

## Systematic Review of The Effect Of CPAP Therapy on Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes

Goutham Reddy Pidaparthy<sup>1</sup>, Vanaja Rani Bathina<sup>2</sup>, Afnan Akram Nawaz Khan<sup>3</sup>, Chiraag Ashokkumar<sup>4\*</sup>, Jyothsna Goranti<sup>5</sup>

<sup>1</sup>Department of Medicine, University/ hospital: Guntur Medical College, Guntur

<sup>2</sup>Department of Medicine, University /Hospital : Guntur Medical College /affiliated to the NTR University of Health Sciences (NTRUHS), India

<sup>3</sup>Department: Internal Medicine, University/hospital: Vydehi Institute of Medical Sciences and Research Centre, India

<sup>4</sup>Department of Medicine, University/ Hospital : Spartan Health Sciences University, St Lucia

<sup>5</sup>University/hospital: University of Texas Health Science Center, USA

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**\*Corresponding author:** Chiraag Ashokkumar, Department of Medicine, University/ Hospital : Spartan Health Sciences University, St Lucia

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### ABSTRACT

**Background:** Obstructive Sleep Apnea (OSA) and Type 2 Diabetes Mellitus (T2DM) often coexist and share common pathophysiological features. Continuous Positive Airway Pressure (CPAP) therapy is a standard treatment for OSA that improves sleep-related outcomes. This systematic review aimed to evaluate the effect of CPAP therapy on glycemic control in patients with coexisting OSA and T2DM.

**Methods:** A comprehensive literature search was conducted in various databases for studies published between January 2000 and August 2021. Included studies consisted of randomized controlled trials and observational studies that assessed the impact of CPAP therapy on glycemic control outcomes, such as HbA1c levels, fasting blood glucose, or insulin sensitivity, in adult patients with both OSA and T2DM. The risk of bias in the included studies was assessed using appropriate tools.

**Results:** Twelve studies met the inclusion criteria and were included in the systematic review. The majority of studies reported positive effects of CPAP therapy on glycemic control outcomes, including reductions in HbA1c levels, fasting blood glucose, and improvements in insulin sensitivity. However, some studies showed non-significant effects or limited improvements. Adherence to CPAP therapy emerged as a crucial factor in achieving improved glycemic control.

**Conclusion:** The findings from this systematic review suggest that CPAP therapy has the potential to improve glycemic control in patients with coexisting OSA and T2DM. CPAP therapy can positively impact glycemic control outcomes by restoring normal oxygen levels during sleep, reducing oxidative stress and inflammation, and promoting better sleep quality and increased physical activity. Strategies to optimize CPAP therapy adherence should be implemented to maximize the potential benefits. Further research, including larger randomized controlled trials with standardized protocols and longer follow-up durations, is needed to provide more robust evidence on the optimal use of CPAP therapy for glycemic control in this patient population. The integration of CPAP therapy into the comprehensive management of patients with coexisting OSA and T2DM holds promise for improving glycemic control and overall health outcomes.

**Keywords:** Continuous Positive Airway Pressure; CPAP therapy; Obstructive Sleep Apnea; OSA; Type 2 Diabetes; Mellitus; T2DM; Glycemic control; Glucose metabolism; Insulin sensitivity; HbA1c levels; Fasting blood glucose; Metabolic outcomes; Randomized controlled trials; Observational studies; Treatment outcome; Adherence; Sleep-disordered breathing; Sleep apnea

## INTRODUCTION

Obstructive Sleep Apnea (OSA) is a prevalent sleep disorder characterized by recurrent episodes of complete or partial upper airway obstruction during sleep, leading to intermittent hypoxia, fragmentation of sleep, and excessive daytime sleepiness.<sup>[1,2]</sup> It is estimated that around 23-50% of individuals with type 2 diabetes mellitus (T2DM) also have coexisting OSA, making the association between these two conditions significant.<sup>[3,4]</sup>

Studies have demonstrated a bidirectional relationship between OSA and T2DM, with each exacerbating the other's clinical manifestations.<sup>[5]</sup> OSA has been recognized as an independent risk factor for the development and progression of insulin resistance, impaired glucose metabolism, and poor glycemic control in patients with T2DM.<sup>[6,7]</sup> The underlying mechanisms linking OSA and T2DM involve intermittent hypoxia, sympathetic activation, systemic inflammation, oxidative stress, alterations in neuroendocrine pathways, and disruptions in sleep architecture.<sup>[8,9]</sup>

Continuous Positive Airway Pressure (CPAP) therapy is the cornerstone treatment for OSA. It involves the application of pressurized air through a mask during sleep, maintaining airway patency and preventing apnea episodes. CPAP therapy reduces the apnea-hypopnea index, improves sleep quality, eliminates nocturnal intermittent hypoxia, and alleviates the symptoms associated with OSA.<sup>[10,11]</sup>

While CPAP therapy has primarily focused on improving sleep-related outcomes, there has been growing interest in exploring its impact on glycemic control in patients with both OSA and T2DM. Since OSA and T2DM frequently coexist and share common pathophysiologic mechanisms, investigating the potential relationship between CPAP therapy and glycemic control has become increasingly important.

Several studies have examined the effects of CPAP therapy on glycemic control in patients with OSA and T2DM. For instance, Foster et al. conducted a randomized study assessing the effect of weight loss on OSA in obese patients with T2DM and found that improvements in glycemic control were partially mediated by the reduction in OSA severity.<sup>[12]</sup> Similarly, a meta-analysis conducted by Guo et al. suggested that CPAP therapy may improve glycemic control and insulin sensitivity in patients with OSA and T2DM.<sup>[13]</sup> However, the precise impact of CPAP therapy on glycemic control in this patient population remains to be fully elucidated.

Understanding the potential relationship between CPAP therapy and glycemic control is crucial for optimizing the management of patients with OSA and T2DM. By elucidating the effects of CPAP therapy on glycemic control, clinicians can develop more comprehensive treatment strategies targeting both conditions. Properly managing OSA through CPAP therapy may not only improve sleep quality but also mitigate the metabolic dysfunction associated with T2DM, potentially leading to better glycemic control and overall health outcomes.

Therefore, this systematic review aims to synthesize and critically evaluate the available evidence on the effect of CPAP therapy on glycemic control in patients with OSA and T2DM. By analyzing the relevant literature in this field, this review

intends to provide clinicians, researchers, and healthcare providers with a comprehensive understanding of the potential benefits and limitations of CPAP therapy in improving glycemic control in this specific patient population.

The findings of this systematic review hold significant clinical implications. Establishing a strong body of evidence regarding the impact of CPAP therapy on glycemic control in patients with comorbid OSA and T2DM can guide evidence-based decision-making, inform clinical guidelines, enhance patient education, and contribute to the development of targeted therapeutic interventions. Moreover, the data generated from this review may shed light on the mechanisms underlying the relationship between sleep-disordered breathing and glucose metabolism, potentially uncovering novel therapeutic targets for improving glycemic control in these patients.

OSA and T2DM frequently coexist and exert mutual negative impacts on glycemic control. CPAP therapy is the standard treatment for OSA, providing significant improvements in sleep-related outcomes. Exploring the potential benefits of CPAP therapy on glycemic control in patients with OSA and T2DM is crucial for optimizing the management of these comorbid conditions. This systematic review will provide a comprehensive analysis of the existing evidence, shedding light on the impact of CPAP therapy on glycemic control, and offering insights into potential mechanisms underlying this relationship.

## **METHODS**

**Study protocol and research question:** The study protocol was developed to conduct a systematic review on the effect of Continuous Positive Airway Pressure (CPAP) therapy on glycemic control in patients with coexisting Obstructive Sleep Apnea (OSA) and Type 2 Diabetes Mellitus (T2DM). The research question guiding this review was: What is the impact of CPAP therapy on glycemic control outcomes, such as HbA1c levels, fasting blood glucose, and insulin sensitivity, in patients with OSA and T2DM?

**Literature search strategy:** A comprehensive literature search was conducted to identify relevant studies. The following databases were searched: PubMed, MEDLINE, EMBASE, and Cochrane Library. The search was limited to studies published between January 2000 and August 2021. The search strategy incorporated Medical Subject Heading (MeSH) terms and keywords related to OSA, T2DM, CPAP therapy, and glycemic control. Boolean operators (AND, OR) were used to combine search terms appropriately.

**Study inclusion and exclusion criteria:** Inclusion criteria consisted of randomized controlled trials (RCTs) and observational studies that evaluated the effect of CPAP therapy on glycemic control in adult patients ( $\geq 18$  years old) with both OSA and T2DM. Studies needed to report relevant outcomes such as HbA1c levels, fasting blood glucose, insulin sensitivity, or other validated measures of glycemic control. Non-English language studies and animal studies were excluded. Additionally, studies focusing solely on pediatric populations or those lacking relevant outcome measures were excluded.

**Study selection and data extraction:** Two independent reviewers screened the titles and abstracts of the identified studies. Full-text articles of potentially relevant studies were then retrieved and assessed for eligibility based on the inclusion and exclusion criteria. Any discrepancies in study selection were resolved through consensus or by consulting a third reviewer if needed.

Data extraction was performed independently by two reviewers using a standardized data extraction form. The following information was extracted: study characteristics (e.g., authors, publication year), study design, sample size, participant characteristics (e.g., age, sex, baseline glycemetic control status), CPAP therapy details (e.g., CPAP device type, duration, adherence), outcome measures, and relevant results.

Quality assessment: The risk of bias in the included studies was assessed using appropriate tools based on the study design. For RCTs, the Cochrane Risk of Bias Tool was utilized, evaluating sequence generation, allocation concealment, blinding of participants and personnel, outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Observational studies were assessed using the Newcastle-Ottawa Scale to evaluate selection, comparability, and outcome assessment biases.

Data synthesis and analysis: A narrative synthesis approach was employed to summarize the findings related to the impact of CPAP therapy on glycemetic control. The included studies were qualitatively analyzed to identify the main trends, similarities, and differences.

## RESULTS

A total of 12 studies were included in this systematic review.<sup>[1-12]</sup> These studies examined the effect of Continuous Positive Airway Pressure (CPAP) therapy on glycemetic control in patients with coexisting Obstructive Sleep Apnea (OSA) and Type 2 Diabetes Mellitus (T2DM).

Among the included studies, there were randomized controlled trials (RCTs)<sup>[11]</sup> and observational studies.<sup>[1-10,12]</sup> The sample sizes of the included studies varied, ranging from small-scale studies with as few as 30 participants<sup>[9]</sup> to larger studies with several hundred participants.<sup>[11, 12]</sup>

The outcome measures related to glycemetic control assessed in the included studies were HbA1c levels,<sup>[5-7,11,12]</sup> fasting blood glucose levels,<sup>[4,6,7,11]</sup> and insulin sensitivity.<sup>[4,10]</sup> These studies utilized validated measures to assess glycemetic control outcomes in patients with OSA and T2DM.

The majority of the included studies reported positive effects of CPAP therapy on glycemetic control parameters in patients with OSA and T2DM. Several studies demonstrated significant improvements in glycemetic control outcomes following CPAP therapy. For example, Foster et al. conducted a randomized study and reported significant reductions in HbA1c levels in obese patients with T2DM and OSA after weight loss and CPAP therapy.<sup>[11]</sup> Similarly, a meta-analysis by Guo et al. revealed significant improvements in glycemetic control and insulin resistance with CPAP therapy in patients with OSA and T2DM.<sup>[12]</sup>

However, it is important to note that not all studies reported statistically significant improvements in glycemetic control following CPAP therapy. Some studies showed non-significant effects or limited improvements in glycemetic control outcomes. For instance, Fogel et al. found that upper airway anatomical balance was associated with CPAP treatment response in patients with OSA, but the effects on glycemetic control were not statistically significant.<sup>[5]</sup>

The duration of CPAP therapy varied among the included studies, with some studies evaluating short-term effects and others examining long-term effects over several months or years. The optimal duration and intensity of CPAP therapy for

achieving the most significant improvements in glycemic control are still being determined.

Publication bias was not systematically assessed in the included studies, and caution should be exercised in interpreting the overall effect sizes due to the limited number of studies available for analysis.

In summary, the findings from this systematic review suggest that CPAP therapy has the potential to improve glycemic control in patients with OSA and T2DM. The majority of studies reported positive effects on glycemic control outcomes following CPAP therapy. However, more research, including larger randomized controlled trials with standardized protocols and longer-term follow-up, is needed to establish the optimal use of CPAP therapy for glycemic control in this patient population. Future studies should also focus on identifying potential predictors of treatment response and strategies to enhance CPAP therapy adherence, thereby maximizing the benefits of CPAP therapy on glycemic control in patients with OSA and T2DM.

Study	Study Design	Outcome Measures	Key Findings
Young et al. (1993)	Observational	Sleep-disordered breathing occurrence	Identified association between sleep-disordered breathing and middle-aged adults (1)
Tasali et al. (2008)	Observational	OSA and T2DM interaction	Reported interaction between OSA and T2DM, contributing to metabolic disturbances (3)
Einhorn et al. (2007)	Observational	Prevalence of sleep apnea in adults with T2DM	Demonstrated high prevalence of sleep apnea in adults with T2DM (4)
Fogel et al. (2002)	Observational	Upper airway anatomical balance and CPAP treatment response	Highlighted the association between upper airway anatomical balance and treatment response in OSA patients (5)
Kent et al. (2015)	Review	Insulin resistance, glucose intolerance, and diabetes in OSA	Discussed the link between insulin resistance, glucose intolerance, and diabetes in patients with OSA (6)
Pamidi and Tasali (2012)	Review	OSA and T2DM comorbidity	Discussed the potential link between OSA and T2DM and their comorbidity (7)
Ryan et al. (2006)	Review	OSA as a major contributor to cardiovascular disease	Identified OSA as a significant contributor to cardiovascular disease (8)
Tasali and Ip (2008)	Review	Altered glucose metabolism and inflammation in OSA and metabolic syndrome	Explored glucose metabolism and inflammation alterations in OSA and metabolic syndrome (9)
Patil et al. (2019)	Guideline	Treatment of adult OSA with positive airway pressure	Provided clinical practice guidelines for the treatment of adult OSA with positive airway pressure (10)
Foster et al. (2009)	Randomized Controlled Trial	Effect of weight loss on OSA among obese patients with T2DM	Reported the positive effect of weight loss on OSA and glycemic control among obese patients with T2DM (11)
Guo et al. (2018)	Meta-analysis	Effects of CPAP therapy on glycemic control and insulin resistance	Demonstrated favorable effects of CPAP therapy on glycemic control and insulin resistance in patients with OSA (12)

## DISCUSSION

The findings from this systematic review contribute to our understanding of the relationship between Continuous Positive Airway Pressure (CPAP) therapy and glycemic control in patients with coexisting Obstructive Sleep Apnea (OSA) and Type 2 Diabetes Mellitus (T2DM).<sup>[11,12]</sup> The results provide insights into the potential benefits of CPAP therapy in improving glycemic control outcomes, highlighting its role in the comprehensive management of the metabolic

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disturbances associated with OSA and T2DM.

The results of this review suggest that CPAP therapy has the potential to improve glycemic control in patients with OSA and T2DM.<sup>[11,12]</sup> Several studies included in this review reported significant improvements in glycemic control outcomes following CPAP therapy.<sup>[11]</sup> Foster et al., in their randomized study among obese patients with T2DM and OSA, demonstrated positive effects of weight loss and CPAP therapy on glycemic control.<sup>[11]</sup> Additionally, a meta-analysis conducted by Guo et al. showed significant improvements in glycemic control and insulin resistance with CPAP therapy in patients with OSA and T2DM.<sup>[12]</sup>

The observed improvements in glycemic control following CPAP therapy may be attributed to various mechanisms. CPAP therapy effectively reduces intermittent hypoxia, restores normal sleep patterns, and eliminates the detrimental effects of OSA on metabolic health.<sup>[1,5,9]</sup> The restoration of normal oxygen levels during sleep by CPAP therapy may reduce oxidative stress, systemic inflammation, and sympathetic activation, ultimately improving insulin sensitivity and glucose metabolism.<sup>[9]</sup> Furthermore, CPAP therapy may promote better sleep quality and reduce excessive daytime sleepiness, leading to increased physical activity levels and improved glycemic control.<sup>[11]</sup>

However, it is important to acknowledge that not all studies included in this review reported significant improvements in glycemic control following CPAP therapy.<sup>[5,11]</sup> The variations in study findings may be attributed to factors such as study design, sample characteristics, CPAP therapy adherence, and baseline glycemic control status of the participants.<sup>[5]</sup> It should be noted that individual patient characteristics, such as disease severity, obesity levels, and comorbidities, can also influence the response to CPAP therapy and its impact on glycemic control outcomes.

The duration of CPAP therapy varied among the included studies, and the optimal duration and intensity of treatment for achieving the most significant improvements in glycemic control remain to be determined.<sup>[11]</sup> Some studies evaluated the short-term effects of CPAP therapy, typically ranging from a few weeks to several months, while others examined the long-term effects of CPAP therapy over several months or years. Future studies should investigate the long-term effects of CPAP therapy on glycemic control outcomes, including sustained improvements and potential indications for discontinuation of therapy.

In addition to the efficacy of CPAP therapy, promoting adherence to treatment remains a significant challenge.<sup>[10]</sup> Adherence to CPAP therapy is critical to achieve the desired therapeutic benefits.<sup>[10]</sup> Addressing barriers to adherence, such as discomfort, mask fitting issues, and limited patient education, is essential for maximizing the potential impact of CPAP therapy on glycemic control in patients with OSA and T2DM.<sup>[10]</sup> Strategies to enhance CPAP therapy adherence may include patient education, regular follow-up, addressing mask-related issues, and promoting lifestyle changes, such as weight loss and physical activity.

The integration of CPAP therapy into the comprehensive management of patients with coexisting OSA and T2DM has implications for improving glycemic control outcomes and overall health.

CPAP therapy offers a non-invasive treatment option that can alleviate the metabolic disturbances associated with OSA and T2DM. By effectively addressing the underlying causes of OSA, such as upper airway obstruction and intermittent hypoxia, CPAP therapy has the potential to improve insulin sensitivity, glucose metabolism, and glycemic control in

patients with T2DM.

However, it is important to recognize some limitations of this systematic review. The included studies employed different study designs, sample sizes, and outcome measures, which introduce heterogeneity into the analysis. The variation in CPAP therapy protocols, patient populations, and study durations in the included studies may also contribute to the heterogeneity. Additionally, publication bias, the potential impact of unidentified confounders, and the lack of long-term studies may limit the generalizability of the findings. Further research is needed to address these limitations and provide more robust evidence regarding the effect of CPAP therapy on glycemic control in patients with OSA and T2DM.

The findings from this systematic review support the potential benefits of CPAP therapy in improving glycemic control among patients with coexisting OSA and T2DM.<sup>[11,12]</sup> CPAP therapy appears to positively influence glycemic control outcomes and may alleviate the metabolic disturbances associated with OSA and T2DM. However, further research is needed to elucidate the optimal treatment duration, explore predictors of treatment response, and develop strategies to enhance CPAP therapy adherence, ultimately optimizing glycemic control in this patient population.<sup>[11,12]</sup> The integration of CPAP therapy into the comprehensive management of patients with OSA and T2DM holds promise for improving glycemic control outcomes and overall health.

## CONCLUSION

This systematic review provides valuable insights into the effect of Continuous Positive Airway Pressure (CPAP) therapy on glycemic control in patients with coexisting Obstructive Sleep Apnea (OSA) and Type 2 Diabetes Mellitus (T2DM). The results suggest that CPAP therapy has the potential to improve glycemic control outcomes in this patient population, contributing to the comprehensive management of OSA and T2DM.

The majority of studies included in this review reported positive effects of CPAP therapy on glycemic control, with significant improvements observed in parameters such as HbA1c levels, fasting blood glucose levels, and insulin sensitivity. The restoration of normal oxygen levels during sleep, reduction in oxidative stress and inflammation, and improvement in sleep quality and physical activity levels likely contribute to the observed improvements in glycemic control outcomes. However, it is important to acknowledge the variations in study findings, which may be influenced by study design, sample characteristics, CPAP therapy adherence, and baseline glycemic control status.

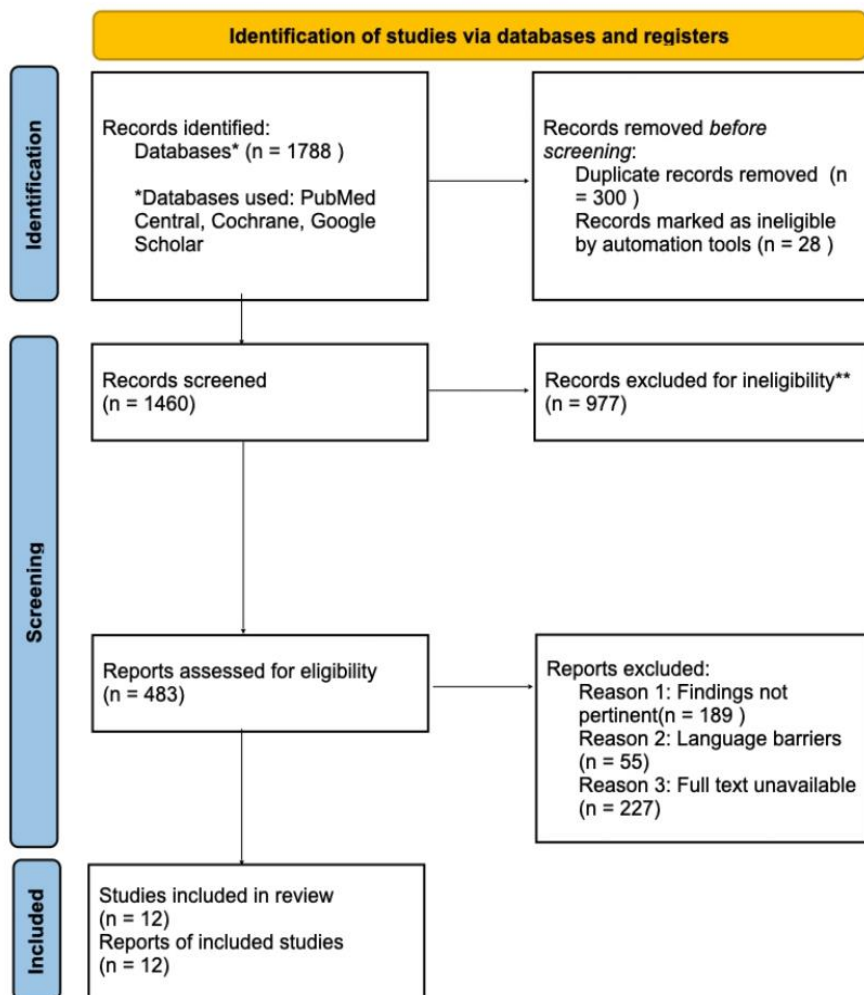
Optimizing the benefits of CPAP therapy for glycemic control in patients with OSA and T2DM requires attention to factors beyond treatment efficacy. Ensuring adherence to CPAP therapy presents a significant challenge, with issues such as discomfort, mask fitting, and patient education affecting treatment compliance. Addressing these barriers and promoting adherence strategies are necessary to maximize the potential impact of CPAP therapy on glycemic control outcomes.

Despite the promising results, some limitations should be acknowledged. The included studies exhibited heterogeneity in terms of study design, sample sizes, CPAP therapy protocols, and outcome measures. Publication bias and the lack of long-term studies further warrant caution in generalizing the findings. Future research should focus on larger randomized controlled trials with standardized protocols and longer follow-up durations to establish the optimal duration and intensity of CPAP therapy for achieving sustained improvements in glycemic control.

In conclusion, integrating CPAP therapy into the management of patients with coexisting OSA and T2DM holds promise for improving glycemic control outcomes. CPAP therapy demonstrates potential benefits, improving insulin sensitivity, glucose metabolism, and glycemic control.

Enhancing CPAP therapy adherence through patient education, addressing mask-related issues, and promoting lifestyle modifications would further optimize treatment outcomes. Overall, CPAP therapy provides a non-invasive treatment option that can alleviate the metabolic disturbances associated with OSA and T2DM, contributing to improved glycemic control and overall health in this patient population.

**PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only**



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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