuda and DeFronzo, 1999)) and the Stumvoll ISI index ($0.226 - 0.0032 \times \text{BMI} - 0.0000645 \times I_{120} - 0.00375 \times G_{90}$, where I_{120} and G_{90} represent insulin concentration at t120 and glucose concentration at t90 respectively (Stumvoll et al., 2000)). Beta-cell function was assessed by calculating the Stumvoll first-phase ($1.283 + 1.829 \times I_{30} - 138.7 \times G_{30} + 3.772 \times I_0$) and second-phase insulin release ($287 + 0.4164 \times I_{30} - 26.07 \times G_{30} + 0.9226 \times I_0$; where I_{30} and G_{30} represent insulin and glucose concentrations at t30 respectively (Stumvoll et al., 2000)).

2.2.6. Sleep measurement

Subjective sleep quality. Subjective sleep quality was assessed 5–10 min upon awakening with the Leeds Sleep Evaluation Questionnaire (Parrott and Hindmarch, 1978) with ten visual analog scale questions assessing four parameters of sleep quality: getting to sleep (more difficult - easier than usual; slower - more quickly than usual; less sleepy - more sleepy than usual), quality of sleep (more restless - calmer than usual; with more wakeful periods - with less wakeful periods than

a. Less eventful group (LE), n=11 (5 women)

Baseline (BL) ●	Noise (NN2)	Noise (NN3)	Noise (NN4)	Noise (NN5) ●	Recovery (RC) ●

b. More eventful group (ME), n=10 (4 women)

Baseline (BL) ●	Noise (NN2)	Noise (NN3)	Noise (NN4)	Noise (NN5) ●	Recovery (RC) ●

c. Control group, n=6 (only men)

Night1 ●	Night2	Night3	Night4	Night5 ●	Night6 ●

Night sleep at habitual bed time:

● **Oral Glucose Tolerance Test**

Noise-free nights: Scenario 0
with an hourly LAeq of 30 dB

Less eventful noise nights (LE): scenario A and B
More eventful noise nights (ME): scenario C and D
with an hourly LAeq of 45 dB

Fig. 1. Schematic illustration of the study protocol.
Sleep episodes were scheduled according to habitual bedtimes. Glucose tolerance and insulin sensitivity were assessed via three oral glucose tolerance tests (OGTTs) (red circles). The two intervention groups (a., LE-group n = 11 and b., ME-group n = 10) started and ended the laboratory stay with the noise-free Scenario 0. LE-group slept with a less eventful noise scenario during the night preceding the second OGTT (NN5) whereas the ME-group slept with a more eventful noise scenario. The order of less (A or B) vs. more (C or D) eventful noise scenarios was balanced across the night NN2 to NN5. The control group (c.) slept each night with the noise-free Scenario 0. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

usual), awake following sleep (more difficult - easier than usual; requires a period of time longer - shorter than usual), and behavior following wakening (tired - alert).

Polysomnographic sleep recordings. Sleep and wakefulness were continuously recorded via polysomnography (PSG) including 12 electroencephalographic (EEG; F3, FZ, F4, C3, CZ, C4, P3, PZ, P4, O1, OZ and O2), two electro-oculographic, two electromyographic and two electrocardiographic derivations (Vitaport-3 digital recorder; TEMEC Instruments BV, Kerkrade, The Netherlands). Each 30-s epoch during scheduled sleep was scored according to the AASM standard criteria (Berry et al., 2012) by four experienced scorers in our laboratory blind to the respective noise scenario (scorer agreement > 85%). All nights of a single participant were scored by the same scorer. The following sleep variables were analyzed: total sleep time (TST, time spent asleep between lights OFF and lights ON), sleep efficiency (percentage of time spent in rapid eye movement (REM) and non REM sleep between lights OFF and lights ON), time spent in light NREM (NREM1 + NREM2), in SWS and in REM sleep, sleep latency (time between lights OFF and NREM2 onset) and wake after sleep onset (WASO, time awake between sleep onset and the final morning awakening). EEG slow wave activity (SWA, EEG power density between 0.75 and 4.5 Hz) was computed, after removal of artifacts by visual inspection, over frontal EEG derivations (F3, Fz, F4) in 4-s bins using fast Fourier transforms (Hamming window, frequency resolution

of 0.25 Hz, overlap of 50%) collapsed in to 30-s epochs in order to match the time resolution of the sleep stage scoring. Arousals were scored as an abrupt shift of EEG frequency that lasted at least 3 s and with at least 10 s of stable sleep preceding the change (Berry et al., 2012). Sleep stage changes (SSC) to deeper stages were defined as the sum of the number of wake-NREM, NREM-REM and wake-REM stage changes per hour while SSC to lighter stages were defined as the sum of the number of NREM-wake, REM-NREM and REM-wake stage changes per hour.

2.3. Statistical analysis

For all analyses, the SAS statistical software package was used (SAS Institute Inc., Cary, NC; version 9.4). Comparisons between the intervention (LE-group and ME-group) versus the control group were only explorative because the number of controls was too small to allow for formal statistical testing. We compared baseline metabolic and sleep variables between the two noise groups (LE-group vs. ME-group) with a non-parametric Mann-Whitney *U* test. Mixed model analysis of variance (PROC MIXED) were carried out for each variable (glucose, insulin and sleep variables) separately and included the fix factor "group" (LE-group vs. ME-group), the repeated within-subject factor "condition" (BL, NN5 and RC) and the random factor "subject" with a variance component covariance structure. Contrasts were assessed with the LSMEAN statement and p-values were based on Kenward-Roger's

Table 1
Acoustical characteristics of the noise scenarios. "0" represents the noise scenario used during the noise-free baseline and recovery nights in the experimental group and during all 6 nights in the control group. A, B, C and D are the four different noise scenarios randomly introduced during the four noise nights in the noise group. LAeq: average level, LA50: median level, IR: Intermittency ratio (Wunderli et al., 2015).

Scenario	Source	LAeq [dB]	LA50 [dB]	LAeq-LA50 [dB]	IR	Noise eventfulness
0	Ambient	30	29	1	0.3	
A	Road	45	44	1	0.3	Less eventful
B	Road	45	39	6	0.7	Less eventful
C	Road	45	33	12	0.8	More eventful
D	Rail	45	31	14	0.9	More eventful

corrected degrees of freedom (Kenward and Roger, 1997). In presence of an interaction between group and condition the statistical significance of each group was separately reported. Residual outliers were removed from analysis. Multiple post-hoc comparisons were corrected using the Tukey-Kramer method. Correlations were calculated with the Pearson correlation coefficient when data were normally distributed; otherwise the Spearman correlation coefficient was used. Normality of the distribution was evaluated by using the Shapiro-Wilk W test ($p > 0.05$ for all comparisons). Statistical significance was set at $p < 0.05$; $p < 0.10$ was reported as marginally significant.

3. Results

Twenty-seven healthy participants were included in the analysis; during the last intervention night (NN5), 11 and 10 participants respectively were exposed to a less eventful (LE-group) and more eventful noise scenario (ME-group) (see Fig. 1). The six remaining participants belonged to the control group. Table 2 summarizes the demographic and metabolic variables at baseline for these three groups. No significant differences were observed for any of these variables between the two intervention groups. Sleep variables did not differ between the

two intervention groups (TST (min), $p = 0.97$; SE (%), $p = 0.97$; light NREM (min), $p = 0.57$; SWS (min), $p = 0.67$; REM (min), $p = 0.83$; arousal (n/h), $p = 0.11$; SWA (μV^2/Hz), $p = 0.70$, see Table 3 for values). Study participants lost on average 493 ± 20 g ($F_{2,40} = 3.89$, $p = 0.03$) during the laboratory stay without a significant difference between the LE and ME group.

3.1. Sleep

Sleep characteristics are summarized in Table 3. Subjectively, the intervention groups, the ME-group in particular, had more difficulties getting to sleep and scored their quality of sleep worse after NN5 compared to BL (and RC for quality of sleep). For both groups combined, awake following sleep and behavior following wakening scores decreased after NN5 and RC compared to BL. All participants from the intervention group scored the noise scenario during NN5 as more annoying than during BL and RC. Objectively measured TST, sleep efficiency, WASO, the amount SWS, SWA and SSC to deeper and lighter stages did not significantly differ between the noise conditions. However, sleep latency significantly increased by 8 ± 2 min during NN5 and by 11 ± 2 min during RC compared to BL. Participants spent 15 ± 5 min more in REM sleep during the RC compared to BL night. This increase in REM sleep came at the cost of a decrease of time spent in light NREM sleep (18 ± 7 min between BL and RC). The number of arousals per hour TST, as well as per hour REM and NREM sleep increased throughout the study. On average, participants had 1.8 ± 0.6 more arousals per hour TST during NN5 compared to BL. Compared to the intervention groups, the control group showed rather an improvement of all the subjective sleep quality parameters during NN5 compared to BL and RC. Noise annoyance and the objectively measured sleep parameters (TST, sleep efficiency, WASO, amount SWS, SWA, SSC and number of arousals) did not differ throughout the week. However, the increase in sleep latency and REM sleep throughout the week was also present in the control group.

Table 2
Participants' characteristics for the control group, the less eventful (LE) and the more eventful (ME) groups. Data are expressed as mean ± SE when normally distributed and as median (25th–75th percentile) when not normally distributed. p values were calculated between the LE-group and ME-group using the Mann-Whitney U test.

	Control group	Less eventful (LE) group	More eventful (ME) group	U test between LE and ME groups (p-value)
	n = 6	n = 11	n = 10	
Demographics				
Sex				
Women (n)	0	5	4	
Men (n)	6	6	6	
Age (years)	26.7 ± 1.3	24.7 ± 1.0	25.1 ± 1.2	0.89
Baseline BMI (kg/m²)	21.7 ± 0.6	21.6 ± 0.70	23.4 ± 0.54	0.06
Noise sensitivity				
LEF-K	12.0 ± 2.5	10.3 ± 1.4	11.5 ± 0.97	0.62
NoiSeQ Global	1.0 ± 0.29	1.2 ± 0.16	1.3 ± 0.11	0.65
NoiSeQ Sleep	0.88 ± 0.17	1.0 ± 0.19	1.2 ± 0.23	0.67
Baseline metabolic variables				
Fasting glucose (mmol·L⁻¹)	5.0 (4.8–5.2)	4.9 (4.8–5.3)	5.1 (4.9–5.5)	0.18
Fasting insulin (pmol·L⁻¹)	34 (16–103)	29 (20–41)	34 (24–42)	0.60
HOMA-IR	1.1 (0.50–3.4)	0.97 (0.62–1.4)	1.1 (0.79–1.4)	0.65
Glucose_AUC (mmol·L⁻¹·min·10¹)	79 ± 2.8	70 ± 3.8	71 ± 3.1	0.92
Insulin_AUC (pmol·L⁻¹·min·10³)	36 ± 7.3	33 ± 4.1	34 ± 4.0	0.97
Matsuda index	9.1 ± 2.9	9.2 ± 1.4	7.4 ± 0.64	0.64
Stumvoll ISI index (µmol·kg⁻¹·min⁻¹·pM⁻¹)	0.12 ± 0.003	0.12 ± 0.004	0.12 ± 0.004	0.39

Table 3

Sleep characteristics between the noise conditions (BL = baseline night, NN5 = last noise night, RC = recovery night) for the control group, the less eventful (LE) and the more eventful (ME) groups. Mean ± SE; TST: total sleep time; SWA: slow wave activity; WASO: wake after sleep onset; SSC_deeper: sleep stage changes to deeper stages per hour; SSC_lighter: sleep stage changes to lighter stages per hour (n/h: number per hour).

	Control group (n = 6)			LE-group (n = 11, 5 women)			ME-group (n = 10, 4 women)			LE vs. ME (p-values)			Tukey post-hoc (p-values)		
	Night1	Night5	Night6	BL	NN5	RC	BL	NN5	RC	Condition	Group effect	Inter-action	BL-NN5	BL-RC	NN5-RC
Subjective assessment															
Subjective sleep quality															
Getting to sleep	42 ± 5.8	47 ± 8.3	36 ± 6.6	48 ± 5.3	39 ± 4.5	50 ± 3.8	53 ± 6.3	34 ± 5.0	36 ± 4.1	0.01	0.38	0.09	0.01	0.18	0.36
Quality of sleep	33 ± 8.2	37 ± 3.8	34 ± 10	34 ± 4.5	31 ± 4.6	46 ± 5.6	40 ± 4.0	19 ± 5.0	30 ± 6.1	0.02	0.1	0.07	0.04	0.98	0.03
Awake following sleep	57 ± 9.8	66 ± 5.9	64 ± 4.1	64 ± 5.2	54 ± 6.3	47 ± 4.4	57 ± 4.0	39 ± 5.6	47 ± 4.1	0.01	0.1	0.34	0.02	0.02	0.99
Behavior following wakening	40 ± 9.6	45 ± 9.4	45 ± 6.1	49 ± 7.8	35 ± 6.8	38 ± 7.8	52 ± 6.4	24 ± 5.1	35 ± 6.8	0.004	0.6	0.46	0.003	0.06	0.47
Noise annoyance	44 ± 13	53 ± 9.9	35 ± 8.4	33 ± 8.0	53 ± 8.7	25 ± 7.2	16 ± 5.2	60 ± 8.7	20 ± 6.9	< 0.0001	0.56	0.31	0.0003	0.97	0.0002
Objective assessment															
TST (min)	437 ± 15	429 ± 17	439 ± 8.3	448 ± 8.0	447 ± 6.8	459 ± 1.9	456 ± 5.0	452 ± 4.3	449 ± 6.4	0.74	0.87	0.18			
Sleep efficiency (%)	91 ± 3.1	89 ± 3.4	91 ± 1.7	93 ± 1.7	93 ± 1.4	96 ± 0.4	95 ± 1.0	94 ± 0.89	94 ± 1.3	0.74	0.87	0.17			
Sleep latency (min)	19 ± 12	28 ± 6.6	24 ± 5.8	12.7 ± 1.9	18.2 ± 2.3	20.7 ± 2.0	12.5 ± 2.9	24.2 ± 4.0	27.0 ± 4.2	< 0.0001	0.31	0.19	0.0001	< 0.0001	0.26
Sleep architecture															
Light NREM (min)	272 ± 20	246 ± 18	267 ± 11	280 ± 15	276 ± 12	281 ± 9.3	283 ± 7.1	266 ± 12	254 ± 10	0.02	0.55	0.16	0.2	0.02	0.49
SWS (min)	70 ± 12	72 ± 13	69 ± 14	74 ± 14	76 ± 10	69 ± 8.3	80 ± 8.8	81 ± 9.2	87 ± 11	0.64	0.52	0.4			
SWA (μV^2/Hz)	1.45 ± 0.05	1.47 ± 0.05	1.46 ± 0.03	1.52 ± 0.07	1.53 ± 0.06	1.56 ± 0.07	1.49 ± 0.07	1.53 ± 0.08	1.54 ± 0.08	0.06	0.84	0.82	0.47	0.05	0.41
REM (min)	94 ± 12	111 ± 9.3	102 ± 13	95 ± 6.2	96 ± 7.6	109 ± 4.7	93 ± 5.6	105 ± 5.9	108 ± 6.3	0.01	0.8	0.41	0.36	0.01	0.18
WASO (min)	37 ± 14	34 ± 16	23 ± 5.2	24.8 ± 7.6	21.2 ± 5.8	10.3 ± 1.9	16.2 ± 4.9	12.4 ± 3.3	16.7 ± 6.3	0.38	0.84	0.31			
SSC_deeper (n/h)	5.4 ± 0.68	5.0 ± 0.84	5.3 ± 1.3	3.6 ± 0.31	3.9 ± 0.36	3.8 ± 0.43	3.6 ± 0.38	4.1 ± 0.52	3.8 ± 0.40	0.34	0.95	0.89			
SSC_lighter (n/h)	4.8 ± 0.59	4.1 ± 0.64	4.3 ± 0.98	3.3 ± 0.27	3.6 ± 0.31	3.3 ± 0.41	3.0 ± 0.35	3.5 ± 0.43	3.4 ± 0.36	0.42	0.76	0.83			
Arousal (n/h)	13 ± 2.3	10 ± 1.5	12 ± 2.0	11 ± 0.82	12 ± 1.3	11 ± 0.97	8.4 ± 0.98	11 ± 0.85	9.8 ± 0.86	0.01	0.33	0.3	0.01	0.45	0.13
Arousal (n/h REM)	16 ± 3.8	13 ± 2.8	15 ± 3.6	11 ± 1.4	13 ± 1.5	12 ± 1.8	9.1 ± 1.4	13 ± 1.7	13 ± 0.8	0.01	0.83	0.34	0.02	0.02	0.99
Arousal (n/h NREM)	13 ± 2.1	8.7 ± 1.0	10 ± 1.9	10 ± 1.0	12 ± 1.6	10 ± 1.2	8.2 ± 1.2	11 ± 0.9	8.8 ± 1.1	0.02	0.31	0.6	0.03	0.05	0.05

Table 4

Comparison of metabolic values between the noise conditions (BL = baseline night, NN5 = last noise night, RC = recovery night) for the less eventful (LE) and the more eventful (ME) groups. Mean ± SE.

	LE-group (n = 11, 5 women)			ME-group (n = 10, 4 women)			LE vs. ME (p-values)			Tukey post-hoc (p-values)		
	BL	NN5	RC	BL	NN5	RC	Condition	Group effect	Inter-action	BL-NN5	BL-RC	NN5-RC
Fasting state												
Fasting glucose (mmol·L^{-1})	5.0 ± 0.11	4.8 ± 0.07	4.8 ± 0.09	5.2 ± 0.11	4.8 ± 0.08	4.9 ± 0.08	< 0.0001	0.15	0.31	0.0003	0.0003	1
Fasting insulin (pmol·L^{-1})	31 ± 5.3	28 ± 3.8	36 ± 3.3	35 ± 4.8	33 ± 4.9	35 ± 4.7	0.23	0.7	0.54			
HOMA-IR	1.1 ± 0.20	0.87 ± 0.13	1.1 ± 0.11	1.2 ± 0.19	0.98 ± 0.18	1.1 ± 0.15	0.15	0.75	0.78			
Response to an oral glucose load												
Glucose$_{AUC}$ (mmol·L^{-1}·min·10^1)	70 ± 3.8	78 ± 3.9	71 ± 3.8	71 ± 3.1	83 ± 2.7	83 ± 2.9	< 0.0001	0.22	0.004	< 0.0001	0.001	0.09
Insulin$_{AUC}$ (pmol·L^{-1}·min·10^3)	33 ± 4.1	47 ± 3.9	45 ± 3.8	34 ± 4.0	49 ± 4.2	51 ± 5.2	< 0.0001	0.58	0.71	< 0.0001	< 0.0001	1
G$_{120}$ (mmol·L^{-1})	5.3 ± 0.32	5.8 ± 0.27	5.4 ± 0.44	5.1 ± 0.22	6.1 ± 0.39	6.0 ± 0.26	0.001	0.62	0.08	0.001	0.02	0.48
Post load indexes												
Matsuda index	9.2 ± 1.4	7.2 ± 0.62	6.5 ± 0.61	7.4 ± 0.64	6.8 ± 0.92	6.6 ± 1.0	0.0002	0.22	0.74	0.005	0.0002	0.53
Stumvoll ISI index (μmol·kg^{-1}·min^{-1}·pM^{-1})	0.12 ± 0.004	0.11 ± 0.003	0.11 ± 0.01	0.12 ± 0.004	0.11 ± 0.004	0.10 ± 0.003	< 0.0001	0.04	0.07	< 0.0001	0.002	0.56
Stumvoll first-phase (pmol·L^{-1})	1064 ± 152	1272 ± 145	1405 ± 229	1257 ± 119	1275 ± 123	1244 ± 142	0.2	0.95	0.16			
Stumvoll second-phase (pmol·L^{-1})	279 ± 35	327 ± 34	357 ± 52	320 ± 26	333 ± 27	325 ± 31	0.12	0.9	0.21			

3.2. Glucose metabolism

Glucose values are presented in Table 4.

3.2.1. Fasting state

For both the LE and ME groups combined, G$_0$ decreased from BL to NN5 and RC (Fig. 2a). The I$_0$ (Fig. 2b) and HOMA-IR (Fig. 2c) did not change throughout the study.

3.2.2. Response to an oral glucose load

Glucose$_{AUC}$ increased in both groups after NN5 compared to BL (Fig. 2d). However, only the LE-group returned to baseline levels after RC (p = 1.0 for LE-group and p < 0.0001 for ME-group (Fig. 2d)). Together, both groups had increased insulin$_{AUC}$ after NN5 and RC compared to BL (Fig. 2e). Concerning G$_{120}$, only the ME-group showed an increase from BL to NN5 and RC (Fig. 2f). Glucose and insulin OGTT profiles are presented in Appendix A (Fig. A).

Matsuda index decreased after NN5 and RC for both groups combined compared to BL (Fig. 2g). Stumvoll ISI index decreased after NN5 compared to BL for both groups (Fig. 2h) and tended to return to baseline levels after RC only for the LE-group (p = 1.0 for LE-group and p = 0.002 for ME-group). Although overall insulin$_{AUC}$ was found to be increased after NN5 and RC compared to BL, for both groups combined the first-phase and second-phase Stumvoll insulin secretion indexes showed no significant changes throughout the week. None of these changes in the glucose metabolism variables significantly correlated with any of the sleep variables or with the noise annoyance rating (glucose$_{AUC}$-SWS and glucose$_{AUC}$-arousal correlations are shown in Appendix A (Fig. B)).

3.3. Effect of the laboratory setting on glucose variables

The control group experienced the same laboratory conditions without being exposed to transportation noise during the night, which gave us the possibility to assess the effect of the laboratory stay per se on the glucose regulation. Fig. 3 represents the percentage change in glucose variables between the OGTT in the morning of the BL and NN5 or RC for the three groups ME-group, LE-group and the control group. The control group did not show any changes in G$_0$. Similar to the intervention groups, the control group showed a small increase (5 (−0.8–40) %) in glucose$_{AUC}$ after night 5, but the effect was weak compared to the intervention groups. After the RC, the glucose$_{AUC}$ of the ME-group remained clearly high whereas the LE-group returned to baseline levels, similar to control group levels. Insulin$_{AUC}$ increased by comparable levels between the control group and the intervention groups. In line with these results, Stumvoll ISI index decreased for the control group however the median stayed higher than the ME-group. Refer to Appendix A for details on the time course of glucose and insulin OGTT profiles in the control group (Fig. C).

4. Discussion

Previous studies have suggested that exposure to transportation noise impairs glucose regulation leading to long term increased risk for developing T2D (Eze et al., 2017; Sorensen et al., 2013). To our knowledge, this is the first experimental study evaluating the effects of nocturnal transportation noise exposure for different scenarios over several nights on glucose regulation, accounting for the potential role of sleep. Despite the mild effect of transportation noise on sleep variables, we found that glucose tolerance and insulin sensitivity were significantly decreased after the noise intervention. Additionally, we tested whether the eventfulness of the noise scenarios plays a role in reflecting these effects. We found that only participants sleeping with less eventful noise during the last noise night were able to recover to baseline glucose levels after one noise-free recovery night.

Fasting state

Response to an oral glucose load

Post load insulin sensitivity indexes
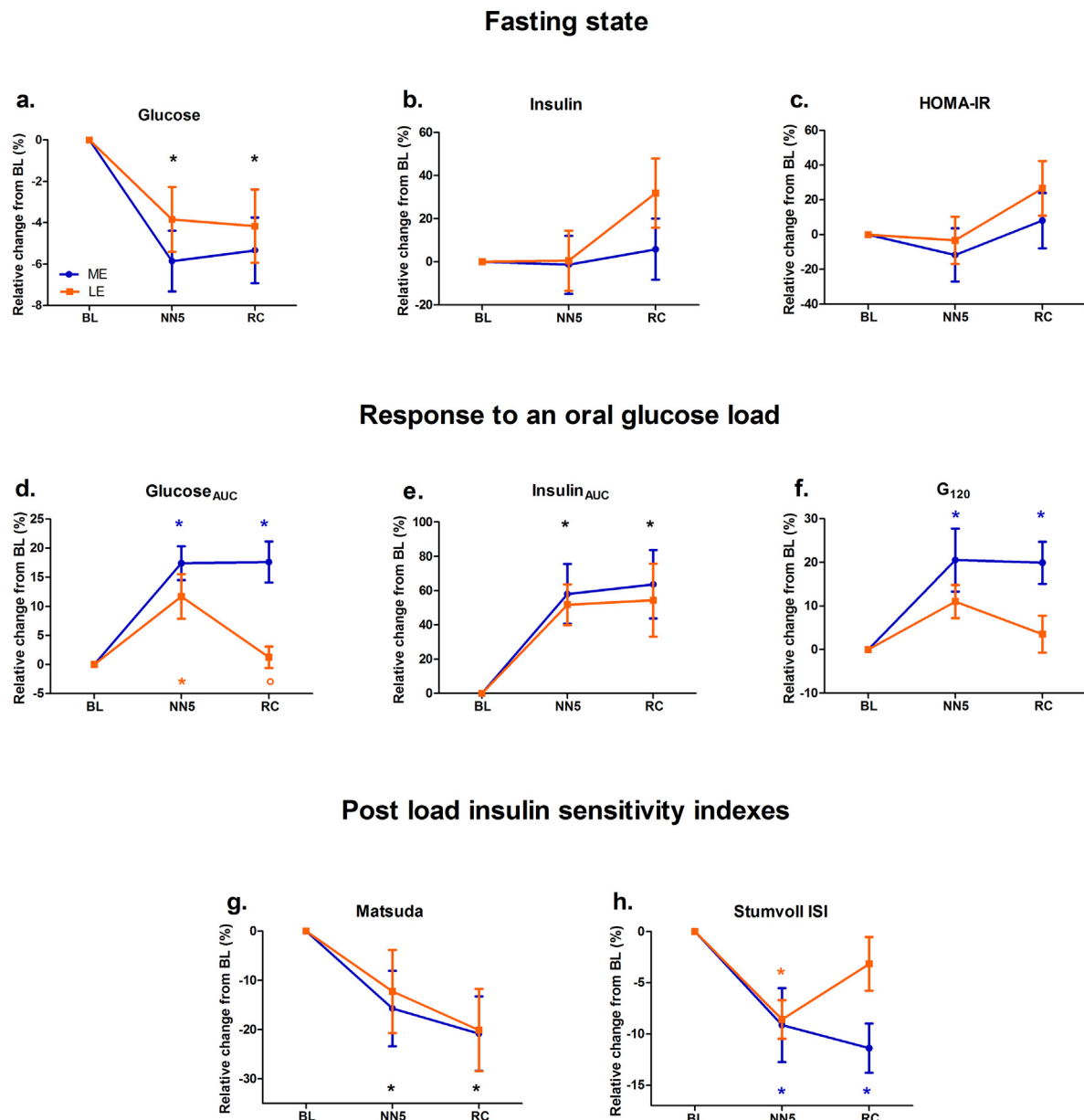
Fig. 2. Relative change in glucose metabolism variables between baseline (BL) and the last noise night (NN5) and recovery night (RC) (LE-group in orange and ME-group in blue).
Mean ± SE. Fasting state measures (first row): fasting glucose (condition: $p < 0.0001$, interaction: $p = 0.31$, a), fasting insulin (condition: $p = 0.23$, interaction: $p = 0.54$, b) and fasting insulin resistance index HOMA-IR (condition: $p = 0.15$, interaction: $p = 0.78$, c). Response to the oral glucose load (second row): glucose$_{AUC}$ (condition: $p < 0.0001$, interaction: $p = 0.004$, d), insulin$_{AUC}$ (condition: $p < 0.0001$, interaction: $p = 0.71$, e) and glucose level at t120 (G_{120}, condition: $p = 0.0006$, interaction: $p = 0.08$, f). Post load insulin sensitivity indexes (third row): Matsuda (condition: $p = 0.0002$, interaction: $p = 0.74$, g) and Stumvoll (condition: $p < 0.0001$, interaction: $p = 0.07$, h) insulin sensitivity indexes. AUC: area under the curve. * in comparison to BL, ° in comparison to NN5, $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.1. Effect of the noise intervention and laboratory conditions on glucose regulation

Compared to the quiet baseline night, we found that sleeping four nights with transportation noise exposure increased morning glucose response and decreased insulin sensitivity. Changes in overall glucose response and G_{120} indicated a significant decrease in glucose tolerance, without reaching prediabetes levels ($G_{120} > 7.8$ mmol·L^{-1}) (Anon, 2018). Global insulin sensitivity, as quantified with the Matsuda and Stumvoll indexes, decreased after sleeping with transportation noise exposure. Compared to the sleep fragmentation study conducted by Herzog and colleagues, in which the arousal index increased by 172% and Matsuda index decreased by 15% (Herzog et al., 2013), our

changes were more modest: 20% and 7%, respectively. The Matsuda index, considered as the gold standard to evaluate insulin sensitivity from an OGTT, integrates fasting and post-load glucose and insulin levels. The Stumvoll ISI, on the other hand, utilizes demographic data of interest, such as the BMI in our case, and does not integrate G_0 and I_0 in the formula. Given the fact that our participants lost on average 493 ± 20 g, and G_0 decreased throughout the week, the Stumvoll index may be more appropriate for interpreting our results than the Matsuda index. Although the overall insulin response was increased in response to oral glucose, no changes were apparent in the Stumvoll first and second phase of insulin secretion. These results indicate that the β-cells were unable to secrete enough insulin to compensate for the reduced insulin sensitivity, therefore leading to decreased glucose
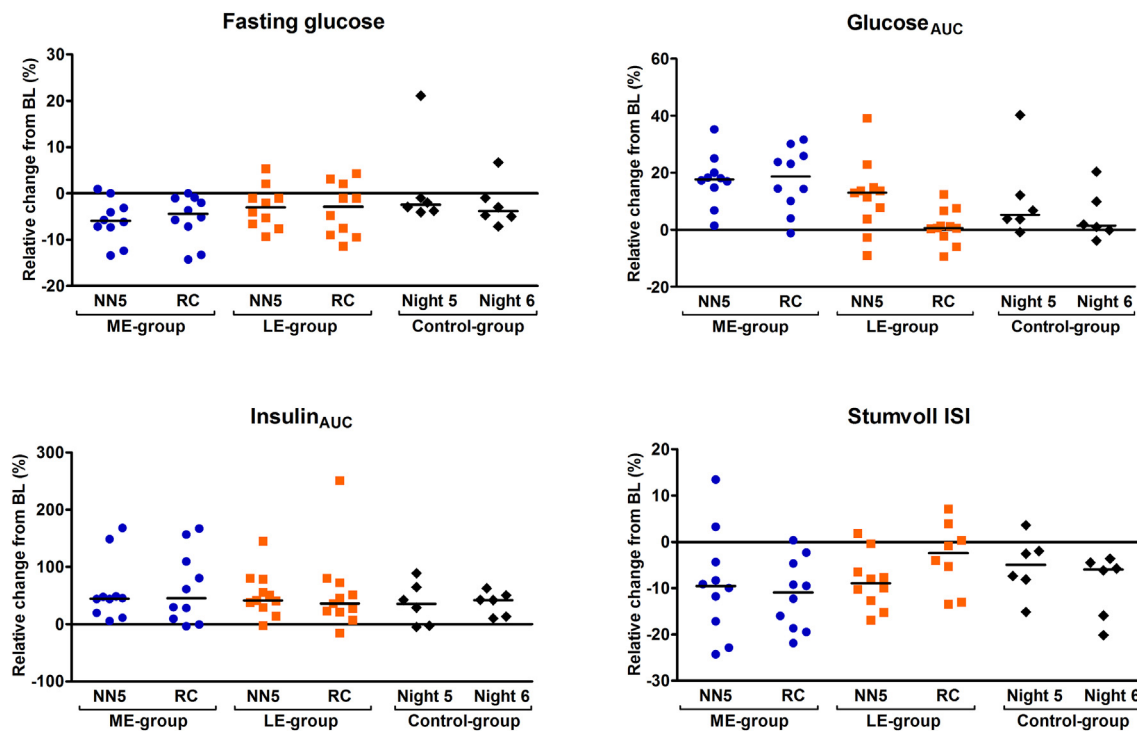
Fig. 3. Relative change in fasting glucose, glucose$_{AUC}$, insulin$_{AUC}$, and Stumvoll ISI between BL and NN5 or RC for the ME (in blue), LE (in orange) and the control group (in black). AUC: area under the curve. Black bars correspond to the median. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tolerance. As impaired glucose tolerance and insulin resistance are the first steps in the development of T2D, our results support the hypothesis that exposure to nocturnal transportation noise may contribute to incident T2D.

G_0 decreased after sleeping four nights with transportation noise. The changes in REM sleep duration may have contributed to these results. Indeed, during REM sleep, cerebral glucose utilization is as high as when awake, while it is reduced by > 40% in SWS (Maquet, 1995). Accordingly, we found a significant correlation between the changes in REM sleep duration and G_0 (see Fig. D in Appendix A). HOMA-IR, which reflects fasting insulin resistance, was unaffected by transportation noise exposure.

4.2. Effect of noise eventfulness on the recovery of noise-induced glucose intolerance and insulin resistance

Unlike participants exposed to less eventful noise during the last noise night, those exposed to more eventful noise at the same LAeq did not return to normal baseline glucose levels after one noise-free night. In contrast to the more eventful group, Stumvoll ISI (but not the Matsuda index) in the less eventful group tended to recover after one noise-free night. Our results indicate that more eventful transportation noise during sleep is more deleterious for glucose regulation compared to less eventful noise with the same hourly average sound pressure level.

4.3. Effect on sleep variables

Both intervention groups felt annoyed from exposure to transportation noise compared to the noise-free baseline and recovery night. In contrast, the control group did not report changes in noise annoyance throughout the week, although they thought to be exposed to

transportation noise. Also only the intervention group showed impaired subjective sleep quality after the last intervention night, in line with field studies indicating that noise annoyance is a mediator for subjective but not objective sleep quality (Frei et al., 2014; Miedema and Vos, 2007). This statement is in accordance with the objective sleep measures of this study that only revealed small effects. TST, sleep efficiency, and the amount of SWS or SWA were not significantly different from the noise-free baseline and recovery nights. However, sleep latency increased after the noise exposure nights as did the number of arousals (i.e. by ca. 2 arousals per hour TST). These observed effects of transportation noise during sleep (LAeq = 45 dB) on objective sleep variables are in line with previous results (Basner et al., 2011, 2014), and are mild compared to clinically relevant sleep disturbances. Similar to Basner et al. (2011), who conducted an eleven-night laboratory study with nocturnal transportation noise exposure, the amount of REM sleep increased during the recovery night compared to baseline. This may reflect the improved sleep hygiene by the imposed regular sleep-wake cycle and the 8 h in bed.

To date, only experimental changes in sleep duration and sleep fragmentation, in particular during SWS, have been shown to play a key role in glucose regulation (Spiegel et al., 1999; Tasali et al., 2008; Stamatakis and Punjabi, 2010). As such, these were our first candidate outcomes to relate to changes in glucose metabolism. The observed traffic noise effects on sleep variables in our study were rather small compared to the above mentioned studies, and thus did not show significant associations with glucose metabolism changes. Another possible pathway through which transportation noise could have impaired glucose regulation may have been via the stress axes as observed in noise-exposed rodents (Liu et al., 2016; Cui et al., 2016). High plasma cortisol levels (Fichna and Fichna, 2017; Mazziotti et al., 2011; Plat et al., 1996), or increased sympathetic nervous activity and catecholamine levels (Lembo et al., 1994; Thorp and Schlaich, 2015), are

known to lead to insulin resistance. The transportation noise scenarios that we presented to our participants could have triggered the activation of these stress axes, without profound sleep alterations, as evoked autonomic arousals during sleep are less likely to habituate than cortical arousals (Basner et al., 2011; Muzet, 2007).

4.4. Strengths and limitations

To our knowledge, this is the first controlled laboratory study investigating the impact of transportation noise on sleep and glucose regulation. The strength of a full time laboratory study is the ability to control many parameters such as food intake, physical activity, ambient light intensity, room temperature and noise exposure during the entire stay. All these factors can potentially influence sleep and glucose regulation and their interaction. Although food intake was quantified with the Mifflin et al. equation (Mifflin et al., 1990) to estimate daily caloric need, an average weight loss of 493 $\pm$ 20 g compared to basal weight was observed; but there was no statistical difference between the LE and ME groups. Thus, the study was carried out in a mild negative energy balance state, suggesting that the harmful effect of transportation noise during sleep on glucose regulation would have been even stronger without this weight loss corroborating the study conclusions of St-Onge et al. (2012).

A limitation of this study is the rather small sample size of the intervention group and the control group of only six young men restricted us to explorative comparisons. Nevertheless, the control group highlighted the impact of the sedentary condition of the laboratory stay on glucose regulation even under low caloric intake. This observation is in line with previous investigations on the harmful effect of physical inactivity on glucose regulation (Bergouignan et al., 2011).

One further limitation could be the retrospective recall of noise annoyance. However, the noise scenario during the baseline and recovery nights was the same and accordingly, the annoyance during these two nights did not significantly differ, supporting the idea that the retrospective recall did not impact the noise annoyance rating.

We assessed individual global noise sensitivity using the LEF-K and the NoiSeQ questionnaires which did not differ between participants. However, individual long-term exposure to transportation noise and lifestyle at home was not known, and these factors could influence susceptibility to noise and metabolic response to acute noise exposure.

5. Conclusion

Our laboratory findings are in line with those from epidemiological studies reporting detrimental effects of nocturnal transportation noise on glucose regulation. The novelty of this study is that it considers a shorter time scale in experimental controlled condition with objective measurements; four nights sleeping with transportation noise were enough to elicit impaired glucose tolerance and insulin sensitivity. The effects may not be clinically significant but could become relevant over a longer time span and in combination with other risk factors for cardiometabolic diseases. One could argue that the observed effect could be related to the sedentary laboratory conditions since the control group also showed mild glucose tolerance impairments; however the extent of the effect was evidently stronger for the intervention groups. Moreover, the efficiency of the recovery night for glucose regulation depended on the eventfulness of the last noise night, with a better recovery for more continuous than intermittent noise exposure. Even without eliciting major sleep disturbances at 45 dB, transportation noise may affect glucose regulation via other mechanisms such as the stress axis. To validate these results, a field study in a more natural and longer term setting is necessary.

Author contributions

L.T., F.R., K.S., R.L., R.P., J.-M.W., M.F., D.V., M.B., N.P.-H., M.R., C.C. conceived the study design; L.T., F.R., M.M. collected the data; R.P. created and analyzed the acoustical stimuli; L.T., F.R., K.S., R.L., C.C. analyzed the data; L.T., F.R., K.S., R.L., R.P., J.-M.W., M.F., H.H., I.C.E., D.V., M.M., M.B., N.P.-H., M.R., C.C. prepared the manuscript and approved the final submitted version.

Conflict of interest

The authors do not report any conflicts of interest in the present study.

Appendix A

Table A
Noise scenarios specifications. LAFmax: maximum level.

Scenario	Source	Type of noise	Posted speed limit (km/h)	Distance (m)	Pass-bys (n/h)	LAFmax (dB)
A	Road	4-Lane highway	120	400	1000	53
B	Road	2-Lane country road	80	50	250	60
C	Road	1-Lane urban road	50	15	100	62
D	Train	Freight and regional Trains			10	62

Less eventful group

a. **Glucose**

b. **Insulin**

More eventful group
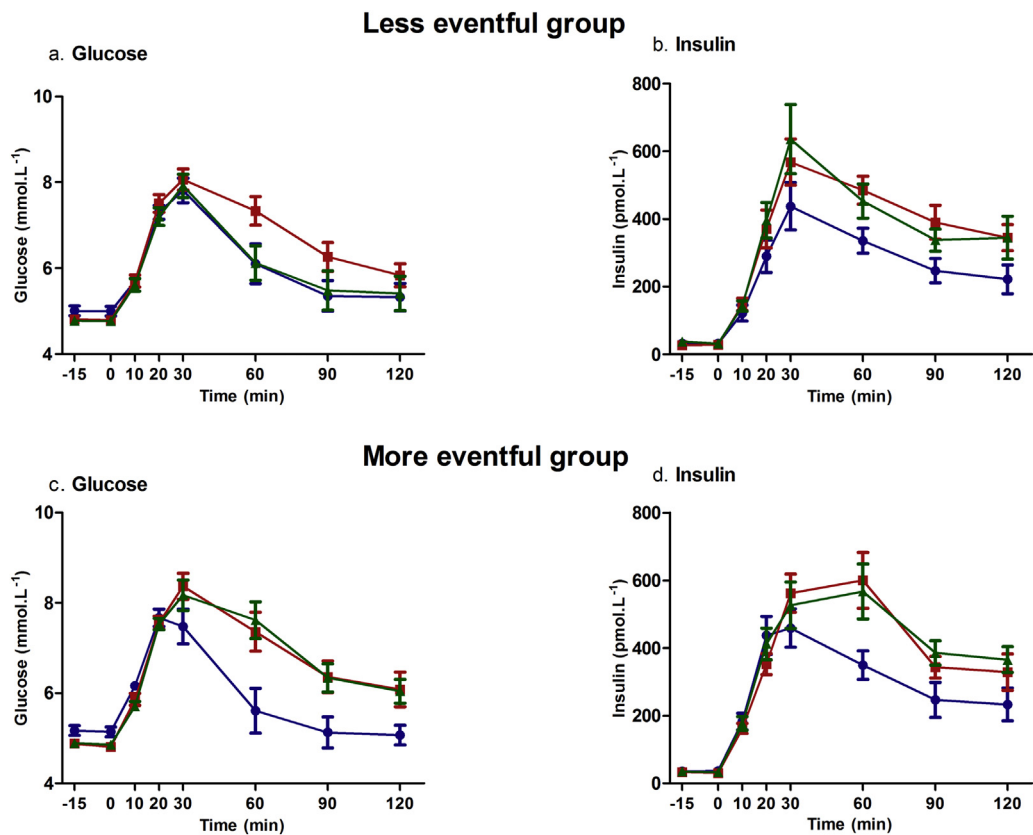
c. **Glucose**

d. **Insulin**

Fig. A. Glucose and insulin profiles during an OGTT in the less eventful group (LE) (a. and b.) and the more eventful (ME) group (c. and d.). Mean $\pm$ SE. After baseline (blue), after NN5 (red) and after one recovery night (green)
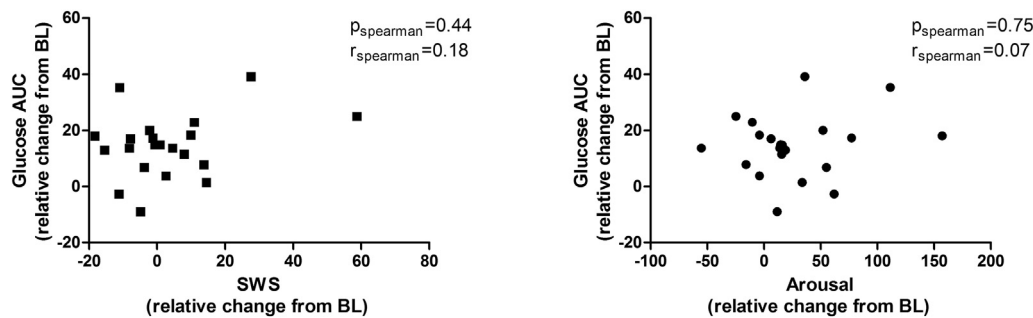

$p_{spearman}=0.44$
$r_{spearman}=0.18$

$p_{spearman}=0.75$
$r_{spearman}=0.07$

Fig. B. Correlations between the relative change in SWS duration or the amount arousals and Glucose$_{AUC}$ during NN5 compared to BL.
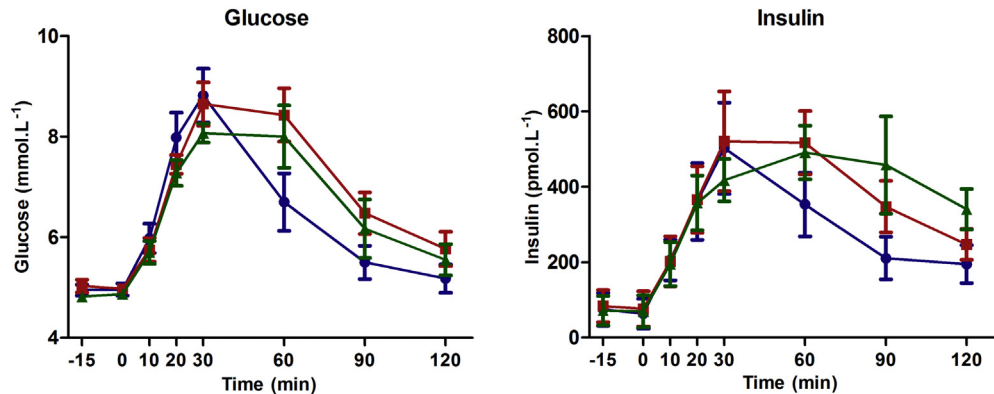
Glucose

Insulin

Fig. C. Glucose and insulin profiles during an OGTT in the control group. Mean $\pm$ SE. After sleeping 1 night (blue), 5 nights (red) and 6 nights (green) in the laboratory.
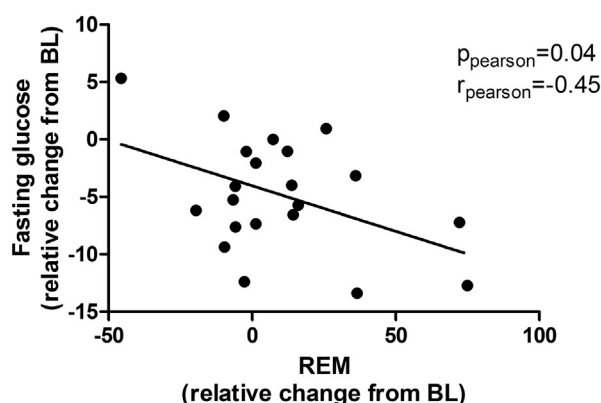
Fig. D. Correlation between the relative change in REM sleep duration and fasting glucose during NN5 compared to BL.

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