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The effect of Ramadan fasting on cardiovascular events and risk factors in patients with type 2 diabetes: A systematic review



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ABSTRACT

Ramadan is the fasting month in Islam. Muslims around the world observe Ramadan every year, including people with diabetes. Data on the association of fasting in people with diabetes are sparse. The purpose of this study is to assess the association of fasting on cardiovascular risk factors and events in people with diabetes. A comprehensive search was conducted in the following database: Embase, Medline, Cochrane library and CINAHL. The following key terms were used: Ramadan, Ramazan, Ramadhan, Muslim, Islam and fasting. Studies were eligible if they included people with Type 2 diabetes who fasted during Ramadan and reporting results on cardiovascular risk factors or events. Overall 22 studies met inclusion criteria for the review; five studies reported cardiovascular outcomes and 17 reported changes in risk factors. There is insufficient evidence to link Ramadan fasting with increased or reduced incidence of cardiovascular events in people with diabetes, though there were some indication stroke risk may be increased. Findings were inconsistent in term of risk factors as some favoured Ramadan and others did not.

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1. Introduction

Ramadan occurs in the ninth month of the Islamic calendar. During this month, Muslims around the world abstain from food and drinks, including medications, from sunrise to sunset. Because Ramadan follows the lunar calendar, the length of fasting varies depending on the season [1]. Fasting is obligatory for all adults who are capable, but individuals who may be placed at risk by fasting, such as certain high risk patients with diabetes mellitus, are exempt from fasting [2]. However, as Ramadan fasting is one of the five pillars of Islam, many Muslims insist on fasting in some cases against medical advice [3].

There are about 148 million Muslims globally with diabetes [4]. Most of the available guidelines for people with diabetes planning to fast on Ramadan are based on expert opinions. However, there is a lack of scientific evidence on the safety of fasting in people with diabetes [4,5].

During Ramadan, there is a sudden change in daily routines, including eating and sleeping patterns as well as physical activity levels. Muslims who are fasting consume two meals a day, the first before sunrise (suhur) and the second, which is the main meal, after sunset (iftar). These changes in meal time can be associated with changes in sleeping patterns, such as reduced sleep duration, delayed sleep time and increased sleeping and reduced physical activity levels during the day [6–8]. Additionally, these changes can result in changes in insulin resistance as well as multiple neurohormonal changes, including the activation of the hypothalamic-pituitary axis and increased catecholamines, which can lead to endothelial dysfunction and increased cardiovascular events [4,9,10]. Furthermore activation of the HPA axis leads to the secretion of cortisol which results in insulin resistance, increased hepatic glucose output and increased gluconeogenesis [11].

In addition, due to the changes in eating habits during Ramadan, fasting individuals with diabetes could be at higher risk due to the increased risk of hyper and hypoglycaemia for example (3.2 to 7.5 fold increase in the risk of hypo or hyperglycemia) [12,13]. Dehydration is another challenge for patients with diabetes during Ramadan. Signs of dehydration

have been categorised by increased levels of haematocrit percentage or haemoglobin concentration, and plasma osmolality [14], which lead to increased blood viscosity. Increased blood viscosity is a secondary effect of dehydration that may increase the risk of thrombosis and, thereby, the risk of stroke [15–17]. Javanmardi, Safari [18] reported that cerebral venous sinus thrombosis increased during Ramadan due to dehydration.

It has been suggested that fasting can induce favourable physiological changes in healthy individuals such as reduction in weight and improve lipid profile [4,19]. However, in people with diabetes mellitus the evidence is not known. Currently there are no systematic reviews on the association between Ramadan fasting and CVD in people with type 2 diabetes. Hence, we conducted a systematic review to determine the association of Ramadan fasting on cardiovascular risk factor and events in people with type 2 diabetes.

2. Methods

The search strategy of the systematic review was designed to access both published and unpublished articles. The following databases were searched: Embase, Medline, the Cochrane Library and CINAHL. The reference lists of the identified studies were also examined in addition to select sources found through Google Scholar and the Journal of Fasting and Health. The following terms were identified in the scoping search and were used as keywords: ‘Ramadan’ or ‘Ramazan’ or ‘Ramadhan’, ‘Muslim’, ‘Islam’ and ‘fasting’. No language or time limit was used in the search. The search was performed in April 2018. An update search was done on April 2019 in Medline and citations of included studies. The search strategy for Medline and Embase can be found in the supplementary materials. A study was considered as eligible if it included adults with type 2 diabetes (population); was carried out during the month of Ramadan (exposure); and compared cardiovascular events or risk factors (outcomes) during Ramadan, up to one month before or after Ramadan. Comparators could be self-controls (before and after studies) or patients who did not fast.

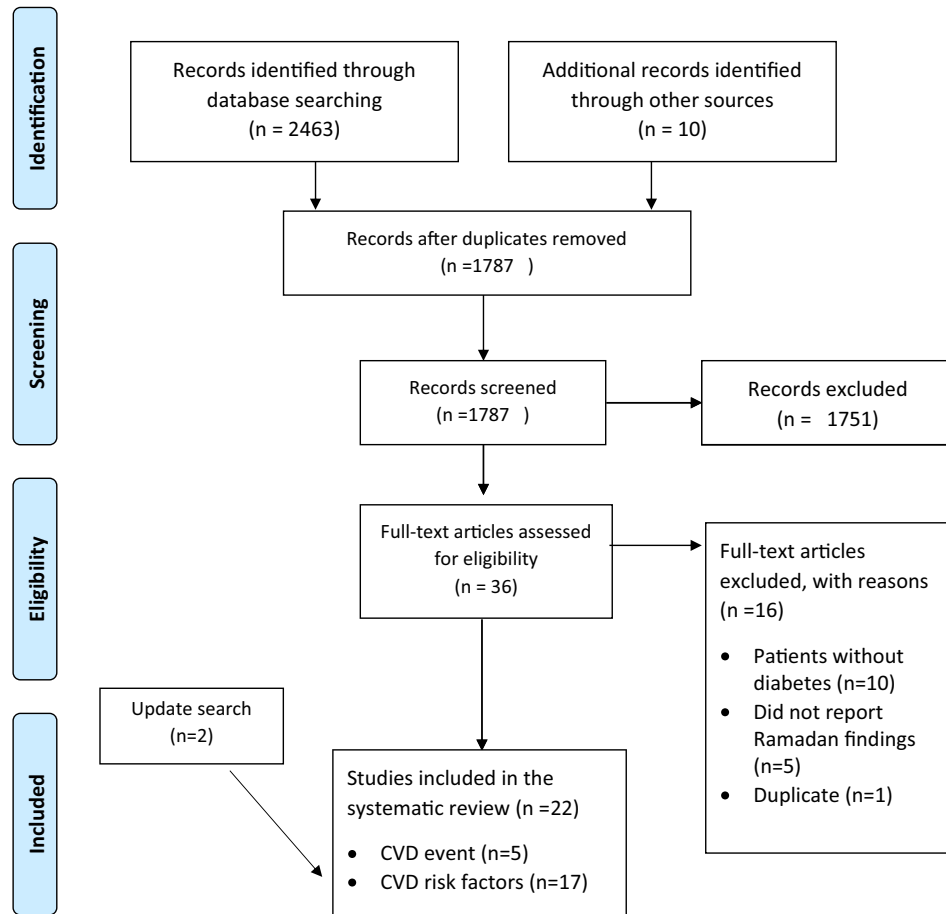


Fig. 1 – Study selection flowchart.

The identified studies were organised using reference manager software (EndNote x8). Duplicate records were removed. Data from studies that fulfilled the inclusion criteria were independently reviewed by two reviewers (MA, RS). The following data were extracted from each study: authors, location, study period, sample size, gender, age of participants, CVD events and CVD risk factors. A standardised, piloted form was used for the extraction. Differences between reviewers were resolved by discussion. ROBINS-E was used to assess the risk of bias [20]. Two reviewers additionally evaluated the risk of bias (MM, LA). Meta-analysis was not appropriate for this review because of the high heterogeneity in population characteristics, study design and utilised statistical parameters ($I^2 > 80\%$). Hence, narrative synthesis was used for analysis. The protocol is registered under PROSPERO CRD42018096018.

3. Results

3.1. Study selection

The search identified 2473 studies and after removing 686 duplicate studies, the titles and abstracts of 1787 articles were screened for inclusion and exclusion criteria. After screening, 36 studies met the criteria for which full text articles were retrieved from which 20 studies were determined as eligible for the review. Two additional studies were included through the update search (Fig. 1).

3.2. Association of Ramadan fasting on CVD events

Of the 22 studies, five studies reported CVD events and 17 studies reported cardiovascular risk factor changes. Table 1 summarises the characteristics and findings of the studies reporting CVD events in people with type 2 diabetes. Three of the five studies were conducted in Qatar [21–23], one in Turkey [24] and one in Egypt [25]. All studies were population level studies but included people with diabetes as a subgroup. Three studies reported on stroke [23–25], including one which reported on both ischemic and haemorrhagic stroke separately [24]. The latter study (175 hospital admissions with diabetes) found a significant increase in ischaemic stroke ratio during the Ramadan period ($P < 0.05$) (23.2% before Ramadan, 31.9% during Ramadan and 21.5% after Ramadan) but did not observe any differences in haemorrhagic stroke during Ramadan period [24]. The other studies reported a non-significant increase in the risk of stroke during and immediately after Ramadan (36% before Ramadan, 55% during Ramadan, 51.7% after Ramadan) [23], and a non-significant increase of stroke hospitalization in Ramadan (28 before, 32 during, 30 after Ramadan) [25]. The studies reporting on congestive heart failure [21] and unstable angina [22] reported a non-significant increase in incident events, whereas the study reporting on myocardial infarction reported a non-significant reduction [22] (Table 1).

Table 1 – Characteristics and findings of studies reporting on CVD events in patients with type 2 diabetes.

Study	Location	Study period	Sample size	Male %	Age	Timing of assessment	Findings
Al Suwaidi, Bener [21]	Qatar	1991 to 2001	1231 hospital admissions for CHF	59.7%	64 ± 11.5	One month before, during and after Ramadan and average of remaining nine months	Insignificant increase in CHF during Ramadan (before 55.5%, during 59.6%, after 59.1%, 9 months after 56.6%)
Al Suwaidi, Bener [22]	Qatar	1991 to 2001	Not reported for diabetic patients	NR	NR	One month before, during and after Ramadan	Insignificant reduction in AMI during Ramadan (before 58%, during 51%, after 53%) Insignificant increase in UA during Ramadan (before 51%, during 56%, after 59%)
Bener, Hamad [23]	Qatar	1991 to 2003	160 admissions for stroke	71%	56.99 ± 13.9	One month before, during and after Ramadan and average of remaining nine months	Insignificant increase in stroke during Ramadan (before 36.7%, during 55.2%, after 51.7%, 9 months after 48.2%)
Comoglu, Temizhan [24]	Turkey	NR	175 admission for ischemic stroke and intracerebral haemorrhage	NR	NR	One month before, during and after Ramadan	Significant increase in ischemic stroke during Ramadan (before 23.2%, during 31.9%, after 21.5%) Insignificant reduction in intracerebral haemorrhage during Ramadan (before 12.2%, during 10.9%, after 12.7%)
Assy, Awd [25]	Egypt	2015	90	48.9%	63 ± 0.4	One month before, during and after Ramadan	Insignificant difference in the frequency of stroke between the three period (before 28, during 32, after 30)

CHF = congestive heart failure, AMI = acute myocardial infarction, UA = unstable angina, NR = not reported.

Table 2 – Characteristics of studies reporting CVD risk factors in patients with type 2 diabetes.

Study	Location	Sample size	Age	Gender	Duration of Diabetes	Timing of assessment
Ait Saada, Selselet Attou [26]	Algeria	66	48.73 ± 2.22	Female	Not reported	1 week before Ramadan and on the 3rd week of Ramadan
Al-Hader, Abu-Farsakh [37]	Jordan	23	43–56	73.9% male	Not reported	Before Ramadan and at the end of Ramadan
Alharbi, Wong [40]	Australia	5	52 ± 5	60% male	Not reported	Before Ramadan and on the 3rd week of Ramadan
Al-Shafei [38]	Egypt	40	55 ± 5	50% male		Before Ramadan, at the end of Ramadan and 6 weeks after Ramadan
Bener and Yousafzai [31]	Qatar	1301	45.9 ± 15.3	51.90% male	Not reported	Before Ramadan and during Ramadan
Khaled, Bendahmane [27]	Algeria	60 obese women	51 ± 10	Female	5 ± 2.5 years	1 month before Ramadan, 3rd week of Ramadan and 3 weeks after Ramadan
Khaled and Belbraouet [28]	Algeria	89 obese women	52 ± 5	Female	4.7 ± 2.6 years	1 week before Ramadan, during Ramadan and 1 month after Ramadan
Khan, Khan [36]	Pakistan	75	52.8 ± 8.5	50.60% male	5.6 ± 5.3 years	10 days before Ramadan, during Ramadan and 1 month after Ramadan
Matar, Abdulrahman [41]	Qatar	34	55 (31–88)	44.12% male	Not reported	1 month before Ramadan, the last week of Ramadan and 1 month after Ramadan
M'Guil, Ragala [30]	Morocco	120	48–60	48.30% male	Female: 4.5 years Male: 5.5 years	1 day before fasting, on days 15 and 29 of Ramadan and 15 days after Ramadan
Tiboura, Khaled [39]	Algeria	80	56 ± 8	38.75% male	4.3 ± 2.4 years	1 month before Ramadan and on the 2nd week of Ramadan
Uysal, Erdogan [34]	Not reported	41	55 (38–70)	26.80% male	Not reported	Before Ramadan, during the last week of Ramadan, 3 weeks after Ramadan and 8 weeks after Ramadan
Khatib and Shafagoj [29]	Jordan	44	52 ± 9	Male	8.37 ± 7.02 years	1–2 days before Ramadan, at the middle of Ramadan and at the end of Ramadan
Paul, Khan [42]	Bangladesh	52	54.7 ± 5.2	62.80% male	5.5 ± 5.2 years	1 week before Ramadan and the last 3 days of Ramadan
Maislos, Abou-Rabiah [33]	Israel	67	53.2 ± 12	51% male	5.6 ± 4.2 years	1 week before Ramadan, during the 4th week of Ramadan and 1 month after Ramadan
Traore, Lemieux [35]	Mali	25	48.5 ± 6.8	44% male	Not reported	Before Ramadan and after Ramadan
Malek, Hannat [32]	Algeria	901	56.99 ± 11.54	41.50% male	7.87 ± 5.97 years	Before, during and after Ramadan

Table 3 – Changes in CVD risk factors in patients with type 2 diabetes.

Study	CVD risk factor								
	FBG	HBA1c	BMI	SBP	DBP	Total cholesterol	Triglycerides	HDL	LDL
Ait Saada, Selselet Attou [26]	↑	↓	↔	NR	NR	↓	↓	↑	↓
Al-Hader, Abu-Farsakh [37]	NR	↔	NR	NR	NR	↔	↓	NR	NR
Alharbi, Wong [40]	↔	NR	↔	NR	NR	↔	↔	↔	↔
Al-Shafei [38]	↔	↔	NR	NR	NR	↔	↓	↔	↔
Bener and Yousafzai [31]	↓	↓	NR	↓	↓	↓	↓	↓	↓
Khaled, Bendahmane [27]	↓	↓	↔	NR	NR	↑	↑	↓	↑
Khaled and Belbraouet [28]	↓	NR	↓	NR	NR	↑	↑	↓	↑
Khan, Khan [36]	↔	NR	NR	↓	↔	↔	↔	↔	↑
Khatib and Shafagoj [29]	↓	↓	NR	NR	NR	↔	↓	↔	↔
Matar, Abdulrahman [41]	↔	↔	NR	NR	NR	↔	↔	↔	↔
M’Guil, Ragala [30]	M: ↔ F: ↓	M: ↔ F: ↔	M: ↔ F: ↔	M: ↔ F: ↓	M: ↔ F: ↔	M: ↔ F: ↓	M: ↔ F: ↔	M: ↔ F: ↔	M: ↔ F: ↓
Tiboura, Khaled [39]	↔	NR	↔	NR	NR	↔	↔	↓	↔
Uysal, Erdogan [34]	NR	↑	↔	NR	NR	↔	↔	↑	↔
Paul, Khan [42]	NR	↔	NR	↔	↔	↔	↔	↔	↔
Maislos, Abou-Rabiah [33]	↔	↓	↔	NR	NR	NR	NR	NR	NR
Traore, Lemieux [35]	↑	NR	NR	↑	↔	↓	↔	↔	↓
Malek, Hannat [32]	↑	NR	NR	NR	NR	NR	NR	NR	NR

FBG = fasting blood glucose, SBP = systolic blood pressure, DBP = diastolic blood pressure. ↑= a significant increasing, ↓= a significant decreasing, ↔= not significant change, NR = not reported.

3.3. Association of Ramadan fasting on CVD risk factors in patients with diabetes

Table 2 summarises the main characteristics of the 17 studies reporting cardiovascular risk factors. Three studies included only females [26–28], and one study only males [29]. The sample sizes ranged from 5 to 1301, with only three studies recruiting more than 100 participants [30–32]. The largest study was conducted in Qatar in one diabetic outpatient clinic recruiting 1301 participants before the start of Ramadan [31], followed by a study in Algeria including 901 patients [32] and then by a study in Morocco with 120 patients [30]. The majority of the studies reported changes in glycaemic control, blood pressure, lipid profile and BMI. Table 3 summarises the study findings on the changes in cardiometabolic risk factors during Ramadan in patients with diabetes.

3.3.1. Glycaemic control

Overall 17 out of the 22 studies reported effects on glycaemic control. Five studies reported a favourable effect of fasting on glycaemic parameters [27–29,31,33]. These studies showed a significant reduction in glycaemic parameters ranging from 0.48% to 0.93% for HBA1c and from 0.82 to 1.6 mmol/l for blood glucose. However, three studies reported a significant

increase in HBA1c and FBG [34,35]. Another study reported conflicting effects on glycaemic parameters [26], including a significant increase in FBG but significant reduction in HBA1c.

3.3.2. Blood pressure

Five studies reported blood pressure changes. Of these, three studies reported a significant reduction during the fasting month [30,31,36] ranging from 5.83 mmHg to 4.04 mmHg. Only one study reported a significant reduction in diastolic blood pressure (3.84 mmHg) [31]. One study reported significant increase in systolic blood pressure [35].

3.3.3. Lipid profile

15 studies reported on lipid profile changes. The lipid profile results were inconsistent across the studies. Four studies reported a significant reduction in total cholesterol [26,30,31,35] in contrast to two studies in Algeria among overweight women reporting a significant increase in total cholesterol [27,28]. Five studies reported a significant reduction in triglyceride [26,29,31,37,38], with another two studies reporting a significant increase [28,38]. Four studies found a significant decrease in the HDL level [28,29,31,39], while two other studies reported an increase [26,34]. Four studies reported a decrease in the LDL level [26,30,31,35] in contrast to three studies reporting an increase [27,28,36].

3.3.4. BMI

Eight studies reported changes in BMI. Only one study reported a significant reduction in BMI [28]. This latter study was conducted in Algeria and included 89 overweight women. However, it appears that the weight was regained one month after Ramadan. Another study in Algeria with 60 overweight women also reported a non-significant reduction [27]. Similar non-significant changes were reported in the other six studies [26,30,33,34,39,40]. None of the studies reported significant increases in BMI during Ramadan.

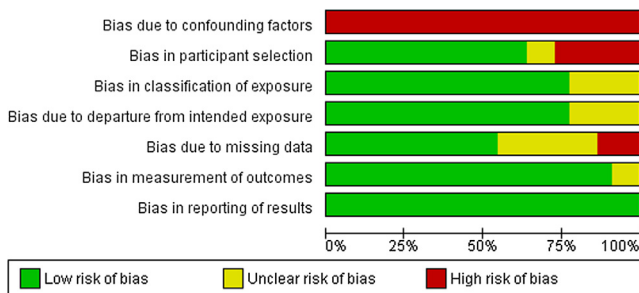


Fig. 2 – Assessment of the risk of bias across studies.

3.4. Quality assessment

Overall results on the risk of bias assessments are reported in Fig. 2. One important issue of the quality of the studies might have resulted from the fact that the studies reporting on CVD events only included diabetes as a subgroup. Also, information on the completeness and validity of the data used was lacking. Of the 17 studies reporting risk factors, only eight studies collected data on lifestyle changes (e.g., diet, sleeping, physical activity and smoking) [26,28–31,33,36,39]. However, these changes were poorly reported, and potential confounding factors were not adequately controlled. Moreover, the small sample sizes undermine the internal and external validity of the studies.

4. Discussion

Diabetes is a risk factor for CVD. Patients with diabetes are two to three times more likely to develop vascular events compared to those without diabetes [43–46]. Of the 22 studies included in the review, only five studies explored the effect of fasting on CVD events, comparing hospitalisation patterns for CVD before, during and after Ramadan retrospectively. Four of the five studies did not find any significant changes in hospitalisation patterns during the month of Ramadan. Meanwhile, Comoglu et al. [24] reported a significant increase in ischemic stroke during Ramadan in patients with diabetes. The findings relating to the association of Ramadan on cardiovascular risk factors were inconsistent but mostly showed that fasting favoured a reduction in glycaemic parameters and systolic blood pressure.

Hence, there is insufficient evidence to make definitive conclusions on the association of fasting during Ramadan with risk of CVD events in people with diabetes. The findings of the current review are consistent with those of Salim, Al Suwaidi [47] and Turin, Ahmed [48], who were unable to demonstrate changes in the incidence of cardiac events during Ramadan, although these studies focused on the general population.

Inconsistent findings on the effect on risk factors particularly blood glucose and lipids may have been driven by different dietary habits and physical activities among participants within and between studies. In any case, people with diabetes are at higher risk of complications, including hypoglycaemia, hyperglycaemia and dehydration. This risk is expected to increase during Ramadan due to the pattern of daytime fasting, night-time meals and poor dietary habits along with the effects of anti-diabetic treatments [17,49]. These changes are likely to be associated with a disturbance in the circadian rhythm, leading to the elevation of diurnal cortisol levels [9]. The disrupted sleep during Ramadan and the misalignment between the time of food intake (overnight) and the circadian cycle (which is typically geared in favour of releasing rather than storing glucose overnight) can result in dysglycemia as well as increased weight. Disrupted sleep has been associated with activation of the HPA axis as well as increased ghrelin, and reduced leptin and adiponectin which favours increased oral intake, insulin resistance and hyperglycaemia [50–52]. Ajabnoor, Bahjiri [53] discussed that dysregulation in

adiponectin production may be an important factor in endothelial dysfunction, increasing the risk of CVD. The increased risk of hypoglycaemia during Ramadan has also been documented [13,54], and hypoglycaemia has been associated with an increased risk of cardiometabolic events [12,55,56]. Due to these factors, the risk of CVD is generally expected to increase during Ramadan in patients with diabetes. However, the limited small studies in this review assessing the incidence of various cardiovascular events and outcomes have failed to consistently demonstrate increased risk.

However fasting in Ramadan can also have a positive metabolic effect on diabetes in terms of reducing HbA1c, weight, decrease in blood pressure and positive lipid profile as demonstrated by some studies. What is important is to delineate the group of patients in whom these positive metabolic profiles are seen.

Diabetes is also commonly associated with CVD risk factors such as obesity, hypertension and dyslipidaemia, placing patients with diabetes at increased risk for cardiac events. During the eating hours of Ramadan, there is an increased tendency to consume large meals rich in fried and sugary foods. Poor nutritional habits during Ramadan can cause fluctuation in blood glucose and lipid levels [2,13,57,58]. Notably, fluctuations in blood glucose levels influence vascular endothelial dysfunction in type 2 diabetes [59]. Additionally, abnormalities in lipid profiles are associated with an increased risk of atherosclerosis [60].

Nonetheless, Ramadan could be a great platform to induce positive lifestyle modifications, in particular for patients with diabetes. Fernando, Zibellini [19] found that, during Ramadan, there was a significant reduction in weight, particularly in overweight individuals. However, it is important to develop strategies to maintain the beneficial effects of Ramadan. Smoking cessation during Ramadan can also improve health [61]. It is possible that focused pre-Ramadan education can empower patients with the necessary skills to maintain a healthy lifestyle during and after Ramadan and also highlight the poor habits that should be avoided to minimise any complications. What is important in terms of Ramadan education is to help people adapt positive lifestyle behaviours. As people are not eating and drinking for most of the day and also have a spiritual fulfilment, positive lifestyle behaviour change could be achieved if supported by good pre-Ramadan education projects [62].

The strengths of this review includes the comprehensive search for eligible studies and the use of a prospective protocol with pre-specified eligibility criteria and outcomes on multiple search engines. In addition, it is the first review focused on the association of fasting on CVD events and risk factors in people with diabetes. However, this review also has several limitations. Due to the nature of the studies we were unable to look at any differences in the incidence of hypoglycaemia between participants with Type 1 and Type 2 Diabetes mellitus. The studies were performed in different geographical locations where daylight hours and climatic conditions differed. Other key limitations were that most studies were small and participants served as their own controls. It is challenging to recruit participants during Ramadan. However,

there is a need to compare fasting and non-fasting individuals to precisely distinguish whether the effects of Ramadan can be attributable to fasting or lifestyle changes and external factors. Due to the importance of Ramadan in the Muslim belief system, a randomised fasting trial would be unethical. Also, recruiting those who are not fasting as a control group in an observational study might bias the findings, as these individuals tend to be exempted from fasting due to medical conditions [63]. One option may be to conduct well-designed and controlled interrupted time-series analysis [64] accounting for cyclical as well as seasonal changes due to moving timing of the months of Ramadan. Additionally, we could utilise large sets of routinely collected data to compare the incidence of CVD events and risk factors between different ethnicities and examine how they differ during Ramadan compared to baseline incidence rates. A further limitation was that we were unable to conduct a meta-analysis due to the heterogeneity of the studies.

Millions of Muslims around the world observe Ramadan and abstain from food and drinks from sunrise to sunset. The effect of Ramadan on patients with diabetes is not fully understood due to the limited number of studies in this area. To the best of our knowledge, this is the first systematic review exploring the effects of Ramadan fasting on CVD events and risk factors in patients with diabetes. This review could not reach a definite conclusion because of the conflicting findings but did not find any evidence suggesting overt harm. However, it emphasises the need for more studies on the effect of Ramadan fasting on diabetes and suggests potential alternative methods to exploring this issue using large sets of routinely collected data.

Supplementary materials:

Sample search strategy for Medline and Embase

1. Ramadan.mp.
2. Ramazan.mp.
3. Ramadhan.mp.
4. muslim.mp. or exp Islam/
5. islam.mp. or exp ISLAM/
6. fasting.mp. or exp FASTING/
7. 5 and 6
8. 4 and 6
9. 1 or 2 or 3 or 7 or 8

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Declaration of Competing Interest

There are no conflicts of interest.

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