The effect of slow-wave sleep and rapid eye-movement sleep interventions on glycaemic control: a systematic review and meta-analysis of randomised controlled trials.

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Abstract

Poor glycaemic control is found in diabetes, one of the most common, serious, non-communicable diseases worldwide. Trials suggest a relationship between glycaemic control and measures of sleep including duration and quality of sleep. Currently, the relationship between specific sleep stages (including slow-wave sleep (SWS), a sleep stage mainly found early in the night and linked to restorative functioning) and glycaemic control remains unclear. This systematic review aimed to synthesise the evidence of the effectiveness of specific sleep stage manipulation on measures of glycaemic control (insulin resistance, fasting and post-prandial glucose and insulin). Public databases (e.g. psychINFO, MEDLINE, Academic Search Complete, psychARTICLES, OpenDissertations, Scopus and Cochrane library) were searched for randomised controlled trials. Trials were included if they involved direct manipulation of SWS and/or rapid eye-movement sleep to explore the impact on measures of glycaemic control (insulin resistance, fasting and post-prandial glucose and insulin). Eight trials met the eligibility criteria, with four providing data for inclusion in one of the three meta-analyses. Insulin resistance was significantly higher in the SWS disruption when compared to the normal sleep condition, (p = 0.02). No significant differences were found for measures of fasting or post-prandial glucose or insulin. Risk of bias was considered low for performance bias, detection bias and incomplete outcome data, with unclear selection bias. This is an emerging area of research and this review provides preliminary findings and recommendations for future research around optimising sleep stage disruption (to further explore mechanisms) and sleep stage enhancement techniques (to explore potential interventions).

Keywords: Glycaemic control, Glucose, Insulin, Slow-wave sleep, Rapid eye-movement sleep.

List of abbreviations

ACLS	Auditory closed-loop stimulation
AUC	Area under the curve
EC	Euglycaemic clamp
HOMA-IR	Homeostasis model insulin resistance
ivGTT	Intraveneous glucose tolerance test
MMTT	Mixed meal tolerance test
OGTT	Oral glucose tolerance test
PICOS	Participants, interventions, comparisons, outcomes and study design
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
REM sleep	Rapid eye-movement sleep
SWS	Slow-wave sleep

1.1 Introduction

Diabetes is one of the most common, serious, non-communicable diseases worldwide. The estimated prevalence of diabetes has risen worldwide from 108 million in 1980 to 422 million in most recent figures, with 1.5 million deaths in 2019 resulting from diabetes [1]. It is characterised by poor glycaemic control in which blood sugar (or glucose) levels and insulin levels (produced in response to glucose levels) are higher than normal (also known as hyperglycaemia). Poor glycaemic control in diabetes typically manifests as problems with fasting (baseline levels of) glucose or insulin, post-prandial glucose or insulin (2-hours after a glucose drink) or insulin resistance (in which sufficient insulin is no longer produced to reduce glucose to normal levels)[2]. Treatment hinges on trying to achieve normoglycemia to prevent complications including higher prevalence of heart attacks, heart failure [3] and stroke [4]. Poor sleep quantity and quality are more prevalent in individuals with poor glycaemic control than those without [5,6]. The importance of sleep in the context of health in all age groups is widely recognised with sleep alteration interventions becoming a popular non-pharmacological intervention for improving health in trials ranging from lab-based basic science in adults [7] to clinical practice randomised controlled trials in children [8].

Research has shown that altering sleep can influence glycaemic control [9,10] and enhancing certain sleep stages through increasing spectral power (increasing energy vibrations within a specific frequency most commonly found within each sleep stage) or sleep durations may improve sleep quality, which can have therapeutic benefits [11,12]. The impact of sleep on glucose metabolism has been explored in the context of: sleep duration [13,14], sleep restriction [10,15] and sleep enhancement [16]. The influence of sleep duration on glycaemic control has also been systematically reviewed with most trials suggesting a relationship between both longer and shorter than average sleep and glycaemic control [17], but the

literature surrounding the role of specific sleep stages in glycaemic control is still an emerging area of research.

Slow-wave sleep (SWS) is prevalent in the earlier periods of the night and is characterised by slow-oscillations. These slow-oscillations are of synchronised EEG activity which correspond to neuronal states of depolarisation (up-states) and hyperpolarisation (down-states) which characterise the slow-oscillation found commonly within SWS [18]. SWS has many restorative functions and has been linked with improved metabolic and psychological functioning [19,20]. Rapid eye-movement (REM) sleep is prevalent in the later periods of the night and is characterised by theta activity. The precise role of REM sleep is currently debated [21,22], however, SWS and REM sleep stages have both been related to glycaemic control [23,24]. Specifically, REM sleep may be a marker of circadian misalignment (suggesting a misalignment of sleep and wake), as REM sleep is reduced when circadian misalignment is enforced on participants, which then increases insulin resistance [25]. For SWS, a relationship between SWS and homeostatic regulation is proposed, which metabolism more generally is suggested to rely on [26], however the roles of REM sleep and SWS are still debated. To explore this further, other trials have assessed the impact of direct SWS or REM sleep manipulation including disruption [27–33], or enhancement [11] on measures of glycaemic control.

Sleep stage manipulation has typically been achieved using acoustic stimulation. Acoustic disruption involves increasing intensities of acoustic stimuli until participants display microarousals, indicating a change in sleep stage. As the research is still emerging, sleep stage disruption interventions have primarily targeted populations with normal glycaemic control [27–31,33], although trials are beginning to recruit participants with diabetes who have impaired glycaemic control [32]. More recently, trials have attempted to extend SWS activity using auditory closed-loop stimulation (ACLS) [11,20,34]. During SWS, a specific

auditory stimulus comprising individual ‘clicks’ with a particular sound is played, known as pink noise. Stimulation occurs after an individually determined delay using this paradigm, which will ensure that the stimulation occurs at the correct time-points to extend SWS. These participants with poor glycaemic control have lower amounts of SWS on average [35,36] and therefore enhancing SWS should be more beneficial for the participant.

To the authors’ knowledge, no previous research has attempted to systematically review the impact of direct SWS or REM sleep manipulation on measures of glycaemic control. Exploring the importance of specific sleep stages including SWS and REM sleep for glucose metabolism may reveal the potential of targeted interventions for improving metabolic health, which could then benefit individuals with poor glycaemic control.

The aim of this systematic review and meta-analysis was to synthesise evidence of the effectiveness of interventions manipulating SWS and REM sleep on measures of glycaemic control in humans.

1.2 Material and methods

This systematic review was conducted following the 'preferred reporting items for systematic reviews and meta-analyses' (PRISMA) guidelines [37] (see supplementary file 1). The review was *a priori* registered with the International Prospective Register of Systematic Reviews (PROSPERO 2019; registration number: CRD42019122808 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019122808).

1.2.1 Eligibility

The 'participants, interventions, comparisons, outcomes and study design' (PICOS) framework [38] helped to shape the research question and facilitated the search process.

Participants: Humans. *Intervention:* sleep stage alteration, specifically SWS or REM sleep. *Comparator:* a non-intervention/placebo group. *Outcomes:* changes in glycaemic control as reported in primary trials (e.g. blood glucose, glucose tolerance, glycated haemoglobin, glycaemic index, insulin, insulin resistance, insulin sensitivity, and homeostatic model assessment). *Trial Designs:* only randomised controlled trials were included. Published trials and "in press" articles were eligible for inclusion, as were dissertations.

1.2.2 Trial Identification

To identify existing relevant systematic reviews, published, unpublished and ongoing trials, the following electronic databases were searched from inception to 1st November 2021: psychINFO, MEDLINE, Academic search complete, CINAHL library, psychARTICLES, OpenDissertations, Scopus, Cochrane library, PROSPERO, Web of knowledge (core collection) using pre-specified search terms (see supplementary file 2). Supplementary searches included DART-EUROPE e-theses and reference lists. Database searching was supplemented with internet searching (e.g. Google scholar), and forward and backward

citation tracking from systematic reviews and included trials. Trials were included if they were published in English only.

References were imported into Microsoft excel software for removal of duplicates. Titles and abstracts were then screened in Excel independently by two reviewers (JMJ & FC) for potential inclusion. Full-texts were retrieved for all trials that could not be excluded based on title and abstract screening. Two reviewers independently assessed full papers for relevance. Any discrepancies were resolved through discussion or, where required, through involvement of a third reviewer.

1.2.3 Trial Search Results

A total of 807 distinct citations were identified from electronic databases, with another five located from other sources. After removing duplicates, screening titles and abstracts, eight trials met the inclusion criteria for the systematic review which explored the effect of SWS enhancement [11], SWS disruption [27–33] and REM sleep disruption [28] on measures of glycaemic control (see Figure S1). Four trials provided data for inclusion in one of the meta-analyses.

1.2.4 Data Extraction

Data was extracted by one reviewer (JMJ) using an adapted Cochrane data extraction template for interventions, and cross checked by a second reviewer (FC). Important trial features extracted included information about the *journal:* author, year, title, journal, aims, *trial characteristics:* country, date, design, inclusion criteria, recruitment, randomisation, blinding, *participants:* sample size, age, gender, ethnicity, completion rate of intervention, *intervention details:* description, sleep phase targeted, how targeted, comparator details, mode of delivery, specific details about delivery, follow-up, *outcome details:* all primary and secondary outcomes as reported within the papers. Where data was missing, the original

authors were contacted or if data could not be obtained, a web plot analyser was used [39] as in previous trials [40].

1.2.5 Risk of bias (quality) assessment

Two reviewers independently assessed risk of bias (Cochrane risk of bias assessment tool) on key dimensions including: Random sequence generation, allocation concealment, blinding, and incomplete outcome data. Each domain was classified as adequate (low risk of bias), inadequate (high risk of bias) or unclear (not possible to determine risk of bias). An overall trial risk of bias was not assessed and data for each domain are presented for readers to interpret in context with review findings. Risk of bias assessment was not used as a reason for exclusion.

1.2.6 Data Analysis

All analyses were conducted using Review Manager version 5.3. The primary outcome was post intervention glycaemia (e.g post-prandial 120 minutes for glucose (mmol/l) and insulin (pmol/l), as well as HOMA-IR insulin resistance). The summary measure of treatment effect for measures of glycaemia were the between groups differences (expressed as mean difference). Where appropriate, glucose values were converted from mg/dl to mmol/l by using the equation mmol/l = (mg/dl)/ 18. Similarly, insulin values were converted from uU/ml to pmol/l using the equation pmol/l = (uU/ml) x 6 [41]. Calculation of HOMA-IR used the equation: (fasting insulin * fasting glucose) / 22.5 [42]. Sleep data was tabulated to explore the effects of sleep alteration in the included trials. Where appropriate, standard error scores were converted to standard deviation using the equation: SD = SE x $\sqrt{N}$. Results are formatted as (mean difference, 95% confidence intervals lower, higher, p-value, statistical heterogeneity %). Two-tailed *p*-values were computed per outcome and a threshold value of $p \leq 0.05$ indicated significance.

Random-effects models were used in all meta-analyses, as they are more conservative than the fixed effects models since, by incorporating within- and between-trial variance, the confidence intervals for the summary effect are wider. Statistical heterogeneity was assessed using the Higgins I^2 test [43], which described the percentage of variability among effect estimates beyond that expected by chance. In cases where heterogeneity was important (I^2 ≥40%), sources of clinical and methodological diversity were explored. Where appropriate, a sensitivity analysis was conducted to explore heterogeneity.

1.3 Results

1.3.1 Trial Characteristics

The primary studies employed four different methods to explore glycaemic control; an oral glucose tolerance test (OGTT) [11,28,30,33], mixed-meal tolerance test (MMTT) [29], euglycaemic clamp (EC) [31,32] or intravenous glucose tolerance test (ivGTT) (see table 1) [27]. An OGTT is typically performed after a 75g oral glucose load, with the glucose values measured at fasting and after 2 hours (post-prandial) [44]. The ivGTT instead involves the measured 75g load directly entering the bloodstream. A mixed-meal tolerance test is similar to the OGTT and ivGTT but is more physiological, with a meal being given instead of a 75g bolus of glucose [29]. The OGTT and MMTT produce comparable outcomes for pooling in the analysis [45,46]. The EC involves a continuous infusion of plasma insulin above fasting level, with glucose intravenously given at a variable rate until a steady state is reached where infusion and disposal rates are recorded [47].

Interventions included SWS enhancement [11], SWS disruption [27–33] and REM sleep disruption [28] (see table 1). In the one included SWS enhancement trial, 15 healthy male participants (19 – 34 years old) with varied BMI scores within the ideal range (19.17–25.03 kg/m^2) took part. The participants all had normal sleep/wake patterns. The participants had one night of SWS enhancement and one night of sham stimulation, i.e. with muted headphones, in a balanced order [11] (see table 1). After SWS was detected for the first time, ACLS using clicks of pink noise started and lasted 210 minutes. These bursts of sound were triggered when a negative slow-oscillation half-wave was detected. The authors reported no significant alterations of AUC or post-prandial glucose or insulin after SWS enhancement when compared to the control condition. This is the only trial to date that has explored the impact of SWS enhancement for measures of glycaemic control.

Table 1: Trial characteristics of included randomised controlled trials.

Authors, date (country)	Population (sample) (within-subjects design)	Intervention	Measures and outcomes	Main findings (compared to control condition)
Dijk M 2015[27] (Netherlands)	Healthy males and females. (n = 11, Males: 6, Age: 32 ± 4, BMI = 23.2 ± 0.5 kg/m^2)	SWS disruption (one night) Acoustic auditory disruption Dur: throughout SWS Time: two or more delta waves in 30s. Vol: 40-110db	EC Glucose (mmol/l) Basal endogenous glucose production Insulin (pmol/l) Clamp endogenous glucose production Clamp glucose infusion rates Clamp glucose disposal rate	No significant alterations of glucose infusion or disposal.
Donga E 2014[28] (Netherlands)	Type 1 Diabetes males and females. (n = 8,	SWS disruption (one night)	EC Glucose (mmol/l)	No significant alterations of glucose disposal.

	Males: 2, Age: 38 ± 3, BMI = 23.4 ± 0.6 kg/m^2)	Acoustic auditory disruption Dur: throughout SWS Time: two or more delta waves in 30s. Vol: 40-110db	Basal endogenous glucose production Insulin (pmol/l) Clamp endogenous glucose production Clamp glucose infusion rates Clamp glucose disposal rate	
Herzog N et al, 2013[24*] (Germany & Sweden)	Healthy males. (n = 16, Age: 22.1 ± 0.8, BMI = 23.2 ± 0.3 kg/m^2)	SWS disruption (one night) Acoustic auditory disruption. Dur: throughout SWS Time: ≥6 delta waves within a 30-second sleep period. Vol: 35-62db.	75g OGTT Plasma glucose (mmol/l) Serum insulin (pmol/l) AUC Matsuda Index Insulin Sensitivity	No significant alterations of post-prandial insulin or glucose. Significant alterations of AUC insulin and glucose. Significant alterations of insulin sensitivity.

	Healthy males. (n = 16, Age: 22.1 ± 0.8 BMI = 23.2 ± 0.3 kg/m^2)	REM sleep disruption (one night) Acoustic auditory disruption. Dur: throughout REM sleep Time: low muscle tone in combination with counterrotating rapid eye-movements Vol: 35-62db.	75g OGTT Plasma glucose (mmol/l) Serum insulin (pmol/l) AUC Matsuda Index Insulin Sensitivity	No significant alterations of post-prandial insulin or glucose. No significant alterations of AUC insulin or glucose. No significant alterations of insulin sensitivity.
Killick R et al 2017[26*] (Australia & USA)	Healthy males. (n = 6, Age: 28.6 ± 2.0, BMI = 26.0 ± 0.8 kg/m^2)	SWS disruption (3 nights) Acoustic auditory disruption (10 hour). Dur: throughout SWS Time: two or more	75g OGTT Plasma glucose (mmol/l) Serum insulin (uU/ml) AUC Insulin sensitivity (minimal	No significant alterations of post-prandial insulin or glucose. No significant alterations of insulin sensitivity.

		consecutive delta waves seen. Vol: 40-95db.	modelling, HOMA-IR, QUICKI).	
Shaw ND et al 2016[25*] (USA & Italy)	Healthy males and females. (n = 14, Males: 7, Age: 11.3-14.1 years, BMI = 29th to 97th percentile)	SWS disruption (one night) Acoustic auditory disruption Dur: throughout SWS Time: two or more delta waves in 15s. Vol: 40-100db.	MMTT Plasma glucose (mg/dl) Serum insulin (uU/ml) AUC Insulin sensitivity (HOMA-IR, minimal modelling)	No significant alterations of post-prandial insulin or glucose. No significant alterations of AUC insulin or glucose. No significant alterations to insulin sensitivity.
Santiago JCP et al 2019[10] (Germany & United Kingdom)	Healthy males. (n = 15, Age: 19-34 years, BMI = 19.17–25.03 kg/m²)	SWS enhancement (one night) ACLS Dur: 210 mins Time: 5 mins into N2 (or deeper)	75g OGTT Plasma glucose (mmol/l) Serum insulin (pmol/l) AUC	No significant alterations of post-prandial insulin or glucose. No significant alterations of AUC insulin or glucose.

		Vol: 60db		
Tasali E et al 2008[23] (USA)	Healthy males and females. (n = 9, Males: 5, Age: 20-31, BMI: 19–24 kg/m^2)	SWS disruption (3 nights) Acoustic auditory disruption Dur: throughout SWS Time: two delta waves seen in 15s Vol: 40-110db.	ivGTT Insulin sensitivity (minimal modelling) Glucose tolerance Insulin response	Significant alterations of insulin sensitivity and glucose tolerance. No significant alterations of insulin response.
Ukraintseva YV et al 2020[29*] (Russia)	Healthy males. (n = 20, Males: 20, Age: 22.5 ± 0.4, BMI: 22.80 ± 0.73 kg/m²)	SWS disruption (one night) Acoustic auditory disruption. Dur: throughout SWS Time: ≥6 delta waves within a 30-second sleep period.	75g OGTT Plasma glucose (mg/dl) AUC	No significant alterations of post-prandial glucose.

	Vol: 35-95db

*Notes: ACLS = auditory closed-loop stimulation, AUC = area under the curve, db = decibels, Dur = duration, EC = euglycaemic clamp, ivGTT = intraveneous glucose tolerance test, mg/dl = milligrams per decilitre, mmol/l = millimoles per litre, MMTT = mixed-meal tolerance test, OGTT = oral glucose tolerance test, pmol/l = picomoles per litre, REM = rapid eye-movement, SWS = slow-wave sleep, Uu/ml = microunit per millilitre, Vol = intervention volume. Format: mean ± standard error. * indicates trials included in at least one of the three meta-analyses. BMI percentile > 95th is obese in an adolescent sample.*

Seven trials focused on the impact of SWS disruption, involving acoustic auditory disruption coinciding with SWS throughout the night (see table 1) [27–33]. Seven trials were published between 2008-2020 including 84 participants cumulatively (73.81% male), with trials having between six [30] and 20 [33] participants. Most participants were healthy [11,27–31,33], with eight participants on insulin pump therapy having Type 1 Diabetes [32]. Trials were mostly conducted on adults (21 - 41 years old) [27,28,30–33] with one focused on adolescents (11 – 15 years old) [29]. BMI scores suggested that most participants were within the limits of ideal weight [27–33], with some obese participants found only in one study [29]. No co-morbid conditions were reported in any study [27–33]. Studies reported that the participants were excluded of they had any sleep disorders [27–33], and some indicated if the participants have normal sleep/wake rhythms [27,28,30–33]. Some trials disrupted SWS for only one night [28,29,31–33], with some doing multiple nights [27,30]. Tasali et al [27] was the only trial to use an ivGTT method of measuring glycaemic control (see table 1). They reported a significantly decreased glucose tolerance and insulin sensitivity after the SWS disruption condition when compared to the control condition, with no significant changes to insulin response.

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The four trials [28–30,33] included in a meta-analysis explored the impact of SWS disruption on OGTT/MMTT measured glucose and insulin. None of the trials reported significant alterations of post-prandial glucose or insulin when compared to the control condition [28–30,33], whilst two reported significant alterations to insulin resistance [27,28]. Of the two trials that reported AUC, one trial reported no significant alterations of AUC glucose or insulin when compared to the control condition [29], whilst the other reported significant alterations of both AUC glucose and insulin [28]. Two trials explored the impact of SWS disruption on EC measured glucose disposal, with no significant alterations compared to control reported [31,32].

One trial that examined SWS disruption also explored the impact of REM sleep disruption in glycaemic control [28], involving an auditory disruption throughout REM sleep (see table 1). They reported no significant changes to measures of post-prandial glucose and insulin, or measures of AUC glucose or insulin after the REM sleep disruption when compared to the control condition.

1.3.2 Effectiveness of the sleep interventions in altering sleep in the included trials.

To explore the effectiveness of the sleep alteration interventions when altering REM sleep and SWS, the specific alterations made were assessed (see table S1). After tabulating the data from the SWS disruption trials, the trials all reported significant decreases in SWS duration compared to the control condition (all $p \leq 0.05$), with no significant alterations to total sleep time [27–33]. Few studies reported sleep efficiency measures [29,30,33], but of those that did, only one reported a small decrease in sleep efficiency ($p = 0.04$) which they assessed was caused by the intervention [33]. The REM sleep disruption trial reported significant decreases to REM sleep [28]. The SWS enhancement trial did not significantly alter SWS duration [11].

1.3.3 Baseline glucose/insulin measures

None of the trials included in the systematic review or meta-analysis reported any significant differences in all OGTT/MMTT measured baseline fasting glucose or fasting insulin, nor EC measured basal glucose or post-intervention clamp conditions between intervention and control conditions.

1.3.4 Meta-analysis

At time 120 minutes of the OGTT no significant differences were observed for post-prandial glucose (0.10 mmol/l, 95% CI -0.37, 0.57, $p = 0.68$, $I^2 = 0\%$) (see table 2). There was no evidence of statistical heterogeneity.

Table 2: The impact of SWS disruption on sub-group post-prandial (120 min) glucose (mmol/l).

	SWS Disruption			Control			Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Herzog, 2013	6.35	1.60	16	6.02	1.20	16	22.9%	0.33 [-0.65, 1.31]
Killick, 2017	5.10	0.76	6	5.82	1.10	6	19.2%	-0.72 [-1.79, 0.35]
Shaw, 2016	5.31	1.38	14	5.18	1.46	14	19.9%	0.13 [-0.92, 1.18]
Ukraintseva, 2020	5.48	1.08	20	5.12	1.36	20	38.0%	0.36 [-0.40, 1.12]
Total (95% CI)			56			56	100%	0.10 [-0.37, 0.57]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.92$, df = 3 (P = 0.40); $I^2 = 0\%$

Test for overall effect:	Z = 0.42 (P = 0.68)

Notes: SD = standard deviation, IV = independent variable, CI = confidence intervals, I^2 = measure of statistical heterogeneity, df = degrees of freedom.

Substantial heterogeneity was evident in a meta-analysis of the three trials reporting post-prandial insulin (-25.10 pmol/l, 95% CI -175.08, 124.87, $p = 0.74$, $I^2 = 52\%$) [28–30]. This suggests that one or more of the included studies were too different to the others to be adequately compared in a meta-analysis. A sensitivity analysis was conducted with the removal of one trial [28], with the resulting analysis demonstrating no significant between groups difference in post-prandial insulin (-136.15 pmol/l, 95% CI -304.2, 31.90, $p = 0.11$, $I^2 = 0\%$) and no evidence of heterogeneity (see table 3).

Table 3: The impact of SWS disruption on post-prandial (120 min) insulin (pmol/l)

	SWS Disruption			Control			Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Killick, 2017	174	82.4	6	321	187	5	90.4%	-148 [-324, 29.3]
Shaw, 2016	256	716	14	285	747	14	9.60%	-29.4 [-572, 513]
Total (95% CI)			20			19	100%	-136 [-304, 31.9]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.68); $I^2 = 0\%$

Test for overall effect:	Z = 1.59 (P = 0.11)

Notes: SD = standard deviation, IV = independent variable, CI = confidence intervals, I^2 = measure of statistical heterogeneity, df = degrees of freedom.

Similarly, substantial heterogenity was evident in the meta-analysis of three trials reporting insulin resistance (0.07 units, 95% CI -0.20, 0.34, $p = 0.59$, $I^2 = 87\%$) [28–30]. This suggests that one or more of the included studies were too different to the others to be adequately compared in a meta-analysis. To explore heterogeneity a sensitivity analysis was conducted where the removal of Killick et al., [30], resulted in a significant increase in insulin resistance being observed for the SWS disruption compared to the control condition, (0.19 units, 95% CI 0.03, 0.35, $p = 0.02$, $I^2 = 0\%$) (see Table 4).

Table 4: The impact of SWS disruption on insulin resistance.

	SWS Disruption			Control			Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Killick, 2017	0.67	0.35	16	0.51	0.1	16	82.7%	0.16 [-0.02, 0.34]
Shaw, 2016	2.07	0.56	14	1.75	0.49	14	17.3%	0.32 [-0.07, 0.71]
Total (95% CI)			30			30	100%	0.19 [0.03, 0.35]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.54$, df = 1 (P = 0.46); $I^2 = 0\%$

Test for overall effect:	Z = 2.27 (P = 0.02)

Notes: SD = standard deviation, IV = independent variable, CI = confidence intervals, I^2 = measure of statistical heterogeneity, df = degrees of freedom.

1.3.5 Risk of Bias

Selection bias (random sequence generation and allocation concealment), was unclear in seven of the included trials [11,27–29,31–33]. Whilst trials were described as being randomised controlled trials, all except one who reported using computer software randomisation method [30] did not describe the process of randomisation to sleep conditions adequately to allow an assessment of potential risk of bias. Low levels of performance bias and detection bias (blinding of participants and personnel, blinding of outcome assessment) were found in all included trials, as it is unlikely that the outcome could be affected by a lack of personnel or participant blinding due to the nature of the metabolic outcome variables. Finally, no trials had <80% of their starting cohort completing the final trial, demonstrating low levels of bias from incomplete outcome data (see table S2).

1.4 Discussion

1.4.1 The effect of SWS disruption on insulin and glucose

Eight trials were included in the systematic review, of which four sufficiently homogeneous trials [28-30,33] were included in meta analyses while others concerned with SWS enhancement [11], T1D participants rather than healthy controls [32], or lacking comparitive glycaemic control measures were included in the narrative review. Meta-analyses showed no effect of SWS disruption on post-prandial glucose [28-30,33] or post-prandial insulin [29,30], but there was a significant increase in insulin resistance after SWS disruption [28,29]. However, higher levels of SWS disruption led to greater change in post-prandial glucose and insulin, suggesting a dose-dependent relationship; the lack of significant effect in the meta-analysis may therefore reflect an insufficient number of trials or lack of overall statistical power and future studies may show a significant effect in this area.

Findings reported in the primary trials that were included in the systematic review but not a meta analyses [11,27,31,32] had mixed results. One reported that ivGTT measured insulin sensitivity and glucose tolerance was significantly decreased by SWS disruption [27], another two reported that EC measured glucose disposal was not significantly altered by SWS disruption in either healthy participants [31] or participants with Type 1 Diabetes [32]. The other explored SWS enhancement, reporting no significant differences between conditions for OGTT measured insulin or glucose [11]. One trial explored OGTT measured glucose and insulin for REM sleep disruption, reporting no significant differences in post-prandial or AUC measures [28].

1.4.1 Comparison with previous reviews

To the authors knowledge, no previous trials have compared the impact of specific sleep stages on glycaemic control. We are aware of one previous review [17] which has explored

the impact of both long and short sleep duration on glucose control in people with risk of and development of Type 2 Diabetes. Two of the main conclusions of the paper were that *more research is needed in the areas of establishing direction of effects* and it is important to *explore sleep interventions that may offer benefits*. By conducting the current systematic review and meta-analysis, we were able to further explore the direction of effects by including trials that manipulate sleep directly to look at the effects on glycaemic control. We were also able to further explore in detail an existing intervention trial attempting to enhance specific sleep stages. Expanding on previous research, this review is the first to synthesise findings to calculate measures of glycaemia following a range of sleep interventions.

1.4.2 Strengths and weaknesses

The review was carried out rigorously, adhering to PRISMA guidelines for reporting [37] with a pre-specified protocol as published on PROSPERO, limiting the potential for reporting bias. We developed a comprehensive search strategy and searched multiple databases to ensure inclusion of relevant trials to inform our findings.

Due to variations in trial design, trial population and outcomes reported, we had limited data availability for synthesis (meta-analysis). Whilst eight trials met the inclusion criteria for this systematic review, only four presented appropriate data for inclusion within the meta-analysis. A meta-analysis was conducted to assess the strength of evidence, allowing an exploration of heterogeneity among trials and generate novel questions from the data [48], including; what is the impact of ageing on glycaemic control? and does the amount of SWS reduction dictate alterations in glycaemic control?

Seven of the included trials were considered to have unclear levels of selection bias [11,27–29,31–33]. Future trials should detail their participant randomisation techniques and methods of allocation concealment to improve selection bias. Risk of bias was considered low for

performance bias, detection bias and incomplete outcome data. Although not formally assessed, the risk of publication bias within the trials was also considered relatively unlikely as the trials presented a mixture of significant [27,28,30,33] and non-significant [11,29,31,32] results for their main outcomes. Two of the trials included were theses (grey literature) [31,32].

Statistical heterogeneity was explored within our meta-analyses. Two planned analyses exploring AUC glucose and AUC insulin were not included in the final review due to substantial heterogeneity being observed and sensitivity analyses were possible with only two trials providing data for both of these outcomes [28,29]. Moderate to substantial heterogeneity was identified in a further two analyses (post-prandial insulin and insulin resistance), suggesting that one or more of the included studies were too different to be compared to the other studies within the meta-analysis, however, as more than two studies were included in the analysis, a sensitivity analysis was able to be performed to determine which of the studies were too different to the others and therefore required removal. As a result, one trial was removed from each meta-analysis [28,30]. Potential sources of heterogeneity were explored for both post-prandial insulin and insulin resistance, which we suggest may be related to the reduction in SWS achieved in the primary trials. Herzog et al [28] were able to reduce SWS duration by 79%, whilst the other two trials reduced SWS duration by 23% [30] and 39% [29], with direction of effects being related to the percentage of SWS decrease. When removing the Herzog et al [28] results from the post-prandial insulin analysis, therefore, the direction of effects favoured the control condition, potentially suggesting that interventions to reduce SWS should reduce SWS by more than 39% to significantly alter post-prandial insulin. Likewise, removing Killick et al [30], resulted in significant alterations of insulin resistance, potentially suggesting that SWS needs to be reduced by more than 23% to alter insulin resistance. These findings, based on the results of

three trials, should be interpreted with caution but offer preliminary evidence to inform research development in this field.

1.4.3 Implications of the research

SWS disruption was successful in significantly increasing insulin resistance, which although driven mainly by the results of two trials, provides preliminary support for SWS disruption increasing insulin resistance [28,29]. This finding is supported by the literature in that SWS disruption successfully decreases glucose tolerance and insulin sensitivity, with no changes observed in insulin responses [27]. These responses may all contribute to poor glycaemic control and increased risk of diabetes [27]. Mechanistically, it is suggested that SWS disruption results in an initial increase in circulating insulin levels [27]. It is also reported that there is a lack of compensatory insulin response, resulting in decreased insulin sensitivity [27], as indicated within our findings.

SWS disruption significantly increased insulin resistance but did not significantly alter post-prandial glucose or post-prandial insulin. The results of the meta-analyses suggest that the trials with larger percentage decreases in SWS had larger post-prandial insulin and glucose alterations, e.g. SWS alterations of 49% [33] and 79% [28] had a much larger effect on post-prandial glucose than alterations of 15% [30] and 39% [29]. Similar effects were shown for both post-prandial insulin and insulin resistance. When decreasing SWS by 87%, as in one trial within the narrative review [27], significant alterations to glycaemic control were shown. Likewise, decreasing SWS duration by 79% was enough to significantly alter AUC glucose and insulin in one trial within the narrative review [28]. Future research should focus on optimising methods of SWS disruption, which may be key to establishing a relationship between SWS and glycaemic control.

As well as optimising these methods, age is a potential factor affecting the results of the meta-analyses as one included trial was conducted in adolescents [29]. This trial had relatively wide confidence intervals for measures of both post-prandial insulin and insulin resistance which may be attributable to the sample characteristics of a prepubertal population. Children and adolescents are still developing and have a higher homeostatic drive and greater pressure for SWS activity after SWS disruption [29,49], resulting in greater resilience to short-term disruption. In addition, adolescents have greater metabolic resilience [29], which cumulatively could explain why no significant changes were shown for prepubertal participants.

Other methodological selections could account for the differences in results between trials, including participants, for example one EC trial [32] explored glucose disposal in participants with Type 1 Diabetes on insulin pump therapy. Whilst this trial met the inclusion criteria for the systematic review data from this population could not be combined with healthy participant outcomes as whilst insulin pump therapy allows a basal infusion of insulin throughout the day, the basal glucose values differ vastly between the healthy participants and type 1 diabetes, suggesting a difference even at baseline [31,32]. This difference at baseline may also extend to sleep architecture [50]. These differences between participant groups may affect glycaemic control outcomes, and pooling of data from these different populations would undermine any observed outcomes.

1.4.4 Future directions

By employing a narrative synthesis and meta-analysis of glycaemic outcomes from auditory SWS disruption, this review has provided some preliminary findings of the relationship between SWS disruption and glycaemic control. It is, however, essential for future research to optimise the methods of SWS disruption trials in terms adequately disrupting SWS in the

night, stratifying by age and exploring the impact of SWS disruption in participants with impaired glycaemic control.

SWS disruption trials are helpful for initially establishing a relationship between SWS and glycaemic control as well as potentially elucidating the mechanisms behind this interaction, however, enhancing SWS would potentially improve glycaemia as a form of intervention, which should be the long-term focus of future research.

One trial has explored the impact of one night auditory SWS enhancement on glycaemic control, finding non-significant changes to glucose, but more research is needed to optimise SWS enhancement methods [11]. Increasing SWS duration may be effective, as ACLS is limited to altering only SWS power [34]. Initial investigations have shown that pharmacologically increasing sleep during the first half of the night, which is SWS rich, is associated with glucose reductions of 1.6mg/dl, providing initial support for SWS enhancement as an intervention [51]. It is proposed that increasing SWS durations cumulatively over multiple nights may result in larger glucose reductions, providing a promising avenue for intervention research.

The SWS enhancement trials have also been limited to healthy participants (i.e. normo-glycaemic) as a preventative method, however, the sensitivity of the intervention may be more effective as a treatment for individuals with impaired glycaemic control [11].

1.4.5 Conclusions

In conclusion, this trial provides preliminary evidence and recommendations for future research in an emerging field. Only eight trials met eligibility criteria for this systematic review, with just four trials providing data for inclusion in our meta-analyses. The synthesised evidence presented here demonstrated that insulin resistance was significantly increased after SWS disruption, whilst post-prandial glucose and insulin were not

significantly altered by SWS disruption. No trials were assessed as having high risk of bias across any domains. Future research should focus on optimising sleep stage disruption (to further explore mechanisms) and sleep stage enhancement techniques (to explore potential interventions).

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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