The Effect of Ramadan Fasting on the Health of a Predominant Muslim Population in the UK

By

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ABSTRACT:

Background: Ramadan fasting, in which Muslims abstain from food and drinks from dawn to sunset, is one of the five Pillars of Islam. Millions of Muslims observe this month every year. However, little is known on the effect of Ramadan fasting on health. There is a lack of research investigating the effect of Ramadan on health. Ramadan fasting is associated with sudden changes in lifestyle including changes in mealtime and sleeping pattern. These changes lead to circadian misalignment that could lead to cardiometabolic dysfunction and cardiovascular disease. Moreover, dehydration resulting from the prolonged fasting is claimed to increase the risk of infection in Ramadan. The aims of this thesis are (1) to assess the impact of Ramadan fasting on different aspects of health (2) to strengthen the available evidence on the effect of Ramadan fasting on health using a robust method that have not previously been employed in Ramadan research.

Methods: The overall methods (1) using The Health Improvement Network (THIN) database for a retrospective cohort design to explore the cardiometabolic profile of a predominate Muslim population in the UK, (2) systematic review to summarise the available evidence on the effect of Ramadan fasting on cardiovascular disease (CVD) and risk factors for CVD in patients with diabetes (3) controlled interrupted time series using THIN database and hospital data to explore (a) infection (all infections), using antibiotics prescriptions as a proxy measure and (b) ischemic heart disease (IHD) risks in a predominant South Asian Muslim population in the UK to a predominantly non-Muslim white ethnic population as a control group.

Results: The retrospective cohort study showed that compared to white population, South Asian (SA) are at higher risk of diabetes, hypertension and IHD with some variations between SA sub-groups. Systematic review showed that there is insufficient evidence suggesting that Ramadan fasting is associated with increased risk of CVD events in patients with diabetes. The interrupted time series studies show that there is no evidence that Ramadan fasting is associated with increased risk of infection or IHD.

Conclusion: Up to date there is no evidence that Ramadan fasting is associated with detrimental effect on health. However, more well conducted studies are needed to validate the findings.

Dedication

I dedicate this thesis to my parents.

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I must give a special thanks to my father who accompanied me most of the time while I am in the UK. I am grateful for the endless support, engorgement and motivation. Thank you for being there with me. Thank you for listening to me when I needed to talk. Thank you for everything you have done to me to finish this PhD.

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Contributorship statement

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List of Abbreviation

AF	atrial fibrillation
aHR	Adjusted Hazard ratios
AMR	acceptable mortality reporting
aOR	adjusted odd ratios
BNF	British National Formulary
BMI	Body mass index
CHF	congested heart failure
CITS	Controlled interrupted time series
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
HCPs	healthcare professionals
HF	Heart failure
HR	Hazard Ratio
HTN	Hypertension
ICD	International Classification of Diseases
IHD	Ischemic heart disease
IMRD	IQVIA Medical Research Data
IQR	interquartile range
ITS	Interrupted time series
MI	myocardial infarction
ONS	Office for National Statistics
OR	odd ratios
PICS	Prescribing Information and Communications System
SA	South Asian
SD	standard deviation
T2DM	Type 2 diabetes mellitus
THIN	The Health Improvement Network
TIA	transient ischaemic attack
UHB	University Hospitals Birmingham
UTI	Urinary tract infection
WE	White Europeans

THESIS FORMAT

This thesis is formatted in accordance with the University of Birmingham alternative format thesis guidelines; Regulation 7.4.1 (g) (https://intranet.birmingham.ac.uk/as/studentservices/graduateschool/documents/public/rsa/alternative-format-thesis-guidelines.pdf)

As a result, accepted, published or manuscripts under submission (Chapters 3-6) will be inserted directly into the thesis. As stand-alone published works and manuscripts under submission/peer review are directly inserted into this thesis, there will be duplication amongst chapters especially relating to the introduction, methods (particularly where these are similar for the outcome studies) and discussion sections throughout the thesis. As per the alternate thesis guidelines, the pages of publications will not be included in the pagination sequence of the submitted thesis.

In order to maintain numerical clarity of the references, tables and figures, these are self- contained within each chapter.

Publications related to the thesis:

Chapter 3

Almulhem M, Chandan JS, Gokhale K, et al. Cardio-metabolic outcomes in South Asians compared to White Europeans in the United Kingdom: a matched controlled population-based cohort study. *BMC Cardiovascular Disorders* 2021; **21**(1): 320.

Chapter 4

Almulhem M, Susarla R, Alabdulaali L, et al. The effect of Ramadan fasting on cardiovascular events and risk factors in patients with type 2 diabetes: A systematic review. *Diabetes Research and Clinical Practice* 2019: 107918.

Manuscripts under review from the thesis:

Chapter 5

Munerah M, Thayakaran T, Hanif S,et al. Ramadan is not Associated with Increased Infection Risk in Pakistani and Bangladeshi Populations: Findings from Controlled Interrupted Time Series Analysis of UK Primary Care Data

Chapter 6

Munerah M, Thayakaran T,Tahrani A,et al, Ramadan is not Associated with Increased Ischemic Heart Disease Risk in Pakistani and Bangladeshi Populations: Findings from controlled interrupted time-series analysis of University Hospitals Birmingham ,UK

1 Chapter one: Background

1.1 Contents of Chapter One

In this introductory chapter, I will first describe Ramadan, explain why it is important and identify the lifestyle and physiological changes that occur when it is observed. Thereafter I will describe the existing literature and discuss the potential mechanisms whereby Ramadan interacts with health outcomes. Finally, I will highlight the need to raise and answer my research questions and set out the objectives of the thesis.

1.2 Ramadan

Ramadan is the 9th month of the Islamic calendar. Fasting during Ramadan is one of the five pillars of Islam. In Islam there are five religious acts or 'pillars' that are considered the core beliefs and practices of the religion. They are as follows: *Shahada*, which is a declaration of faith (believing that there is no God but Allah, and Muhammed (peace be upon him) is his messenger); *Salah*, which is praying five times a day; *Zakat*, which is the giving of alms; *Sawm*, which is fasting for the month of Ramadan; and *Hajj*, which is the pilgrimage to Makkah. Ramadan fasting is obligatory for all healthy adults, because in the holy Quran Allah says "**O you who believe, fasting is prescribed for you as it was prescribed for those before you, that you may develop God-consciousness**".[1]

For a whole month, from dawn till dusk, Muslims around the world refrain from certain behaviours and habits. These include eating, drinking, using oral medications, sexual activity and smoking.[1] However, there are some people who are excused from fasting during Ramadan. They include children, women during their menstrual period or undergoing postnatal bleeding, travellers, pregnant or breastfeeding women who believe fasting for long hours may

cause harm to either themselves or their babies, those elderly who cannot tolerate fasting, the mentally disabled, and the sick for whom fasting will aggravate their condition.[1] Where possible, missed fasting days should be made up before the next Ramadan. Ramadan month follows the lunar calendar and, depending on the lunar state, it can last either 29 or 30 days. Based on the Muslim's geographic location, their daily fast could last up to 20 hr. Each year Ramadan moves back by 11 days, and it can take up to 33 years to occur across all seasons.

1.2.1 The Importance of Ramadan Month for Muslims

Islam is the fastest growing religion in the world. The Muslim population represents nearly 1.6 billion people, comprising 23% of the world's population in 2010 and projected to increase by 73% by 2050.[2] According to a Pew Research Centre survey of more than 38,000 Muslims around the world, most Muslims (93%) practise fasting during Ramadan.[3] Ramadan month is a holy month for Muslims as in this month they can practise the fourth pillar of Islam (fasting), and because it was the month in which the Quran, the holy book of Islam, was revealed.[1] Muslims around the world keenly anticipate the arrival of Ramadan. Muslims believe that the purpose of fasting is to learn self-restraint from indulgence in everyday pleasures, self-discipline, develop God-consciousness and self-control, to purify the body, and to empathize with the poor and hungry.[4,5]

1.2.2 Lifestyle Changes during the Month of Ramadan

Ritual behaviours and routines tend to change suddenly in Ramadan. During Ramadan, the three daily meals (breakfast, lunch, dinner) become two main meals. The first is *suhur*, which is the meal taken before dawn or before starting the fast, and the second is *iftar*, which is the meal taken after sunset to break the fast.

Ramadan fasting not only changes the timing of meals, but it may also disturb sleeping patterns. Studies on sleep and Ramadan reported that sleep is disturbed in Ramadan.[6-8] In a typical Ramadan day, sleep is broken before dawn to eat *suhur*, the meal before the start of fasting. Many Muslims will return to sleep afterwards and wake for a second time to start the day. Following *iftar*, the evening meal, many will choose to stay awake until midnight or later.[9] Changes in sleep patterns include decreased total sleep time, delayed sleep, decreased sleep period time, decreased rapid eye movement and decreased sleep duration.[8,10,11] However, it should be noted that studies reported different sleep patterns in different countries.[12-16] This could reflect variation in the cultural and lifestyle changes that occur in Ramadan in different countries, different assessment methods, or due to differences in daylight hours and time of the years in the countries the surveys were undertaken. When assessing the impact of Ramadan fasting on sleep, it is essential to consider the accompanying lifestyle changes during the holy month. For example, in some Muslim countries such as Saudi Arabia, the beginning of work is delayed, and work duration is shortened during Ramadan. Some of the earlier studies that assessed sleep patterns during Ramadan used sleep diaries and self-reported data, while others measured it objectively using tools such as actigraphy. Heterogeneity between studies poses a challenge in reaching a causal inference that is generalised to all Muslim populations.

In terms of physical activity in Ramadan, some studies reported reduction in the physical activity level during the day,[17] while other studies did not identify changes in activity level during Ramadan.[18] It must be noted that during Ramadan many Muslims participate in *Tarawih* prayer, which is a ritual prayer performed at night and which can last for 1-2 hrs. Moreover, in the last 10 days of Ramadan, many Muslims participate in *Tahajud* prayers, which is non-

obligatory prayer performed after midnight. These additional prayers performed in this month may, arguably, constitute a moderate level of physical activity.

1.3 Ramadan and the Circadian Rhythm

During Ramadan, Muslims have two meals between sunset and sunrise. This means that most food and fluid intake is shifted to the hours of darkness, reversing the normal circadian pattern of eating and drinking. These changes may affect fasting Muslims' circadian rhythm and biological clock. Different physiological systems in the body exhibit circadian rhythms, including some hormones and core body temperature patterns. Normally the temperature rises during the day and falls at night. However, it has been reported that during Ramadan, body temperature decreases during the day and increases at night.[8,19] BaHammam, Alrajeh [7] reported a delay in acrophase of skin temperature during Ramadan, suggesting a temporary shift in the circadian pattern of body temperature.[6] A similar pattern was observed in cortisol levels during Ramadan, decreasing in the morning and increasing at night.[20,21] Exclusively nocturnal eating during Ramadan could be responsible for these changes.[8,12]

Circadian disruption occurs when the endogenous circadian rhythms of the body are not synchronised with the environment or each other. Changes in lifestyle that occur in Ramadan may contribute to the disruption of the circadian rhythm. Such changes include intermittent fasting, increased nocturnal activities, decreased diurnal activities, delays in the start time for work, increased light exposure at night and sudden shifts in meal times.[11]

All body organs, tissues and cells are under the control of a biological clock that follows a circadian pattern. The circadian rhythm is influenced by light, mealtimes and neurohormonal

factors.[22] Changes in these factors lead to circadian misalignment. Studies have shown that disruption in the circadian system can lead to cardiometabolic dysfunction, such as impaired glucose tolerance, reduced insulin sensitivity, increased blood pressure and reduced energy expenditure (which can lead to obesity).[23]

The negative effect of circadian misalignment on cardiometabolic risk is supported by studies on shift work. Studies have shown that shift workers could be at higher risk of developing cardiometabolic diseases than normal day workers.[24-26] Shift work can be an extreme example of circadian disruption effects on health. However, studies show that even mild forms of circadian disruption can have detrimental effects on health.[23] Those who have a late chronotype ('evening people') or preference to sleep late have a higher risk of cardiovascular disease (CVD), diabetes and hypertension .[23,27] Moreover, studies on patients with diabetes reported an association between late chronotype, poor glycaemic control and lipid profile.[28,29]

Mealtime is another factor that plays an important role in metabolic regulation, because it interacts closely with circadian rhythms.[30] Evidence suggests that eating in the nocturnal "inactive phase" is likely to be associated with poor cardiometabolic health and increased risk of obesity, hyperglycaemia and diabetes.[31-33]

The evidence presented in this section indicates that changes that occur during Ramadan could lead to circadian dysfunction and consequent negative effects on health. The next part of this chapter will summarise the available literature on the effect of Ramadan fasting on different health outcomes.

1.4 Effects of Ramadan Fasting on Health

As indicated earlier, Ramadan is associated with sudden changes in the daily routines including shifts in mealtimes and sleep. These sudden changes can lead to dysfunctions in the body's circadian rhythms and consequently affect health. The impact of Ramadan fasting on health has been an area of interest for many researchers. In the last 30 years there has been a substantial increase in the volume of studies investigating various aspects of Ramadan health-related areas.[34] Figure 1 provide. A summary for the Potential mechanisms by which Ramadan fasting might influence health outcomes.

1.4.1 Effects of Ramadan Fasting on Lipid Profile

Several studies investigated the changes in lipid profile during Ramadan. There is a suggestion that Ramadan fasting induces favourable changes in lipid profile in healthy individuals.[35-38] A meta-analysis that included 30 publications on the effect of Ramadan fasting on different biomarkers found an overall decrease in total cholesterol and LDL.[39] However, the review did not find significant changes in HDL or Triglyceride levels.

Similar favourable changes in lipid profile were reported in those with a history of disease. A study in Kuwait found that Ramadan fasting could lead to improvements in lipid parameters in patients with hyperlipidaemia.[40] Similar positive effects of fasting were reported in patients with hypertension.[41] An Iranian study on patients with a history of CVD found that fasting was associated with favourable effects on lipid profile,[42] while a Tunisian study on patients with stable coronary artery disease reported similar positive effects from fasting.[43] However, findings for patients with diabetes were conflicting.[44] [45] [46]

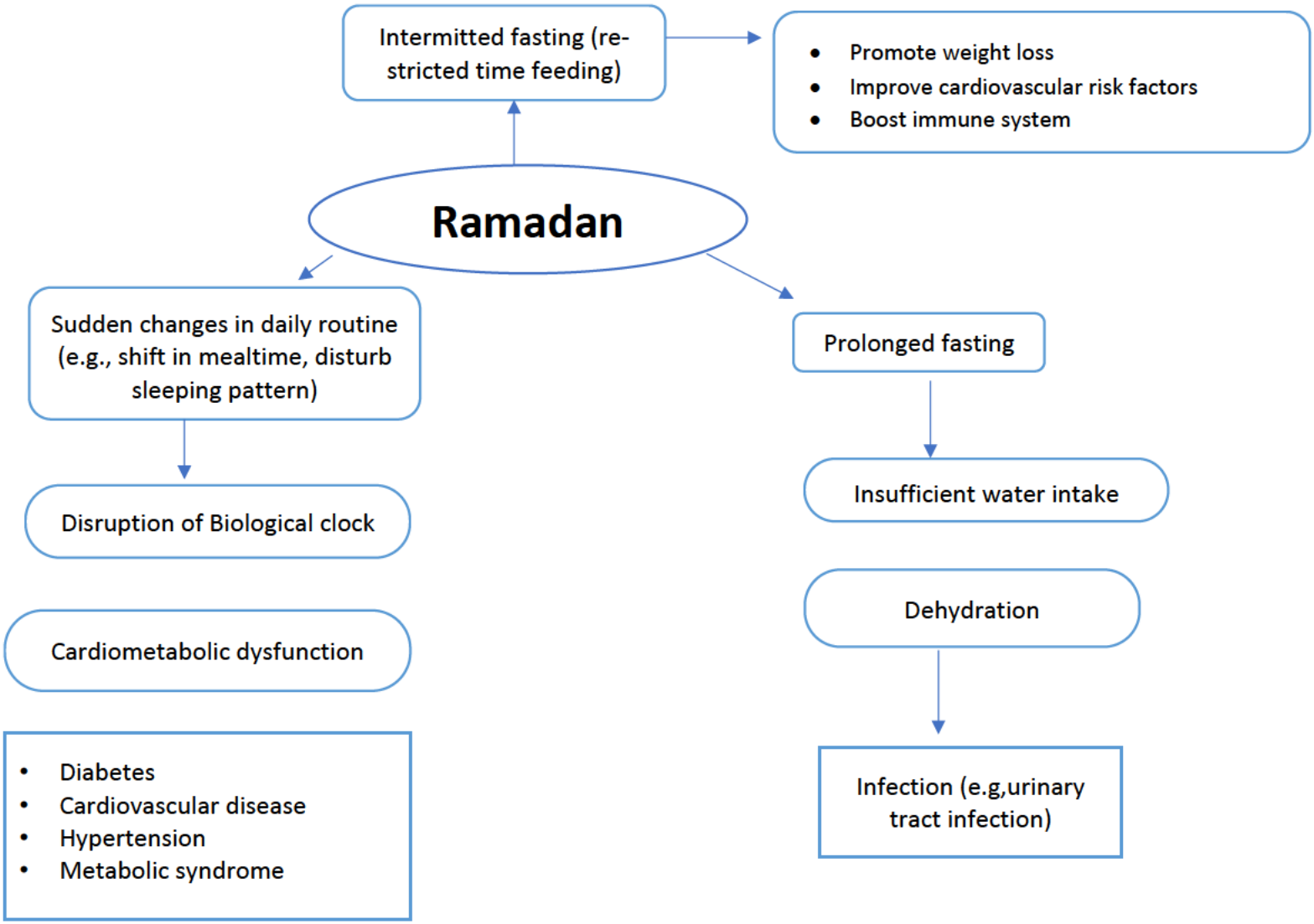

Figure 1: Potential mechanisms by which Ramadan fasting might influence health outcomes.

1.4.2 Effects of Ramadan Fasting on Body Weight

In theory, Ramadan provides an encouraging environment for weight loss, as it involves abstaining from food and drink for long hours for a whole month. Recently, intermitted fasting regime that involve regular periods with no or very limited caloric intake are promoted to as a useful strategy to lose wight. Studies showed that intermitted fasting can produce mild to moderate weight loss in participants with overweight and obesity.[47,48] However, Ramadan fasting is different from of fasting at Ramadan fasting last from sunrise to sunset with no food or drink for a whole month and fasting length or restrictions can not be modified as intermitted fasting .Morover,Ramadan has known as a month of fasting and feasting. In Ramadan, meals tend to be rich in fat (fried food) and sugars, and many of them are prepared specially for Ramadan. The question on the effect of fasting on body weight has been explored in several, albeit small, studies. Kul, Savaş [39] conducted a meta-analysis and showed a small significant weight loss in males (SMD = -0.24, 95% CI: -0.36, -0.12), but not in females. Another meta-analysis of 35 articles from different geographic locations found a significant reduction of weight by the end of Ramadan (-1.24 kg) in both genders (-1.51 kg in men and -0.92 kg in women).[49] However, this reduction did not last after Ramadan. The review pointed out that the reduction was more obvious in South Asian populations. This pattern of weight loss and re-gain among fasting individuals has been reported in a more recent systematic review and meta-analysis that investigated the effect of Ramadan fasting on healthy adults without introducing any change in term of diet and physical activity in Ramadan.[50] The review identified a positive association between BMI and weight loss, suggesting that those with higher BMI have the potential to lose more weight during Ramadan.

Jahrami, Alsibai [51] conducted a systematic review of 85 studies on the effects of Ramadan fasting on body weight. They reported that Ramadan fasting was associated with a significant reduction in body weight (-1.022 kg, 95% CI: -1.164 to -0.880 kg). Subgroup analysis did not find that either age or sex were correlated to the weight change; however, they identified that duration of fasting was positively associated with weight change at the end of Ramadan. suggesting that the longer the fasting time duration, the more substantial the reduction in body weight at the end of Ramadan.

1.4.3 Ramadan Fasting and its Effects on Patients with Diabetes

In general, Ramadan fasting is not associated with any risk in healthy people. But it can induce some risks in people with medical conditions, such as those with diabetes. In 2019, it was estimated that the number of people living with diabetes had reached 463 million.[52] It seems that the prevalence of diabetes is higher in countries with substantial Muslim populations and it is predicted to increase.[52] Despite being exempted, many people with diabetes choose to fast.[53] The Epidemiology of Diabetes and Ramadan (EPIDIAR) study, which included 12,914 patients in 13 countries, was one of the largest studies ever conducted to address the characteristics and management of diabetic patients during Ramadan.[54] The study found that 42.8% of people with type 1 diabetes and 78.7% of those with type 2 diabetes mellitus (T2DM) fasted for at least 15 days during Ramadan.[54] Similarly, CREED, a multinational retrospective study, reported that 94.2% of participants with T2DM fasted for at least 15 days, and 63.6% fasted for every day of Ramadan.[55] A more recent study conducted in the Middle East and North Africa regions (DAR-MENA T2DM) reported that 86% of participants fasted for at least 15 days and 57.3% fasted for the full duration of Ramadan.[56]

Due to the metabolic nature of the disease, people living with diabetes could be at greater risk of complications from marked changes in their food and fluid intake. Patients who choose to fast are at risk of developing complications such as hypoglycaemia, hyperglycaemia, dehydration and acute metabolic complications such as diabetic ketoacidosis (DKA).[57] The main risks reported with fasting are hypoglycaemia and hyperglycaemia. These complications are faced by people with diabetes on a daily basis. However, studies have shown that fasting may increase the risk.[54,55]

The effect of fasting on patients with diabetes during Ramadan is not fully understood due to the limited number of studies in this area.[34,58,59] Patients with diabetes are at high risk of complications, including hypoglycaemia, hyperglycaemia and dehydration. This risk is expected to increase in Ramadan due to the pattern of daytime fasting and nighttime meals, together with the use of anti-diabetic treatment.[60,61] The landmark EPIDIAR study found that the risk of severe hypoglycaemia increased 4.7-fold and 7.5-fold during Ramadan in patients with types 1 and 2 diabetes respectively, compared to non-fasting months.[54] The CREED study reported that approximately 8.8% of participants complained of at least one episode of hypoglycaemia during Ramadan.[55] In this study, although the need for hospitalisation was rare, about half the patients who experienced a hypoglycaemic episode required either assistance or had to break their fast.[55] The more recent DAR-MENA T2DM study reported that confirmed hypoglycaemia increased significantly in type 2 diabetic patients during Ramadan compared to before Ramadan , 10.4% - 4.9% respectively .[56] A study in Pakistan on 388 patients found episodes of hyperglycaemia in 35.29% and 23.18% of individuals with type 1 and type 2 diabetes, respectively.[62]

Similarly, higher hyperglycaemia rates have been reported during Ramadan. The EPIDIAR study reported a five-fold increase in the incidence of severe hyperglycaemia in patients with diabetes during Ramadan when compared to other months.[54] Ahmedani, Alvi [62] reported episodes of hyperglycaemia in 33.3% and 15.4% of individuals with type 1 and type 2 diabetes, respectively. There are some claims that Ramadan fasting may increase the risk of DKA.[57] However, a study conducted in the United Arab Emirates over 10 years did not find any difference in the incidence of DKA during Ramadan and other months.[63] Beshyah, Chowdhury [64] reviewed the literature claiming that Ramadan fasting could be associated with an increased risk of DKA and concluded that there is no evidence of increased risk of DKA during Ramadan. This non-systematic review highlighted that the increased episodes of DKA detected in earlier studies could be precipitated by factors unrelated to fasting. The more recent retrospective, prospective and database studies could not document any increase in observed DKA during Ramadan. It worth noted that this there is limited studies on DKA and Ramadan and that most of the reviewed studies were small, limiting their power in detecting any impact.

Different patients have different risks; therefore, it is recommended that those who plan to fast to consult their doctors and receive a treatment plan that is specific to their needs.[57-59,65] Evidence-based guidelines are extremely important in supporting the advice that is given to patients with diabetes planning to fast for Ramadan. Though the amount of research in this area has increased recently, there is still a lack of well-designed studies.[66] In the latest update to the IDF-DAR Diabetes and Ramadan Practical Guidelines, published in 2021, it was pointed that more studies are needed in this area as many questions remain unanswered.[67] One of the questions that has been raised is “is fasting associated with significant risks or benefits in

patients with diabetes?". There have been several attempts to summarise the available evidence on the effect of Ramadan fasting on cardiovascular risk factors. Currently the evidence suggests that Ramadan fasting could induce beneficial effects in healthy people. However, the effect on patients with diabetes is uncertain. Hence, in chapter four I tried to summarise and appraise the available evidence in this area through conducting a systematic review.

1.4.4 Ramadan Fasting and Cardiovascular Disease

The changes that happen during Ramadan to meal timings, as well as the quality and quantity of food intake, could affect body composition and metabolic profiles.[68] As I said earlier, there is increasing evidence that links intermittent fasting, time restricted feeding, and mealtime and circadian rhythm dysfunction to cardiometabolic risk.[69] Circadian rhythm dysfunction causes impaired cardiometabolic function, which can lead to increased risk of CVD.[23] Studies suggest that changes in mealtimes, particularly those that increase caloric intake at night, as practiced in Ramadan, may increase the risk of CVD.[23,31] On the other hand, studies on intermittent fasting suggest that intermittent fasting could be beneficial for cardiometabolic function and thus reduce risk of CVD.[70]

Several studies investigating the effect of Ramadan fasting on acute coronary syndromes suggest that there is no increased risk of cardiac events during Ramadan.[71-73] Two studies conducted in the Middle East on the effect of fasting on heart failure (HF) did not identify any differences in the admissions pattern during Ramadan and other months[74,75]

However, the findings on the effect of Ramadan on stroke were inconsistent. A retrospective study in Turkey reported a significant increase in ischemic stroke hospitalisations in Ramadan

compared to other months.[76] A study in Iraq suggested that Ramadan fasting is associated with a higher risk of stroke.[77] Similarly, a study in Israel found that the risk of stroke increased significantly in Ramadan and the association was greater in the first fortnight of Ramadan.[78] This association was not observed in the non-Muslim control group.[78] Conversely, other studies failed to find any significant association between fasting and risk of stroke.[79-82]

Unsafe fasting that include behaviours such as high carbohydrate intake, low physical activity, poor sleeping habits and poor medication compliance could increase the risk of cardiovascular events in high-risk patients such as those with diabetes.[67] A study conducted in Saudi Arabia on the effect of Ramadan fasting on HF found that those who were less rigorous in adhering to their medication requirements had worse symptoms.[83] Patients with diabetes are two to three times more likely to develop cardiovascular events compared to those without diabetes.[84] The available evidence suggests that hypoglycaemia could trigger cardiovascular events.[85] There are some suggestions that the risk of CVD increases as glucose levels increase, regardless of whether or not they reach the diabetic level.[86] However, studies on the effect of Ramadan fasting on cardiovascular events in patients with diabetes are scarce. There are few systematic reviews that have investigated the effect of Ramadan fasting on CVD,[87-89] and none that have investigated the risk of CVD with a focus on patients with diabetes. As a result, I chose to conduct a systematic review of the effect of Ramadan fasting on cardiovascular outcomes in patients with diabetes (chapter four).

It is suggested that Ramadan fasting induces beneficial effects on cardiovascular risk factors, such as weight reduction, improved lipid profile and glycaemic control.[42,88] This is supported

by findings from intermitted fasting studies. intermittent fasting improves multiple cardiovascular indicators in both animal and human, including blood pressure; resting heart rate, lipid profile; and insulin resistance.[90-92] However, Ramadan fasting has unique characteristics, which include the long duration of the practice for 1 month that may lead to some adaptations to new behaviours. Therefore, physiological changes in the first week of the month may not be similar to the changes at the end of the month. Additionally, the geographic location away from the equator affects the duration of light and dark cycles and hence the fasting hours. The available evidence suggests that there is no increased risk of cardiovascular events in Ramadan.[89,93] However, until recently, there has been no reliable evidence that is based on robust, well-designed research. One of the major issues to be noted is that most studies have small sample sizes and participants serve as their own controls. It is understood that it could be difficult to recruit participants in Ramadan, but there is a need to compare fasting to non-fasting individuals to make sure that any effect attributed to fasting is not due other factors. Apart from Zimhony, Abu-Salameh [78] no study added a control group in their analysis. This emphasises the need for better-designed studies in this area to better understand the effect of Ramadan fasting on CVD. Therefore, in this thesis I used a controlled interrupted time series design, which is considered one of the strongest quasi-experimental designs for evaluating the longitudinal effects of interventions/exposure. See chapter two for more details.

1.4.5 Ramadan fasting and immunity

The effect of Ramadan fasting on immunity is unclear. There are ongoing claims of the potential negative consequences of fasting due to dehydration. Prolonged fasting, particularly in the summer, may lead to dehydration which can increase the risk of infection.[94] Insufficient water intake and possible dehydration is one of the most compelling and challenging claims

that has been raised to link Ramadan fasting to susceptibility to infection. Though Ramadan fasting involves abstaining from food and fluid intake, there is no evidence supporting any detrimental effects on health directly attributable to negative water balance during Ramadan.[94]

There is increasing evidence that fasting enhances immunity and the body's ability to fight microbial agents.[95-97] A study was conducted on healthy people to test the body's ability to fight the pathogenic bacteria that cause Tuberculosis.[98] The study found that Ramadan fasting was associated with increased numbers of macrophages, which reduced the pathogenicity of the bacteria.[98] Evidence suggests that Ramadan fasting is associated with a reduction in pro-inflammatory cytokines (cytokines that promote inflammation) such as IL-1β, TNF-α, IL-6 and IL-8.[99,100] The changes that occur in the immune system during Ramadan are believed to be mild and transient, with it returning to its pre-Ramadan state shortly afterwards.[97]

The ritual and social behaviours that are practiced in Ramadan constitute another challenge that could increase the risk of infection. The month of Ramadan is not only a month of fasting, but also a social and devotional month. Attending social gatherings, usually for *iftar* meals, or attending religious gatherings such as *Tarawih* and *Tahajud* prayers, could increase the risk of contracting an infection.[95] Moreover, the nature of food consumed during Ramadan, which tend to be rich in sugar and fat, can weaken the immune system. Evidence suggests that such unhealthy food can increase the risk of infection.[101] Another behavioural risk factor that could affect immunity in Ramadan is the disturbance of sleep patterns. Evidence suggests that in Ramadan, sleep is reduced significantly by about one hour and diurnal sleepiness is in-

creased.[10] Insufficient sleep and sleep deprivation could weaken the immune system and increase susceptibility to infection.[102,103] Many Muslim populations have high burden of chronic disease, especially diabetes and CVD, and is therefore already at an increased risk of complications and infections.[104,105] Much uncertainty still exists about the risk of infection during Ramadan. No previous study has been conducted to explore the risk of infection during Ramadan in a Muslim population. Therefore, in chapter five I conducted a study to describe infection risk during Ramadan in a predominate Muslim population in the UK.

1.5 Muslims in the UK:

As Islam is the world's fastest-growing religion, Muslim populations are increasingly becoming part of many non-Muslim countries. In the UK, Islam is the second-largest religious group after Christianity. Muslims compromise about 5% of the UK population.[106] In the 2011 census , around 2.7 million people identified themselves as Muslims.[106] In 2016, the Pew Research Center estimated that there were 4 million Muslims in the UK, representing 6.3% of the UK population.[107]

The largest Muslim group in the UK consists of individuals from Asian backgrounds, who comprise 68% of the Muslim population.[108] The Muslim Asian population can be further subdivided as follows: 38.0% of British Muslims are Pakistanis, 14.9% are Bangladeshi and 7.3% are Indians. Pakistanis and Bangladeshis represent the largest Muslim ethnic group. The focus of this thesis will be on the Pakistani/Bangladeshi population as representative of the Muslims in the UK.

1.6 Rationale of the Thesis:

Fasting during Ramadan is an important practice for Muslims. Healthcare professionals should expect to deal with Muslim patients as part of their routine practice, as Islam is the second-largest religious group in the UK after Christianity. Healthcare providers taking care of Muslim patients may face difficulties in advising patients about the safety of fasting. Most of the available evidence and guidelines are based on experts' opinions.[67] Evidence-based guidelines are extremely important to support healthcare providers dealing with patients wishing to fast for Ramadan safely. Though there is increased interest in the impact of Ramadan fasting on health, there is a major concern in that most of the available studies are conducted in small observational settings that lacked proper quality assurance and internal and external validation.[34] This thesis is exploratory in nature. I chose to explore different aspect to widen the knowledge in this area rather than only focusing in one area. Exploring different aspects enables me to learn and use different methods and analysis. leading to gain much experience through the PhD journey. It is acknowledged that there are other health aspects that worth exploring in Ramadan, however cardiovascular outcomes and infections were specifically focussed on and prioritised for this thesis over other potential health outcomes as there is a gap in the knowledge in these two areas. I recent review on the recommendation for patients with CVD in Ramadan emphasized the lack of studies in this area and the need for more research on the safety of Ramadan fasting on CVD .[109] Studies on infections in Ramadan are scare, recently there is increase interest in the area with the COVID-19 pandemic.[110] Moreover, data accessibility and availability played an important role in the choices of outcomes for this thesis.

Aims and objectives:

The aims of this thesis are (1) to assess the impact of Ramadan fasting on different aspects of health (2) to strengthen the available evidence on the effect of Ramadan fasting on health using robust methods that have not previously been employed in Ramadan research.

Objectives:

- To describe the cardiometabolic profile in a predominant Muslim population in the UK (chapter three).
- To review the literature on Ramadan and CVD risk in patients with diabetes (chapter four).
- To assess the risk of infection before, during and after Ramadan in a predominant Muslim population in the UK using a controlled interrupted time series design (chapter five).
- To estimate the incidence of hospital admissions for ischemic heart disease (IHD) before, during and after Ramadan in a predominant Muslim population in the UK using a controlled interrupted time series design (chapter six).

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2 Chapter two: General method

2.1 Contents of chapter two

This thesis consists of four studies using three underlying methods: a retrospective cohort study, a systematic review and two interrupted time series (ITS) analyses. This chapter will provide an overview of the methods used in the thesis. Data for the retrospective cohort study and one controlled interrupted time series analysis were derived from 'The Health Improvement Network' (THIN), while data for the other controlled interrupted time series study came from the University Hospitals Birmingham (UHB), UK. This chapter will give an overview of the data and methods used in this thesis. More details on the methods will be available in each study.

2.2 Overview of THIN

Two studies used data from The Health Improvement Network database (THIN): a retrospective cohort study (chapter 3) and a controlled interrupted time series analysis (chapter 5). The THIN database is a large database of primary care records from UK general practices that use Vision electronic health record software. It includes data for approximately 17 million patient records over the last three decades in over 750 primary care practices. It is estimated that THIN covers 6% of the total UK population at a given time point (active patients)[1]. THIN provides longitudinal records with data on sociodemographic characteristics, diagnoses, medical tests, results, prescriptions and additional information (e.g. lifestyle). It uses a hierarchal coding system, called ReadCodes, for diagnosis. Prescriptions are currently entered using Multilex codes issued by First Databank, which can easily be linked to British National Formulary (BNF) codes. It is representative of the UK population in terms of demographics

and prevalence of the major medical conditions. Therefore, it is believed to be a valid source of data for epidemiological studies in the UK.[1]

Data were extracted through DExtER, a tool developed at the University of Birmingham for epidemiological research. DExtER is softwere that applies an extract, transform and load mechanism to extract data.[2] To facilitate the extraction process the study should be designed with well-defined set of inputs. DExtER requires the definition of the following inputs to initiate the extraction process[2]: study period, study population, exposed and unexposed groups, matching criteria, study variables (baseline characteristics and outcome of interest), and patient exit date.

2.3 University Hospitals Birmingham database

In chapter six I used anonymised hospital data as data source. The data obtained from the UHB. UHB is a large teaching hospital trusts in England (approximately 1200 beds). The data were extracted from Prescribing Information and Communications System (PICS), which is an IT system created by UHB NHS Foundation Trust. The Office for National Statistics (ONS) estimates that Birmingham's resident population was 1,141,800 in 2019.[3] Birmingham is the largest Local Authority District and is home to around 20% of residents in the West Midlands[4]. With an ethnic composition of; White (57.9%),Pakistani (13.5%),Indian (6.0%), Caribbean (4.4%) Bangladeshi (3.0%), African (2.8%),Chinese (1.2%) other ethnicity (11.1%).[5] It is estimated that Muslims represent about 7.5% in Birmingham making Islam the 2nd largest religion in Birmingham.[4] Birmingham is one of the UK's most diverse city in the UK and it contains large Muslim communities [6] , Therefore it was an appropriate place for the study.

2.4 Systematic review study design

Systematic review is a multistage process used to appraise and synthesize evidence on specific questions in a systematic and standardised manner.[7,8] In chapter four I conducted a systematic review to summarise the available evidence on the effect of Ramadan fasting on cardiovascular events and risk factors in patients with diabetes.

To minimise potential bias in the review process, it is suggested that one should publish a detailed protocol before starting the review.[9] Registering systematic reviews before starting the review reduces duplication efforts, allow peer review of planned methods, promotes transparency and reduces publication bias.[9,10] The protocol developed for the systematic review in this thesis is registered under PROSPERO CRD42018096018.

Systematic reviews undergo different stages and involve many judgements. The key stages of systematic review are as follows:

2.4.1 Defining eligibility criteria

One of the features that distinguishes a systematic review from a narrative review is that a systematic review use pre-specified criteria for including and excluding studies in the review.[9] These criteria are specified before conducting the review in the protocol. In my case, the population (patients with diabetes), exposure (Ramadan fasting), comparator (non-fasting patients/period) and outcome (cardiovascular events and risk factors for cardiovascular disease) components of the question helped in setting the eligibility criteria of the systematic review. Details on inclusion and exclusion criteria are available in chapter four.

2.4.2 Searching for studies

Search strategy in systematic reviews should be comprehensive, objective and reproducible.[9] Therefore, a search strategy based on the eligibility criteria was developed in the early stage of planning the review. The literature suggests searching more than one database to avoid selection bias[9]: for this study, I searched key medical databases (Embase, Medline, Cochrane library and CINAHL).The search strategy was broad to increase its ability to capture relevant studies that could have been missed in other reviews. There was no language restriction.

2.4.3 Study selection

The study selection was only performed by one person. It is understood that this step should be conducted by two person and that this is a limitation of the review. All articles identified in the search stage were retrieved to a reference manager (EndNote X8) to facilitate the handling of records. Through EndNote X8 all duplicates were removed. The remaining titles and abstracts were then scanned to identify eligible studies. Decisions to select articles for further assessment were based on the pre-specified eligibility criteria. Those studies that failed to meet the criteria were excluded. Full texts of potentially eligible studies were retrieved for further scanning to check their compliance with eligibility criteria.

2.4.4 Data extraction

Data extraction is the process by which researchers obtain the necessary information about study characteristics and their findings from the included studies. I planned in advance what data would be collected for the systematic review. The study question determined what information would be extracted from the included studies. The following data were extracted

from each study to provide an idea of the characteristics of the included studies: study authors, study location, Ramadan season, study period, sample size (and male percentage), and age of participants. In terms of outcome data, the following items were extracted: cardiovascular events (the incidence of stroke, congested heart failure (CHF), myocardial infarction (MI) Unstable angina, acute coronary syndrome); and cardiovascular risk factors (Cholesterol, Triglycerides, HDL, LDL, blood pressure, HBA1c, glucose and BMI). As recommended[9,11], I constructed standardised forms to facilitate the extraction process. These forms were previously piloted on randomized selected studies to ensure that data extraction was performed in a structured manner. To minimize any risk of bias and avoid mistakes in extractions[9], a second reviewer was included at this stage. Differences between reviewers were resolved by returning to the main text or in discussion with my supervisors.

2.4.5 Assessing studies' quality

Appraising the quality of the included studies is an important step in conducting systematic reviews. There are many tools available for assessing study quality. There are different tools available to use. However, most of them are for randomised or interventional studies, which did not fit with the review question. Therefore, for this review, ROBINS-E was considered[12] and modified accordingly. It is recommended that this stage is done by two reviewers independently to reduce bias.[9] Two reviewers therefore evaluate the risk of bias in each study; disagreement were resolved with discussion. The tool contains seven domains (selection of participants, confounding variables, classification of exposure, departure from the intended exposure, measurement of outcomes, incomplete outcome data, and selective outcome reporting) with scores of low, moderate, serious, critical, and not clear.

2.4.6 Data synthesis

Meta-analysis was not appropriate for this review because of the high heterogeneity (I^2 > 80%). It is recommended not to conduct a meta-analysis if I^2 is >50%.[13] The I^2 is a statistic that indicates the percentage of variation across studies due to heterogeneity rather than chance. Hence, narrative synthesis was used for analysis. Tables were used to present the findings. Similarities and differences between the studies were highlighted. Separate analyses of the findings were conducted for both cardiovascular outcomes and cardiovascular risk factors.

2.5 Cohort study design

2.5.1 Study design

In chapter three I calculated the risk rate of developing different cardiometabolic events :T2DM, HTN, IHD, HF, stroke, and atrial fibrillation (AF) in the South Asian population in the UK by conducting a matched retrospective open cohort study. The study period was set from 1st January 2007 to 31st December 2017. Although it may have been possible to obtain more data and hence a bigger sample size by including data from earlier years, I chose only to include data post 2007 to ensure I had good-quality data. This was because the study was based on ethnicity records. Based on the current suggestion that the missing ethnicity records could comprise up to 50% of the data (pre-1990 to the latest available date), I chose 2007 as the start of the study. This suggestion is based on a published exploration of ethnicity recording in primary care data that noted that by 2007, the proportion of patients with a recorded ethnicity was 78.3%.[14] Ethnicity recording was incentivised by the Quality and Outcomes Framework between 2006/7 and 2011/12, leading to a substantially-reduced burden of missing data.[14] It is estimated that proportion of patients with at least one usable ethnicity record

ranged from 27% for the whole dataset to 76% for patients registered from 2006 onwards.[14] With this in mind, when we requested the data extract from the data providers, we were confident that the burden of missing ethnicity in the total dataset was substantially less than 50%.

A cohort study follows participants from the presence of an exposure to the presence of an outcome.[15] Open cohort studies are dynamic, allowing participants to enter or exit the study at different time points, meaning that participants can leave or be added over the study period.

To calculate the time at risk (denominator), the person-year of follow up for each participant is calculated as the time between their enrolment to the study (index date) to the time they leave the study (exit date).

2.5.2 Study population:

The study in chapter three consisted of two main groups: South Asian and White ethnic groups. For additional subgroup comparison analysis, the South Asian group was subdivided into Indian, Pakistani, and Bangladeshi. Therefore, the cohorts were selected through relevant Read Code for South Asian ethnicity (Indian, Pakistani, Bangladeshi) and White. The most recent ethnicity record was used when there were multiple ethnicity records.

Patients were eligible to enter the study one year after their registration. This latent period was introduced so that there was sufficient time to upload historic records prior to their transfer. General practices were eligible to contribute to the study one year after they had acceptable mortality reporting (AMR). AMR is the year from which a practice's mortality records are considered complete.[16] This is important as it affects patient follow-up time.

2.5.3 Matching controls

The South Asian and White groups were matched 1:2 by age, gender, Townsend deprivation index quintile, and study index year. One of the limitations of observational studies is the lack of randomization. As a result, the characteristics of the participants in the studied group could be systematically different, which may lead to biased results. Matching is a method used in observational studies to minimize biases and confounding factors.[17] This allows a balance in the distribution of covariates between the studied groups. There are two commonly used methods in matching: exact matching and propensity score matching.[18,19] The exact matching method involves pairing participants from the studied groups on key variables of interest, ensuring that the paired patients have exactly the same values on all the covariates. However, in this method there is a chance of excluding patients that do not match, reducing the sample size and variability of the population.[19] Patients that are excluded may represent specific populations that could not be captured due the exact matching. Therefore, to increase the sample size and study power, I used propensity score matching. Previous literature has evaluated the impact of using different matching approaches in healthcare data and suggests that they generally produce similar results.[17,20]

2.5.4 Setting index and exit date

The index date is the time point where patients enrolled in the study and start contributing person-years of follow-up to the dataset. The index date was set as either one year after patient registration with the practice or the date the practice was eligible to contribute, whichever was the latest. This helped to ensure consistent data quality and provide adequate time to record historical covariates.

The exit date is the time point at which the patient exited the study and stopped contributing person-years of follow-up. The exit date was set as the earliest of these possible dates: patient transfer from practice (when patients moved to other practices and were censored from the dataset), death date, date the practice ceased contribution to the THIN database, date of outcome of interest or study end date.

2.5.5 Statistical analysis

Baseline characteristics data is described using different descriptive statistics. Mean and median were used for continuous data, while proportion was used for categorical data. Based on statistical advice, missing data was included in the regression model as missing category. Logistic regression was used to calculate the odds ratio (OR), to describe the odds of having the outcomes of interest at baseline. The Cox regression model was used to calculate the Hazard Ratio (HR) for the different outcomes of interest during follow-up. To ensure that the HR reflected outcomes which occurred following cohort entry, patients with pre-existing outcomes of interest at baseline were excluded. In order to account for confounders, a multivariable regression analysis was conducted to calculate an adjusted estimate. Multivariable regression analysis is a model-based method used to control for confounding and can control multiple confounding factors simultaneously.[21]

2.6 Interrupted time series (ITS)

Chapters five and six constitute the main work of this thesis. I used an interrupted time series design to investigate the effect of Ramadan fasting on antibiotics prescriptions and IHD hospitalizations. I applied this method to two different data sources. In chapter five I used data

from the THIN database to describe trends in antibiotics prescriptions before, during and after Ramadan, while in Chapter six I used hospital data from UHB. This is the first time interrupted time analysis design has been applied to research on the effect of Ramadan fasting. Most of the available evidence is based on small studies or observational studies that lacked a robust design. Conducting a randomized control study is challenging and unethical as Ramadan fasting is a holy practice for Muslims. Meanwhile, recruiting those who are not fasting as a control group in an observational study might bias the findings, as these individuals are likely to be exempted from fasting due to health issues. ITS is an increasingly-used design in public health research that adopts an approach that allows for comparisons to be made over time within single populations.[22,23] Interrupted time series is the one of the strongest, quasi-experimental designs to evaluate longitudinal effects exposure, particularly when randomised controlled trials are not possible. It is for this reason that I chose to apply this method in my thesis.

2.6.1 Features of the interrupted time series design

ITS analysis is a quasi-experimental design that can evaluate an exposure effect using longitudinal data. The term 'quasi-experimental' refers to an absence of randomisation. ITS analysis is a tool for analysing observational data when randomisation or a cohort design are not possible. ITS analysis requires data on continuous or counted outcome measures, summarised at regularly-spaced temporal intervals.[23] This model often uses before-and-after comparisons for underlying trends and is particularly useful for assessing the impacts of policies or healthcare initiatives. It can provide information on any changes that could have occurred due to the exposure, whether immediately or over time. Here, the pre-intervention period acts as the control.[24] In this design there is only one group and the comparison is made between the pre- and post-trends. One of the advantages of observing the population over time

is avoiding biases that could develop between group differences, such as selection bias or unmeasured confounders.[24] However, this design cannot exclude the effect of confounders or events that occurred in the same time period as the exposure under investigation (the so-called history bias), which threaten the internal validity of the study. The literature suggests that adding a control group will minimize this bias and strengthen the study design.[24]

2.6.2 Interrupted time series analysis

In general, the same method was applied to both studies in chapters five and six. In both studies there were two groups. The first group comprises a Pakistani/Bangladeshi population who represent the Muslim population. The second is the White population who represent the control group, as this is a population that are unlikely to observe Ramadan month (i.e., they offer a characteristic-based control[24]).

ITS analysis requires clear definitions of the pre- and post-exposure periods. The timing of Ramadan is based on the lunar calendar, in which calendar months can last for 29 or 30 days, depending on the sighting of the moon. I standardised the length of the months to 30 days. I identified the start of Ramadan in each year included in the studies (Table 1), then identified 30 days before Ramadan, the 30 days of Ramadan, and 30 days after Ramadan. I only included 90 days each year for the study as I was only interested in these three periods (before, during and after Ramadan).

Table 1: Start day of Ramadan from 2007 to 2019

Year	Start day of Ramadan
2007	13-Sep
2008	01-Sep
2009	22-Aug
2010	11-Aug
2011	01-Aug
2012	20-Jul
2013	09-Jul
2014	29-Jun
2015	18-Jun
2016	07-Jun
2017	27-May
2018	17-May
2019	06-May

The impact of an exposure is commonly described in terms of a change in level (or intercept), a change in slope (or trend), or a change in both level and slope (figure 1). A change in level can be describe as a jump or drop in the outcome after the exposure, constituting a sudden change in the outcome. A change in trend is defined by an increase or decrease in the slope after the exposure as compared with the period before the exposure.[23,24]

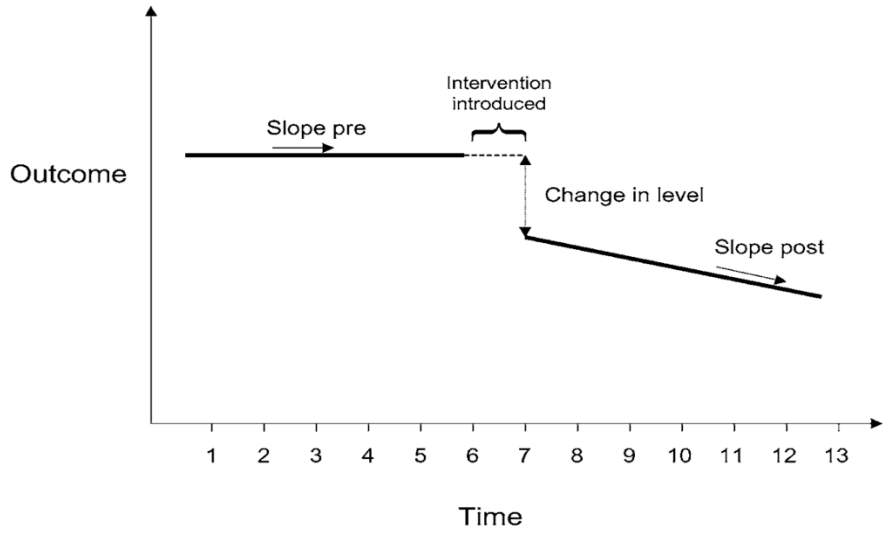

Figure 1: Level and slope changes in interrupted time series design study. Adapted from Ramsayet.al [25]

A sufficient number of time points before and after the exposure is needed to conduct regression analysis. The Literature recommends having at least 8 time points before and 8 time points after the exposure to have a sufficient power for the regression model.[26] In the main analysis the time unit is the day: consequently, I had 30 time points before and 30 time points after. An exception to this was in the stratified analysis conducted in the hospital data study (chapter six), I had to aggregate five days' data together (from 30 time points to 6 time points), to avoid zero outcomes (hospitalization) for some of the days.

Two analyses were performed. The first is single interrupted time series analysis and the second is controlled interrupted time series analysis (Figure 2). The first one tracks changes

within a group before and after the exposure, limiting the selection bias and confounding effects that could happen as a result of between-group differences.[24,27] In this analysis it can prove difficult to distinguish the effect of the exposure from other confounding effects that could have happened at the same time. In other words, if there is a change in the outcomes observed (antibiotics prescriptions or hospital admissions), we can't confirm if this is due to the exposure (Ramadan fasting) or another external factor. Adding a control group helps to separate the effect of the exposure from other confounding effects that could have occurred at the same time[24,27]: this method is called controlled interrupted time series analysis.

1. Single interrupted time series analysis

A minimum of three variables are required for an ITS analysis:

- T is the time since the start of the study (e.g., day, month or year);
- X_t is a dummy (indicator) variable representing the intervention (pre-intervention periods equal 0, otherwise 1); and
- Y_t is the aggregated outcome variable measured at each equally spaced time point t.

The following segmented regression model is used for standard ITS analysis:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \varepsilon_t$$

where β_0 represents the baseline level at T = 0; β_1 represents the change in outcome associated with a time unit increase (representing the underlying pre-intervention trend); β_2 is the level of change following the intervention; β_3 indicates the change in slope pre- and post-intervention; and ε_t is an error term.

2. Controlled interrupted time series (CITS) analysis

A minimum of four variables are required for a CITS analysis:

- T is the time since the start of the study (e.g., day, month or year);
- X_t is a dummy (indicator) variable representing the intervention (pre-intervention periods equal 0, otherwise 1);
- Z_t is a dummy variable to denote the cohort assignment (treatment or control); and
- Y_t is the aggregated outcome variable measured at each equally spaced time point *t.*

The controlled interrupted time series model is indicated by the following equation:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \beta_4 Z_t + \beta_5 Z_t T + \beta_6 Z_t X_t + \beta_7 Z_t T X_t + \varepsilon_t$$

where β_0 to β_3 represent the control group and β_4 to β_7 represent the treatment group. β_4 represents the difference in level between treatment and control prior to the intervention. β_5 represents the difference in the slope between treatment and control prior to the intervention. β_6 represents the difference in level between treatment and control in the period immediately following the intervention initiation. β_7 represents the difference between the treatment and control in the slope after the intervention was initiated, compared to the pre-intervention period. ε_t is an error term.

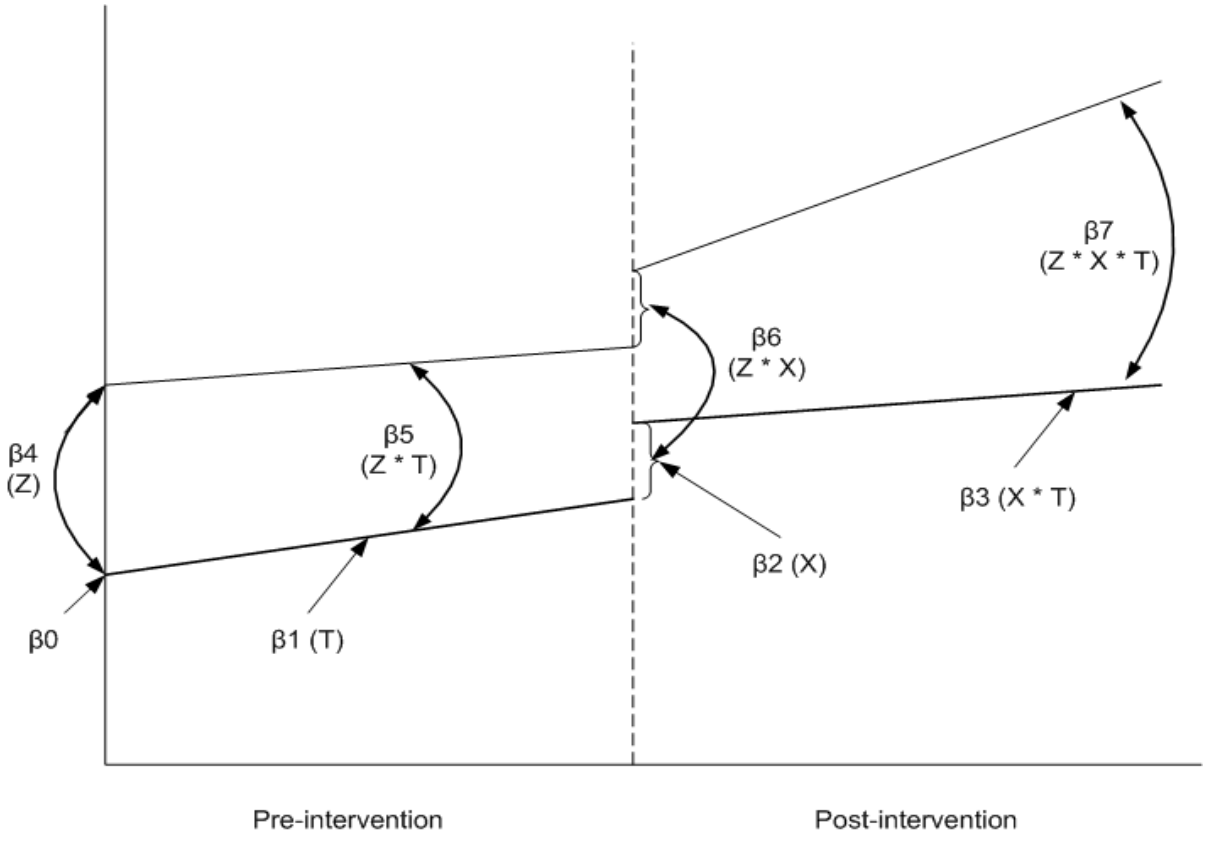

Figure 2: Visual illustration of single interrupted (lower line) and control interrupted (upper and lower lines) time-series design. Adapted from Lindenet.al [28]

2.7 Summary:

In chapter 3 for the objective of exploring the Pakistani/Bangladeshi population I am using THIN database with retrospective cohort design to assess the differences in health outcomes in these ethnic group compared to the white ethnic population. In chapter 4 for the objective of summarise the available evidence on the effect of Ramadan fasting on CVD and risk factors in patients with diabetes I am using the systematic review method. While for objective of exploring the impact of Ramadan fasting on antibiotics prescriptions and IHD, I am using controlled interrupted time series with THIN for chapter 5 and UHB data for chapter 6.

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3 Chapter three: Cardio-metabolic outcomes in South Asians

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Cardio-metabolic outcomes in South Asians compared to White Europeans in the United Kingdom: a matched controlled population-based cohort study

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Abstract

Background: There appears to be an inequality in the risk of cardio-metabolic disease between those from a South Asian (SA) background when compared to those of White Europeans (WE) descendance, however, this association has not been explored in a large European cohort. This population-based open retrospective cohort explores the incidence of cardio-metabolic disease in those without pre-existing cardiometabolic disease taken from a large UK primary care database from 1st January 2007 to 31st December 2017.

Methods: A retrospective open cohort matched population-based study using The Health Improvement Network (THIN) database. The outcomes of this study were the incidences of cardio-metabolic events (type 2 diabetes mellitus, hypertension, ischemic heart disease, stroke, heart failure, and atrial fibrillation).

Results: A total of 94,870 SA patients were matched with 189,740 WE patients. SA were at an increased risk of developing: T2DM (adjusted hazard ratio (aHR) 3.1; 95% CI 2.97–3.23); HTN (1.34; 95% CI: 1.29–1.39); ischaemic heart disease (IHD) (1.81; 95% CI: 1.68–1.93) and heart failure (HF) (1.11; 95% CI: 1.003–1.24). However, they were at a lower risk of atrial fibrillation (AF) (0.53; 95% CI: 0.48–0.59) when compared to WE. Of those of SA origin, the Bangladeshi community were at the greatest risk of T2DM, HTN, IHD and HF, but were at the lowest risk of AF in when compared to Indians and Pakistanis.

Conclusion: Considering the high risk of cardio-metabolic diseases in the SA cohort, differential public health measures should be considered in these patients to reduce their risk of disease, which may be furthered tailored depending on their country of origin.

Keywords: Cardiovascular disease, Hypertension, Type 2 diabetes mellitus, South Asian

Background

The risk of type 2 diabetes is higher in South Asian (SA) populations resulting in an increased risk of macrovascular and microvascular complications, except for neuropathy and diabetic foot [1, 2]. The UK SA population is diverse with a number of sub-ethnicities, varied cultural-religious practices and lifestyle choices which may have an impact on their risk factors for CVD [3]. Indians are

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thought to be the most physically active group among SA, while Bangladeshis are the least active [4]. Bangladeshi men have the highest prevalence of smoking, whereas alcohol consumption is lower among Bangladeshi and Pakistani communities [5, 6]. A study in Newcastle reported that Bangladeshis are the most socio-economically disadvantaged group and have the highest CVD risk profile among Indians, Pakistanis and White Europeans (WE) [3]. Nazroo [7] has shown that SAs do not share the same risk of CVD development. One study (including 2867 WEs, 2001 Indians, and 1776 Pakistanis and Bangladeshis participants) identified Indians having a similar prevalence of CVD compared to WE with Pakistanis and Bangladeshis having a higher prevalence. However, these findings could be limited as CVD was self-reported.

Understanding the relationship between ethnicity and cardio-metabolic disease is essential as this could help with screening, prevention and management strategies. Hence, a population-based study was conducted aimed at comparing the cardio-metabolic outcomes between SAs and WEs in the UK. Our secondary aim was to compare cardio-metabolic outcomes in SA subgroups, namely Indians, Pakistanis and Bangladeshis.

Method

Study design and data source

A retrospective matched population-based open cohort study was carried out using The Health Improvement Network (THIN), an electronic UK primary care database. The database contains data from 787 primary care practices. THIN is a large database covering approximately 6% of the UK population and is demographically representative of the UK population [8]. The crude prevalence of major chronic conditions and death rates adjusted for demographics and deprivation in THIN are comparable to national estimates [9]. THIN provides longitudinal records with data on sociodemographic characteristics, diagnoses, medical tests, results, prescriptions, and additional information using a hierarchal clinical coding system, called Read Codes [10]. IQVIA provided THIN data access to the University of Birmingham. Use of IQVIA Medical Research Data is approved by the UK Research Ethics. In accordance with this approval, the study protocol was reviewed and approved by an independent scientific review committee (reference number: 18THIN071). IQVIA Medical Research Data incorporates data from The Health Improvement Network (THIN), a Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care. Data extraction was facilitated using the Data Extraction for Epidemiological Research (DExtER) tool [11].

Population and follow-up period

The study period was 1st January 2007 to 31st December 2017. The year 2007 was chosen as the starting point as the completeness of ethnicity data had greatly improved due to payment incentivised introduced recording of ethnicity in the Quality and Outcomes Framework in the financial year prior [12]. The inclusion criteria were patients: > 35 years old and had recorded ethnicity data.

The exposed cohort consisted of patients who had a GP inputted Read Code for SA ethnicity (self-reported). Those defined as a mixed ethnicity were excluded from the exposed and control cohorts.

Although in this study we examined the risk associated with self-determined ethnicity, future research may also wish to explore the risk stratified by country of birth.

Exposed patients were matched 1:2 by propensity scores to WE controls by age, gender, Townsend deprivation index quintile, and study index year.

The index date was set as the date one year after patient registration with the practice or the date the practice was eligible to contribute. These criteria ensured consistent data quality and adequacy of covariate recording. Practices were eligible to contribute to the study on the later of one year after the date practice started using electronic medical records or one year after the practice was deemed to have been recording data acceptably as evidenced by acceptable mortality recordings [13]. The exit date was set at earliest date among dates of patient transfer from practice, death date, date the practice ceased contribution to the THIN database, outcome event date or study end date.

Outcomes and covariates

The primary outcome of this study was the incidence of cardio-metabolic events: type 2 diabetes mellitus (T2DM), hypertension (HTN), ischaemic heart disease (IHD), stroke/transient ischaemic attack (TIA), heart failure (HF) and atrial fibrillation (AF). Outcomes were identified by the presence of a Read corresponding to one of these conditions.

Covariates that could impact the development of the outcomes were reported at baseline. These included age at index date, gender, body mass index (BMI), blood pressure, lipid profile, smoking status, and Townsend deprivation quintile. Potential confounders were used as model covariates and were selected on the basis of biological plausibility [14–18].

Patient and public involvement

Patients and the public were not involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. Patients or the public were not asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants, the relevant patient communities or the public.

Statistical analysis

Baseline characteristics of both SA and WE patients were reported using appropriate descriptive statistics (mean and standard deviation (SD) or median and interquartile range (IQR) for continuous data and proportions for categorical data). Logistic regression was used to calculate crude and adjusted odds ratios (OR and aOR, respectively) for outcomes of interest that were present at baseline. ORs were calculated with 95% confidence intervals (95% CIs) and statistical significance was set at $p < 0.05$. Hazard ratios (HR) and 95% CIs were calculated using Cox regression models for outcomes of interest during the follow-up period. For each outcome, patients with a record of the outcome at baseline were excluded. Adjusted hazard ratios (aHR) for cardio-metabolic outcomes were calculated after adjustment for the baseline covariates listed above. In additional analysis, interactions between ethnicity and age, and ethnicity and sex were examined for each outcome.

Variables were complete except for Townsend score, smoking status, BMI, lipid profile and blood pressure. For Townsend score, BMI, and smoking status, missing indicator categories were used in the adjusted analyses. BMI was treated as a categorical variable and grouped into normal weight (18.5–25 kg/m^2), overweight (25–30 kg/m^2) and obese (> 30 kg/m^2).

A sensitivity analysis was conducted using lower BMI cut points for SA patients as proposed in the literature: normal weight (18.5 to 23 kg/m^2), overweight (23–27.5 kg/m^2) and obese (> 27.5 kg/m^2) for SA [19]. STATA v14.2 was used for statistical analysis.

Table 1 Baseline characteristics of the South Asian and White European populations

Characteristic	South Asian (n = 94,870)	White (n = 189,740)
Male, n (%)	49,795 (52.49)	99,594 (52.49)
Age, years, median (IQR)	41 (35 to 53)	41 (35 to 52)
BMI, mean (SD)	26.2 (4.8)	26.8 (5.6)
BMI category, n (%)		
18.5–25 kg/m^2	35,963 (37.91)	68,996 (36.36)
25–30 kg/m^2	31,909 (33.63)	56,424 (29.74)
> 30 kg/m^2	14,878 (15.68)	37,736 (19.89)
Missing	12,120 (12.78)	26,584 (14.01)
Smoking, n (%)		
Smoker	11,656 (12.29)	52,526 (27.68)
Ex-smoker	8459 (8.92)	40,761 (21.48)
Non-smoker	72,551 (76.47)	91,884 (48.43)
Missing	2204 (2.32)	4569 (2.41)
Townsend, n (%)		
1	10,490 (11.06)	22,496 (11.86)
2	10,682 (11.26)	23,429 (12.35)
3	17,959 (18.93)	35,916 (18.93)
4	20,575 (21.69)	38,745 (20.42)
5	16,069 (16.94)	30,186 (15.91)
Missing	19,095 (20.13)	38,968 (20.54)
Lipid profile		
Total cholesterol (mean (SD))	4.9 (1.05)	5.1 (1.01)
Triglycerides (median (IQR))	1.4 (1 to 1.96)	1.3 (0.9 to 1.89)
HDL (mean (SD))	1.26 (0.35)	1.4 (0.42)
Blood pressure, (mean, (SD))		
Systolic	124.1 (16.15)	126.5 (15.6)
Diastolic	76.7 (9.9)	77.57 (9.8)
Comorbidities, n (%)		
Type 2 diabetes	11,487 (12.11)	8052 (4.24)
Hypertension	14,306 (15.08)	22,670 (11.95)
IHD	4135 (4.36)	5061 (2.6)
Stroke or TIA	1283 (1.35)	2812 (1.48)
Heart failure	562 (0.59)	837 (0.44)
Atrial fibrillation	457 (0.48)	1824 (0.96)
Medication, n (%)		
Lipid-lowering drugs	16,311 (17.19)	20,608 (10.86)

Results

Baseline characteristics

A total of 94,870 SA patients were identified in the dataset and matched to 189,740 WEs. Characteristics of both populations are described in detail in Table 1. Across the entire study the population at baseline was 52.49% were male; median (IQR) age was 41 (35 to 52) years; mean (SD) BMI was 26.6 (5.3) kg/m^2. Matching parameters of age, gender, and Townsend deprivation quintiles were similar between the groups. Compared to the SA cohort, the WE cohort contained more smokers, had higher levels of total cholesterol and HDL and higher blood pressure, whereas increased overall levels of triglyceride were found in SAs. The SA patients had a higher proportion of patients with IHD, HTN, HF, and T2DM compared to the WE patients at baseline. SAs experienced less AF and stroke/TIA. Median follow-up was 4.3 (IQR 1.7 to 7.4) and 4.2 (IQR 1.7 to 7.4) years, for SAs and WEs, respectively.

Ethnicity and prevalent cardio-metabolic disease at baseline

Following adjustment, SAs were more likely to have T2DM (aOR 3.89, 95% CI: 3.75–4.02), HTN (aOR 1.16, 95% CI: 1.13–1.20), and IHD (aOR 1.68, 95% CI: 1.60–1.77), compared to WEs at baseline. SAs were less likely to have AF (aOR 0.44, 95% CI: 0.39–0.49) and stroke/TIA (aOR 0.84, 95% CI: 0.77–0.90) at baseline compared to WEs. The study did not find an association between ethnicity and HF at baseline (aOR 1.1, 95 CI%: 0.97–1.25) (Fig. 1).

Risk of incident cardio-metabolic disease

Results are presented in Table 2 and Fig. 2. In the longitudinal analysis, SAs developed 5160 (6.2%) new diagnoses for T2DM compared to WEs who developed 4530 (2.5%) new events. Following adjustment for age, gender, smoking status, BMI category, Townsend deprivation quintile and hypertension, SAs remained at an increased risk of developing T2DM compared to WEs (aHR 3.10; 95% CI: 2.97–3.23, $p < 0.001$).

SAs developed 4998 (6.20%) new diagnoses of HTN compared to 8152 (4.88%) new diagnoses in WEs. After adjusting for age, gender, smoking status, BMI category, Townsend deprivation quintile and T2DM, SAs remained at an increased risk of developing HTN compared to WEs (aHR 1.34; 95% CI: 1.29–1.39, $p < 0.001$).

There were 1720 (1.90%) new IHD diagnoses in SAs compared to 2084 (1.13%) in WEs. After adjustment for age, gender, smoking status, BMI category, Townsend deprivation quintile, hypertension and T2DM, SAs remained at increased risk of developing IHD compared to WEs (aHR 1.81; 95% CI: 1.68–1.93, $p < 0.001$).

Compared to the 988 (1.06%) stroke / TIA events in SAs, there were 1938 (1.04%) stroke /TIA events in WEs. After adjustment for age, gender, smoking status, BMI category, Townsend deprivation quintile, atrial fibrillation, and T2DM, no relationship between

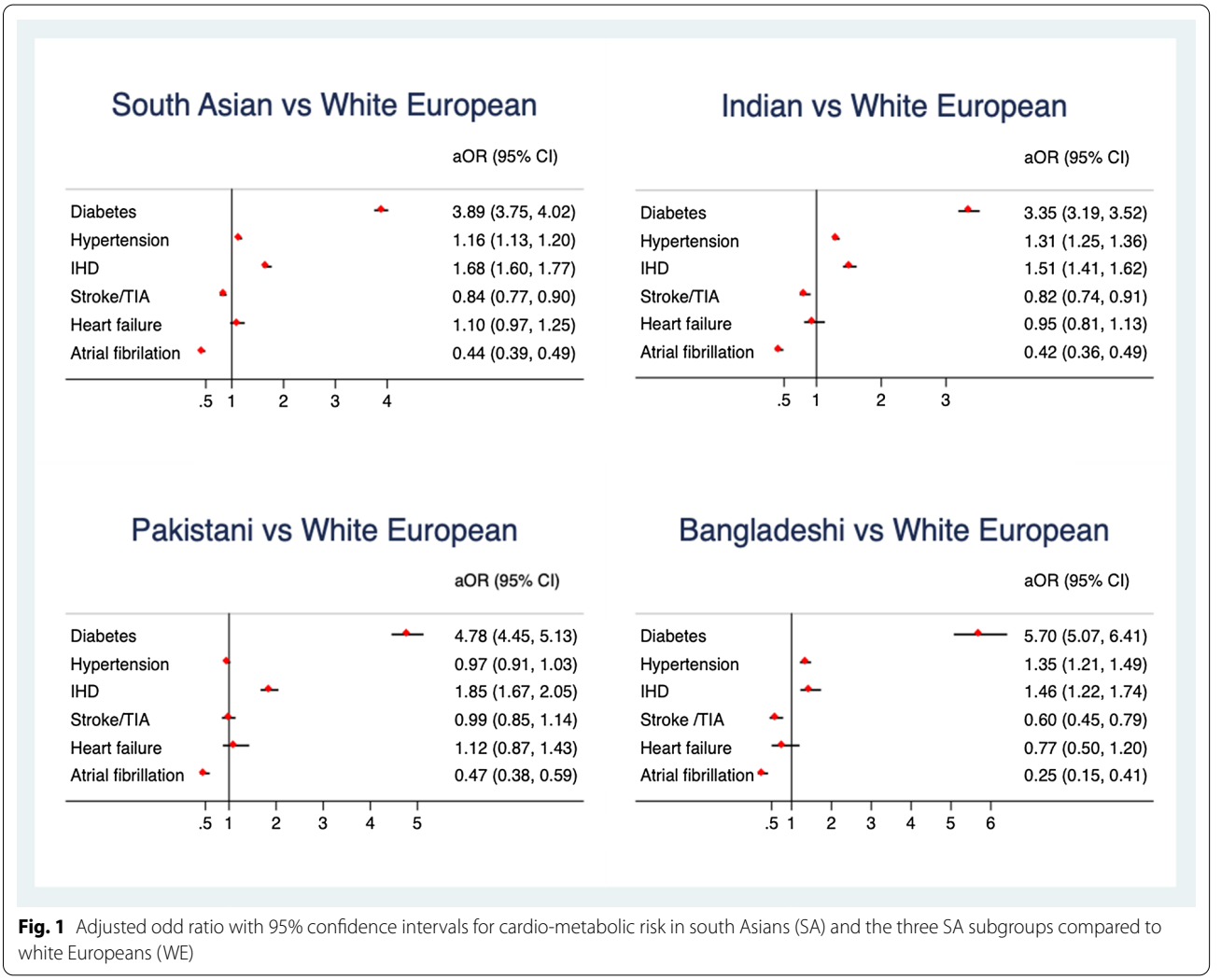

Fig. 1 Adjusted odd ratio with 95% confidence intervals for cardio-metabolic risk in south Asians (SA) and the three SA subgroups compared to white Europeans (WE)

Table 2 Unadjusted and adjusted Hazard ratios (HR) and 95% confidence intervals (95% CI) for White Europeans (WE) and south Asians (SA)

Outcome	Ethnicity	Total n	Incidence n (%)	Person years of follow up	HR (95%CI)	Adjusted HR (95% CI)
T2DM	SA	83,383	5160 (6.19)	370,246	2.54 (2.44–2.65)	3.10 (2.97–3.23)*
	WE	181,688	4530 (2.49)	826,498		
HTN	SA	80,564	4998 (6.20)	348,516	1.27 (1.23–1.32)	1.34 (1.29–1.39)†
	WE	167,070	8152 (4.88)	724,277		
IHD	SA	90,735	1720 (1.90)	419,025	1.66 (1.56–1.77)	1.81 (1.68–1.93)‡
	WE	184,679	2084 (1.13)	848,843		
Stroke/TIA	SA	93,587	988 (1.06)	438,872	0.99 (0.92–1.07)	1.01 (0.93–1.1)§
	WE	186,928	1938 (1.04)	863,750		
HF	SA	94,308	642 (0.68)	444,109	1.2 (1.08–1.32)	1.11 (1.003–1.24)‖
	WE	188,903	1046 (0.55)	876,183		
AF	SA	94,413	615 (0.65)	444,511	0.55 (0.50–0.60)	0.53 (0.48–0.59)‡
	WE	184,679	2084 (1.13)	848,843		

* Age, gender, smoking, BMI category, Townsend deprivation quintile, hypertension

† Age, gender, smoking, BMI category, Townsend deprivation quintile, type 2 diabetes

‡ Age, gender, smoking, BMI category, Townsend deprivation quintile, type 2 diabetes, hypertension

§ Age, gender, smoking, BMI category, Townsend deprivation quintile, AF, type 2 diabetes, hypertension

‖ Age, gender, smoking, BMI category, Townsend deprivation quintile, IHD, type 2 diabetes, hypertension

ethnicity and stroke /TIA was observed (aHR 1.01; 95% CI: 0.93–1.10, $p = 0.75$).

In the SA cohort, there were 642 (0.68%) new diagnoses of heart failure, compared to 1,046 (0.55%) diagnoses in WEs. Following adjustment age, gender, smoking status, BMI category, Townsend deprivation quintile, HTN, IHD, and T2DM, SAs had an increased risk of developing HF compared to WEs (aHR 1.11; 95% CI: 1.003–1.24, $p = 0.04$).

The longitudinal analysis indicates SAs were at lower risk of developing AF compared to WEs. During the follow up, there were 615 (0.65%) cases and 2084 (1.13%) cases, respectively. After adjusting for age, gender, smoking status, BMI category, Townsend deprivation quintile, HTN and T2DM, SAs remained at lower risk of developing AF compared to their matched WEs (aHR 0.53; 95% CI: 0.48–0.59, $p < 0.001$).

When interaction terms for ethnicity and sex, and ethnicity and age were included in the models, both interactions were found to be statistically significant for the T2DM and HTN outcomes; neither were significant for IHD, stroke/TIA or HF; and the ethnicity and sex interaction was significant for the AF outcome. Introduction of the interaction terms led to an increase in the effect estimate for both T2DM and HTN; there was little impact on the observed aHRs for IHD, stroke/TIA, HF or AF (Additional file 1).

South Asian subgroup analysis: cardio-metabolic risk

A total of 49,249 Indians, 22,353 Pakistanis, and 7678 Bangladeshi patients were individuals were compared to WE controls in this subgroup analysis. The three cohorts had similar baseline characteristics (Additional files 2–4) when compared to their matched WE controls. The three matched WE cohorts had more smokers, higher levels of total cholesterol and HDL and increased blood pressure compared to the SA groups. Increased levels of triglyceride, except for Indians (similar triglyceride level), were found in SAs.

All three SA subgroups were more likely than their matched WE control to develop T2DM during follow-up (Fig. 2). In particular, the Bangladeshi subgroup had more than a five-fold increased risk of T2DM diabetes during follow-up (aHR 5.30, 95% CI: 4.61–6.09). Indian subgroup had an aHR of 2.67 (95% CI: 2.52–2.83), whereas the Pakistani subgroup had an aHR of 3.51 (95% CI: 3.23–3.82) in comparison to their WE matched control population.

All subgroups had a higher risk of HTN and IHD compared to their respective WE controls. For hypertension, aHR was 1.35 (95% CI: 1.29–1.42) for Indians,

1.32 (95% CI: 1.22–1.43) for Pakistanis and 1.47 (95% CI: 1.28–1.68) for Bangladeshis. For IHD, the aHR was 1.53 (95% CI: 1.39–1.68), 2.09 (95% CI: 1.83–2.39), and

Fig. 2 Adjusted Hazard ratios (aHR) with 95% confidence intervals for cardio-metabolic risks in south Asians (SA) and the three SA subgroups compared to white Europeans (WE)

2.03 (95% CI: 1.59–2.61), for Indians, Pakistanis, and Bangladeshis, respectively.

Compared to their matched WE controls, all three SA subgroups had lower risk of AF at follow-up (Bangladeshis: aHR 0.41, 95% CI: 0.26 to 0.64; Indians: aHR 0.54, 95% CI: 0.48–0.61; Pakistanis: aHR: 0.51, 95% CI: 0.41–0.63). There was no significant difference in risk of stroke/TIA or heart failure.

Sensitivity analysis

We conducted a sensitivity analysis assigning different BMI cut off points to SA population as follows: overweight 23–27.5 kg/m^2 and obese > 27.5 kg/m^2. Alteration of the BMI cut points decreased the estimated effect size (Fig. 3).

Discussion

Overall, SA patients were at an increased risk of T2DM, IHD and heart failure, but at a lower risk of AF. When compared to WEs, however, the conventional risk factors such as smoking prevalence, increased cholesterol level and systolic blood pressure were lower in SAs. This suggests that the increased incidence of IHD may result from higher triglycerides level, other lifestyle factors and inherent genetic risks. The cross-sectional analysis of prevalence diagnoses at baseline showed that SAs had a higher occurrence of T2DM, HTN and IHD, but a lower occurrence of stroke/TIA and AF than WEs. It has been suggested that the high prevalence of T2DM diabetes in SAs is the key factor for their increased risk of IHD compared to WEs in the UK [20]. The SA population has consistently been shown to have a lower prevalence of AF despite a high prevalence of AF risk factors [21–23]. WEs are more likely to present factors that increase the risk of stroke, such as AF, smoking, and alcohol consumption [24].Similar to Owusu Adjah, Bellary [25], we did not find significant differences in risk of stroke between SA and WE patients.

Obesity and insulin resistance are the main pathophysiological factors linked to the development of T2DM [26].

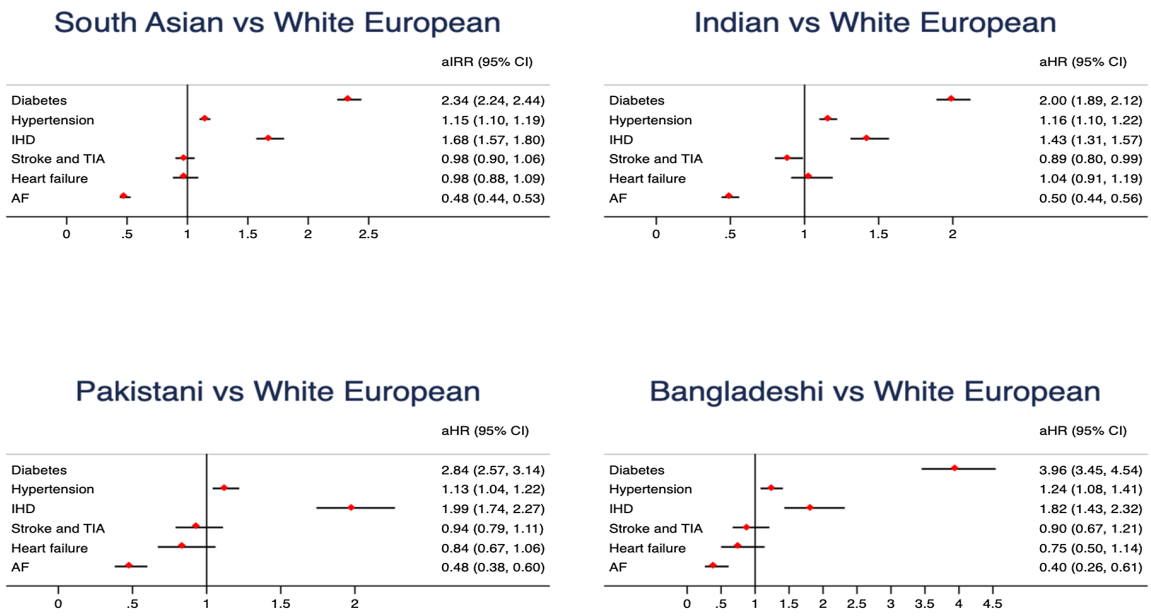

Fig. 3 Sensitivity analysis with a different BMI cut point for south Asians. Normal weight 18.5–23 kg/m^2, overweight 23–27.5 kg/m^2 and obese > 27.5 kg/m^2

A major risk factor for insulin resistance is increased body fat [27] with central obesity an even stronger predictor [28]. Other risk factors associated with insulin resistance include increased blood pressure, hyperglycaemia, central obesity, and dyslipidaemia [29, 30].

It is thought that SAs have greater insulin resistance compared to WEs [31]. Coupled to this, SAs are also known to bear many of the mentioned risk factors for T2DM, namely central obesity and dyslipidaemia, in both prediabetic and diabetic states [26, 32]. Further, SAs are reported to have a higher prevalence of central obesity compared to WEs despite similar or smaller BMIs [33]. In fact, recent evidence suggests that at any age, SAs are at a greater risk of developing T2DM at a lower BMI [34]. This increased risk of T2DM in SAs is posited to stem from inherent impairment of β-cell function rather than insulin resistance [35–37].

Differences in health outcomes across ethnic groups have been documented in the UK [38–40], however, SAs have been tended to be studied as one group. Thus, previous findings may not accurately provide a comprehensive characterization of SA when divided into subgroups. In this study, we have explored variations in outcomes dependent on the SA subgroup. The study indicated that compared to their matched WE controls, Bangladeshis had the highest risk of T2DM. This was consistent with the findings of Hippisley-Cox, Coupland [41] findings, which reported that Bangladeshis had a higher hazard ratio than Pakistanis and Indians when compared to WEs. The heterogeneity across the SA subgroups could be explained by the heterogeneity in health consideration: though the sub groups share the same ethnicity, they bear different risk factors [3]. For example, smoking is known to be more prevalent amongst Bangladeshis men than Indians and Pakistanis [5]. Similar findings were corroborated in our study population. Alcohol consumption is higher in Indians compared to Pakistanis and Bangladeshis [6]. Indians have a lower risk of IHD coupled with the lowest rates of smoking and highest levels of physical activity [42].

The strengths of this study include a large sample size, including separate SA subgroups, which was matched with a white European population. Another strength of this study is the investigation of a wide range of diseases with a large number of events in the different SA groups at baseline and follow-up. Including SA subgroups allowed key insights into the heterogeneities within the greater SA group that are lost when combining all the SA subgroups together. However, a key limitation of this study is that there is a large proportion of patients with missing data for ethnicity, which could affect the generalisability of the study Although, ethnicity information is available for approximately 50% of the primary care population in the total THIN dataset from conception date till present, changes to the Quality Outcomes Framework (incentivised GP payments for improving coding) between 2006 and 2012 improved coding of ethnicity [43]. By 2007 the proportion of patients with a recorded ethnicity improved to 78.3% [43]. Although there were still some patient records with missing ethnicity in the total dataset, to strengthen our approach, we only included records from 2007 onwards. Physical activity level and alcohol consumption are also notable risk factors for cardiovascular disease; however, this information was unavailable at the time of data extraction. Similarly, data on education and diet are not available, therefore we were unable to explore any potential confounding effect of these variables. Moreover, as SAs are considered to be at a higher risk of many cardiometabolic disorders this may lead to a greater predisposition for clinician led investigation of cardiovascular disease in this cohort. Ultimately, this may result in a greater number of diagnoses compared to other ethnic groups and be presented in our results as a possible information bias.

Conclusion

SA are at higher risk of T2DM and IHD compared to the WEs, but a lower risk of AF. Though SA subgroups share the same ethnicity, they present different risks of certain diseases. Combining different subgroups could over- or underestimate the reality. The findings of this study suggest that there is inequality in health factors across the SA subgroups. Further research with further disaggregated data is needed to explore the difference in outcomes amongst the heterogeneous South Asian population.

Abbreviations

SA: South Asian; WE: White European; HTN: Hypertension; T2DM: Type 2 diabetes mellitus; IHD: Ischaemic heart disease; HF: Heart failure; AF: Atrial fibrillation; THIN: The Health Improvement Network; TIA: Transient ischaemic attack; SD: Standard deviation; IQR: Interquartile range; OR: Odd ratios; aOR: Adjusted odds ratios; HR: Hazard ratios; aHR: Adjusted Hazard ratio; BMI: Body mass index.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-021-02133-z.

Additional file 1: Table 1. Adjusted Hazard ratios (HR) and 95% confidence intervals (95% CI) for White Europeans (WE) and south Asians (SA) using interaction terms.

Additional file 2: Table 2. Baseline characteristics of Indian and White participants.

Additional file 3: Table 3. Baseline characteristics of Pakistani and White participants.

Additional file 4: Table 4. Baseline characteristics of Bangladeshi and white participants.

Acknowledgements

Not applicable

Authors' contributions

KN, WH and AT were responsible for the initial conception of the study. MA then contributed to the data collection and analysis of the data. MA, KK, WH, AT, JSC, NA, KG, RT and KN all contributed to the final version of the manuscript for submission. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

THIN data access was provided by IQVIA to the University of Birmingham under the NHS South-East multi-centre research ethics committee approval in 2003, subject to independent scientific review for individual studies. This study was granted study-specific approval (18THIN071) from the Scientific Review Committee. Anonymised data was used throughout the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

3.1 Further clarifications:

3.1.1 Abstract:

Methods: A retrospective open cohort matched population-based study using The Health Improvement Network (THIN) database. The inclusion criteria were patients: > 35 years old and had recorded ethnicity data. Groups were matched 1:2 by age, gender, Townsend deprivation index quintile, and study index year. The outcomes of this study were the incidences of cardiometabolic events (type 2 diabetes mellitus, hypertension, ischemic heart disease, stroke, heart failure, and atrial fibrillation).

3.1.2 Discussion:

SA appeared to have a lower risk of AF compared with white ethnic group despite having higher rates of conventional risk factors and a similar risk of stroke. Moreover, AF is a key risk factor for heart failure. With the lower risk of AF in South Asian, it would be expected that the risk of heart failure to be lower, however, this is not true. It is not clear whether SA are truly experiencing less AF or whether this is due to under detection of AF in this population. The reason for this remains unclear. However, one hypothesis for the reduced prevalence of AF relates to the size of the SA atrium.[1] Evidence suggest that there is a relationship between increasing atrial size and the risk of AF.[2] The SA ethnic group has been shown to have generally smaller atria that is likely to be due to genetic variation.[3]

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

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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 dia betes are sparse. The purpose of this study is to assess the association of fasting on cardio vascular 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 inconsis tent in term of risk factors as some favoured Ramadan and others did not.

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Contents

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.

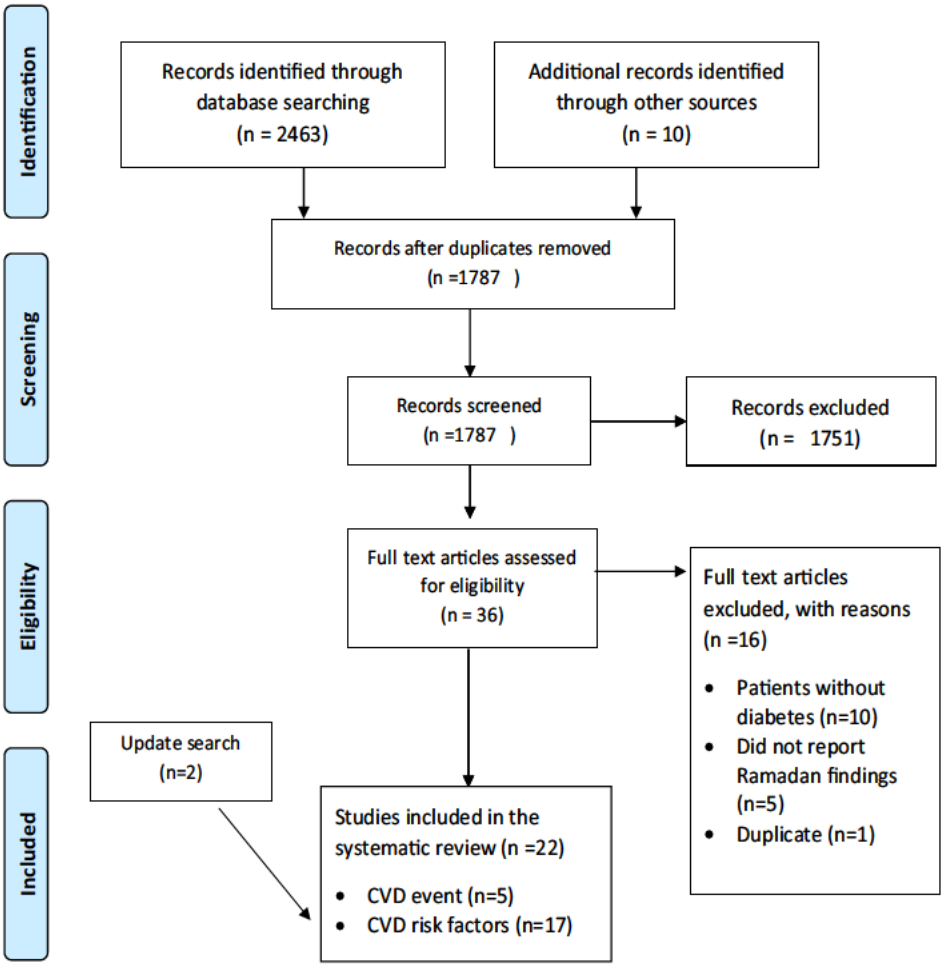

Fig. 1 – Study selection flowchart.

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.

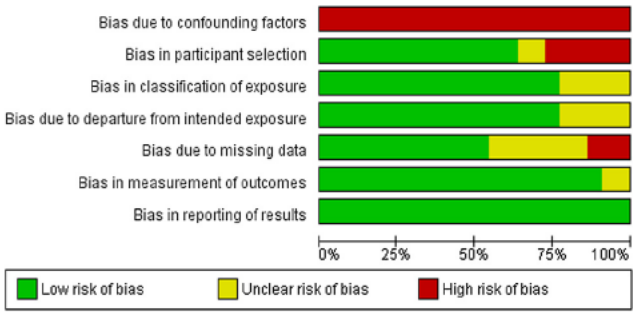

Fig. 2 – Assessment of the risk of bias across studies.

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.

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, Bahijri [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

Acknowledgment

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Declaration of Competing Interest

There are no conflicts of interest.

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4.1 Further clarifications:

4.1.1 Methods:

Eligible study designs: Before and after observational studies.

4.1.2 Results:

All included studies used a pre-post observational study design to report. Most of the studies recruited patients opportunistically from outpatient clinics. There was a lack of information regarding the participants in the studies covering CVD outcomes as patients with diabetes were only a subgroup. There was inconsistency in the information provided regarding the participants. Most of the included studies on CVD risk factors in patient with diabetes stated the type of medication they were taking. Few studies provided description of participants' clinical characteristics such as length of diabetes, comorbidities, diabetes complications, medication, and status of smoking. Though it. Most studies did not state the activity level and diet changes during the study period or in baseline.

5 Chapter five: The association between Ramadan fasting and infection

Infection risk in predominant Muslim population before, during and after Ramadan: control interrupted time series analysis using UK primary care data

5.1 Abstract

Background: The effect of fasting on immunity is unclear. Prolonged fasting is thought to increase the risk of infection due to dehydration. This study describes antibiotic prescribing patterns before, during, and after Ramadan in a primary care setting within the Pakistani and Bangladeshi populations in the UK, most of whom are Muslims, compared to those who do not observe Ramadan.

Method: Retrospective controlled interrupted time series analysis of electronic health record data from primary care practices. The study consists of two groups: Pakistanis/Bangladeshis and white populations. For each group, we constructed a series of aggregated, daily prescription data from 2007 to 2017 for the 30 days preceding, during, and after Ramadan, respectively.

Findings: Controlling for the rate in the white population, there was no evidence of increased antibiotic prescription in the Pakistani/Bangladeshi population during Ramadan, as compared to before Ramadan (IRR: 0.994; 95% CI: 0.988–1.001, p=0.082) or after Ramadan (IRR: 1.006; 95% CI: 0.999–1.013, p=0.082).

Interpretation: In this large, population-based study, we did not find any evidence to suggest that fasting was associated with an increased susceptibility to infection.

5.2 Introduction:

The Muslim population represents nearly 1.6 billion people, comprising 23% of the global population in 2010.[1] As part of the five pillars of Islam, it expected that adult Muslims fast the holy month of Ramadan. Ramadan involves abstaining from the consumption of food, drink, and oral medications between sunrise and sunset for the entire month. Ramadan is the ninth month of the lunar calendar and depending on the time of year this occurs, as well as the geographical location, practising Muslims may go exceptionally long hours without basic, yet vital, necessities for optimal health. While the impact of Ramadan fasting on metabolic parameters and conditions have been moderately investigated[2], other health outcomes during this annual event are poorly understood.

The impact of Ramadan fasting specifically on infection is unclear. However, it is imperative to ascertain the risk of infection in order to provide effective healthcare and advice to this potentially vulnerable population. This is particularly essential during the COVID-19 pandemic, where minority ethnic groups are at an increased risk for adverse medical complications.[3] Though limited, there is evidence that Ramadan fasting transiently improves immune response.[4] For instance, some studies reported reduced levels of leukocytes and circulating proinflammatory cytokines (IL-1β, IL-6, and TNF-α).[5,6]

However, there are claims that Ramadan could influence the risk of infection. One of the key mechanisms is the prolonged fasting. Insufficient water intake and dehydration is one of the most compelling and challenging claims that has been raised to link Ramadan fasting to susceptibility to infection. Urinary tract infection is the most one of the most infections that is expected to increase in Ramadan due to dehydration, particularly in hot weather. Bacterial

growth in the urinary tract is usually prevented by host factors including bacterial eradication by urinary and mucus flow, urothelial bactericidal activity, urinary secretory IgA, and blood group antigens in secretions which interfere with bacterial adherence. Bacterial eradication from the urinary tract is partially dependent on urine flow and voiding frequency. Dehydration and low fluid intake are associated with increased risk of developing renal calculi.[7] Therefore, it seems logical to postulate a connection between fluid intake (as in Ramadan) and the risk infection of infections such as UTI.

In addition to altering their daily routine by only eating two meals a day ('suhur' before dawn and 'iftar' after dusk), practising Muslims also attend additional religious gatherings and social parties during Ramadan, thereby sleeping less at night.[8-10] Insufficient sleep has been associated with reduced immune responses[11], and extensive physical interaction with others can increase the risk of exposure to an infectious agent. The many social and religious gatherings taking place during Ramadan constitute an additional risk factor for infection.[3]

Type 2 diabetes, another risk factor for developing severe illness from COVID-19, is highly prevalent in the Muslim population.[12,13] Extended fasting can result in poor glycaemic control in diabetics, which has been shown to reduce T cell response, neutrophil function, and humoral immunity, exacerbating the risk of infection during dehydration.[14,15] Even though Muslims with diabetes are often exempt from taking part in Ramadan fasting, more than half choose to participate in this holy event.[16,17]

The existing systematic review examining the relationship between Ramadan fasting and infectious diseases does not look at the risk of acquiring infection.[18] Instead, the impact of Ramadan fasting on Muslims with chronic infections, such as HIV, was assessed. While this review provides useful recommendations for physicians already treating patients with infectious diseases who are fasting during Ramadan, there are few guidelines to help address the concerns of healthy patients wishing to participate. The guidelines that do exist are predominately based on expert opinion.[19] Given that the Muslim population has a high burden of chronic disease, especially diabetes and cardiovascular disease, and is therefore already at an increased risk of complications and infections, it is critical for healthcare professionals to be able to provide reliable advice regarding fasting during Ramadan.[20]Much uncertainty still exists about the risk of infection during Ramadan. No previous study has been conducted to explore the risk of infection during Ramadan in a predominant Muslim population.

Most of the available evidence is based on small studies or observational studies that lacked a robust design. Conducting a randomized control study is challenging and unethical as Ramadan fasting is a holy practice for Muslims. Meanwhile, recruiting those who are not fasting as a control group in an observational study might bias the findings, as these individuals are likely to be exempted from fasting due to health issues. ITS is an increasingly used design in public health research that adopts an approach that allows for comparisons to be made over time within single populations.[21,22] Interrupted time series is one of the strongest, quasi-experimental designs to evaluate longitudinal effects exposure, particularly when randomised controlled trials are not possible. However, this design cannot exclude the effect of confounders or events that occurred in the same time period as the exposure under investigation (the

so-called history bias), which threaten the internal validity of the study. The literature suggests that adding a control series will minimize this bias and strengthen the study design (controlled interrupted time series).[23]

According to the 2011 UK census, 4.8% of the population identified as Muslim.[24] This number is projected to be as high as 11.3% by 2050.[1] In the UK, Muslims may fast for nearly 17 hours a day if Ramadan falls during the summer months, which could prove dangerous if temperatures are high. To address the lack of information on the effects of prolonged fasting on infection, we aim to describe antibiotic prescribing patterns before, during, and after Ramadan in the Pakistani and Bangladeshi populations (largely Muslim) in the UK, and compare these patterns to the white population (largely non-Muslim).

5.3 Methods

5.3.1 Study design and data sources:

We performed a retrospective controlled interrupted time series analysis using the IQVIA Medical Research Data (IMRD), also referred to as The Health Improvement Network (THIN) database. This is an electronic primary care patient record in the UK. THIN is a large UK general practice database that contains anonymised longitudinal patient records from over 750 general practices (about 6% of the population at a given time). THIN provides longitudinal records with data on socio-demographic characteristics, diagnoses, medical test results, prescriptions, and additional information (e.g., lifestyle). Diagnoses are recorded as Read Codes, a hierarchal coding system. Prescriptions are entered using Multilex codes issued by First Databank; these can be easily linked to British National Formulary (BNF) codes. THIN data access

was provided by IQVIA to the University of Birmingham. The study protocol was reviewed and approved by an independent scientific review committee (reference number: 19THIN044). IQVIA Medical Research Data incorporates THIN data, a Cegedim Database. References made to THIN are intended to be descriptive of the data asset licensed by IQVIA. Our study uses anonymised data provided by patients as a part of their routine primary care. The Scientific Review Committee (IQVIA) approved the study protocol (no. SRC19THIN044) before its start. Informed consent was not required in this study as the data were anonymized from the provider.

To ensure the quality of the recorded data, we included only general practices that were using electronic medical record software for at least one year, and that also had acceptable mortality recordings for at least one year.[25]

5.3.2 Study period:

The study includes the time periods before, during, and after Ramadan each year from 2007 to 2017. The timing of Ramadan is based on the lunar calendar where months can last for 29 or 30 days, depending on the moon's phases. For this study, we standardised the months to 30 days. We marked the start of Ramadan in each year and based on that date, identified 30 days before, 30 days during, and 30 days after. We only included 90 days for each year of the study.

5.3.3 Population:

The study consists of two groups. The first is the targeted group: Pakistanis and Bangladeshis representing the Muslim population in this study. Pakistanis and Bangladeshis represent the largest Muslim ethnic groups in the UK, constituting 38% and 15%, respectively, of the overall

Muslim population.[26] These populations have a high burden of chronic disease, in particular type 2 diabetes (T2DM) and cardiovascular disease; they also have an increased risk of infection and disease-specific complications.[20] The second group is the white population representing the control group, which predominantly does not observe Ramadan. These cohorts were identified through relevant ethnicity codes (Fig 1). The patients entered the cohort one year after registration with the practice or after the date that a practice became eligible to contribute, whichever was the most recent; this ensured data quality and sufficient covariate recording.

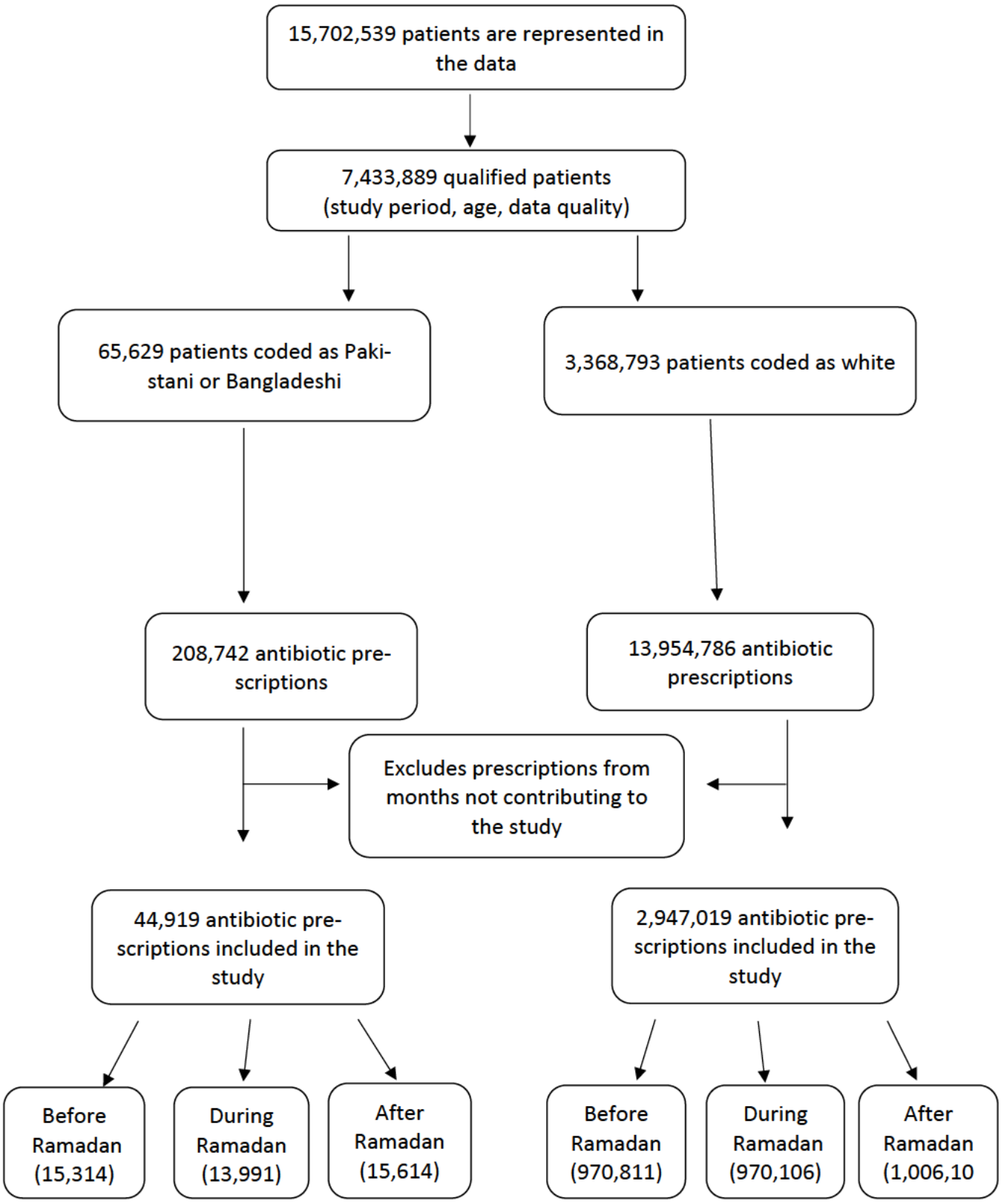

Figure 1: Flow diagram of the study data

5.3.4 Study variables:

We measured antibiotic prescriptions before, during, and after Ramadan. All antibiotic prescriptions recorded in the databases during this period of interest were retrieved. Baseline data on demographic characteristics were collected at cohort entry.

5.3.5 Analysis:

We used descriptive statistics to identify the basic features of the data from before, during, and after Ramadan. We analysed patterns of antibiotic prescription using interrupted time series (ITS) analysis. ITS analysis is a quasi-experimental design that can evaluate an intervention effect using longitudinal data. The term 'quasi-experimental' refers to an absence of randomisation; ITS analysis is a tool for analysing observational data when randomisation or a cohort design are not possible. ITS analysis requires data on continuous or counted outcome measures, summarised at regularly spaced time intervals. This model often uses before-and-after comparisons for underlying trends, and is particularly useful for assessing the impacts of policies or healthcare initiatives. It can provide information on any changes that could have occurred due to the intervention/exposure, whether immediately or over time. Single interrupted time series (SITS) analysis elucidates changes within a group before and after the exposure. Controlled interrupted time series (CITS) analysis, which includes adding a control group, helps separate the effect of the exposure from other confounding effects that could have occurred at the same time.[23,27]

For each group (Pakistani/Bangladeshi and white), we developed a series of 90-day data (30 days before, 30 days during, and 30 days after Ramadan) comprised of aggregated, daily data

from 2007 to 2017. We performed two analyses: ITS and CITS. We then explored effect modification by refitting CITS model using the following factors: sex, age (< 60, >60), and diabetes status.

1. Interrupted time series (ITS) analysis using poison regression model.

A minimum of three variables are required for an ITS analysis[28]:

- T is the time since the start of the study (e.g., day, month, or year);
- X_t is a dummy (indicator) variable representing the intervention (pre-intervention periods equal 0, otherwise 1); and
- Y_t is the aggregated outcome variable measured at each equally spaced time point t.

The following segmented regression model is used for standard ITS analysis[28]:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \varepsilon_t$$

where β_0 represents the baseline level at T = 0; β_1 represents the change in outcome associated with a time unit increase (representing the underlying pre-intervention trend); β_2 is the level of change following the intervention; β_3 indicates the change in slope pre- and post-intervention; ε_t is an error term.

2. Controlled interrupted time series (CITS) analysis using negative binominal regression model.

A minimum of four variables are required for a controlled interrupted time series (CITS) analysis[28]:

- T is the time since the start of the study (e.g., day, month, or year);
- X_t is a dummy (indicator) variable representing the intervention (pre-intervention periods equal 0, otherwise 1);
- Z_t is a dummy variable to denote the cohort assignment (treatment or control); and
- Y_t is the aggregated outcome variable measured at each equally spaced time point t.

The controlled interrupted time series model is indicated by the following equation[28]:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \beta_4 Z_t + \beta_5 Z_t T + \beta_6 Z_t X_t + \beta_7 Z_t T X_t + \varepsilon_t$$

where β_0 to β_3 represents the control group, and β_4 to β_7 represents the treatment group. β_4 represents the difference in level between treatment and control prior to the intervention. β_5 represents the difference in the slope between treatment and control prior to the intervention. β_6 represents the difference in level between treatment and control in the period immediately following the intervention initiation. β_7 represents the difference between the treatment and control in the slope after the intervention was initiated, compared to the pre-intervention period; ε_t is an error term.

An example of the dataset structure for both models is available as supplementary material (Appendix S2)

The validity of ITS design rest of assumptions that imply that a linear extrapolation of the pre period trendline into the post period provides an unbiased representation of the counterfac-

tual for a treated sample [29],We checked these assumption in addition to seasonality (S1 Appendix).

All parameter estimation for ITS and CITS models are available as supplementary material (Appendix S3).We used R for analysis.

5.4 Results

5.4.1 Study population:

Included in the study were 1,097,429 patients and 3,308,463 antibiotic prescriptions. A total of 65,629 patients were coded as Pakistani/Bangladeshi and 3,368,793 patients were coded as white. A total of 2,991,938 antibiotic prescriptions contributed to the study, including 44,919 for the Pakistani/Bangladeshi group and 2,947,019 for the white control group. A total of 18,632 patients contributed to the study, 18,632 Pakistani/Bangladeshi and 1,078,797 White (Table 1). Across the study period the proportion of female prescribed antibiotics is higher in both groups. The mean age at prescription was less in the Pakistani/Bangladeshi population compared to the white population. Compared to the white group higher proportion of patients with diabetes were prescribed antibiotics. Table 2 provides an overview of study populations before, during and after Ramadan.

Table 1: Characteristics of aggregated antibiotic prescriptions data for 90 days each year from 2007 to 2017

	White n=2,947,019	Pakistani/Bangladeshi n=44,919
Number of patients contributing to the prescriptions	1,078,797	18,632
Sex		
Male	404,889 (37.5%)	7,838 (42.1%)
Female	673,908 (62.5%)	10,794 (57.9%)
Age*, mean (SD) (all)	56.2 (19.7)	43.99 (16.5)
Male	57.58 (18.8)	46.22 (17.6)
Female	55.52 (20.1)	42.61 (15.6)
Townsend deprivation index score, n (%)		
1(least deprived)	198,963 (18.4%)	1,255 (6.7%)
2	190,832 (17.7%)	1,644 (8.8%)
3	194,640 (18%)	2,600 (14%)
4	176,188 (16.3%)	4,198 (22.5%)
5 (Most deprived)	133,305 (12.4%)	4,482 (24.1%)
6 (Missing)	184,869 (17.2%)	4,453 (23.9%)
Patients with diabetes	170,428 (15.8%)	5,311 (28.5%)

*Age at prescription

Table 2: Characteristics of aggregated antibiotic prescriptions data from before, during, and after Ramadan each year from 2007 to 2017

	White			Pakistani/Bangladeshi		
Study period	Before Ramadan n=970,811	During Ramadan n=970,106	After Ramadan n=1,006,102	Before Ramadan n=15,314	During Ramadan n=13,991	After Ramadan n=15,614
Number of patients contributing to the prescriptions	554,780	554,340	569,566	9,666	8,872	9,666
Sex						
Male	199,359 (35.9%)	198,547 (35.8%)	203,587 (35.7%)	3,829 (39.6%)	3,600 (40.6%)	3,878 (40.1%)
Female	355,421 (64.1%)	355,793 (64.2%)	365,979 (64.3%)	5,837 (60.4%)	5,272 (59.4%)	5,788 (59.9%)
Age*, mean (SD) (all)	56.38 (19.6)	56.20 (19.7)	56.09 (19.7)	44.05 (16.4)	43.68 (16.6)	44.21 (16.5)
Male	57.73 (18.7)	57.50 (18.8)	57.50 (18.8)	46.39 (17.6)	45.82 (17.6)	46.42 (17.6)
Female	55.67 (20.)	55.53 (20.1)	55.36 (20.1)	42.64 (15.5)	42.33 (15.8)	42.83 (15.5)
Townsend deprivation index score, n (%)						
1(least deprived)	100,918 (18.2%)	100,780 (18.2%)	102,503 (18%)	665 (6.9%)	593 (6.7%)	635 (6.6%)
2	97,584 (17.6%)	96,982 (17.5%)	99,730 (17.5%)	819 (8.5%)	791 (8.9%)	848 (8.8%)
3	99,947 (18%)	99,782 (18%)	102,928 (18.1%)	1,342 (13.9%)	1,235 (13.9%)	1,339 (13.9%)
4	91,659 (16.5%)	92,064 (16.6%)	94,072 (16.5%)	2,179 (22.5%)	2,033 (22.9%)	2,156 (22.3%)
5 (Most deprived)	70,506 (12.7%)	70,600 (12.7%)	73,379 (12.9%)	2,325 (24%)	2,106 (23.7%)	2,325 (24%)
6 (Missing)	94,166 (17%)	94,132 (17%)	96,954 (17%)	2,336 (24.2%)	2,114 (23.9%)	2,363 (24.4%)
Patients with diabetes	56,503 (10.18%)	56,317 (10.16%)	57,608 (10.11%)	1,790 (18.51%)	1,609 (18.13%)	1,751 (18.17%)

*Age at prescription

5.4.2 Single interrupted time series analysis:

Time series analysis did not identify any significant trend change in antibiotic prescriptions during Ramadan (compared to before Ramadan) in the Pakistani/Bangladeshi group (IRR: 0.995; 95% CI: 0.990–1.001, p=0.089). After Ramadan, there was an increase in antibiotic prescriptions compared to during the Ramadan period (IRR: 1.007,95% CI: 1.001–1.013, p=0.025). There was no change observed in prescription patterns in the white population during Ramadan (IRR: 1.001; 95% CI%: 0.997–1.006, p=0.54) or after Ramadan (IRR: 1.001; 95% CI: 0.996–1.005, p= 0.78) (Fig 2, Table 3).

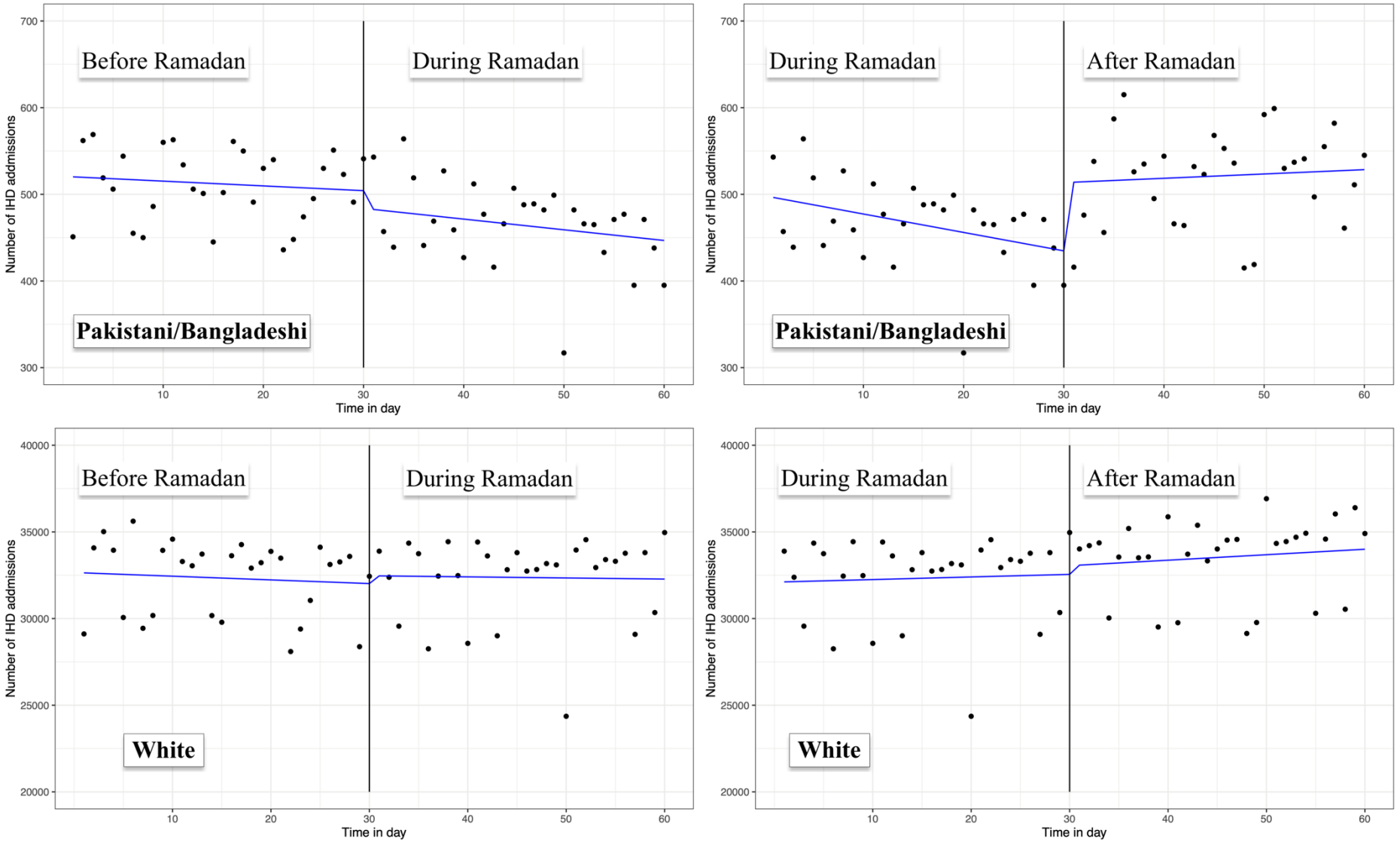

Figure 2: Daily antibiotic prescription patterns (SITS)

5.4.3 Controlled interrupted time series analysis:

Controlling for the background prescription pattern in the white population did not alter our findings when antibiotic prescriptions during Ramadan in the Pakistani/Bangladeshi group were compared to those before Ramadan (IRR: 0.994; 95% CI: 0.988–1.001, p =0.082). The significant increase observed in the post-Ramadan period (compared to during the Ramadan period) in the SITS analysis was not evident in the Pakistani/Bangladeshi group when controlled for background prescription rates in the white population (IRR: 1.006; 95% CI: 0.999–1.013, p=0.082) (Fig 3, Table 3).

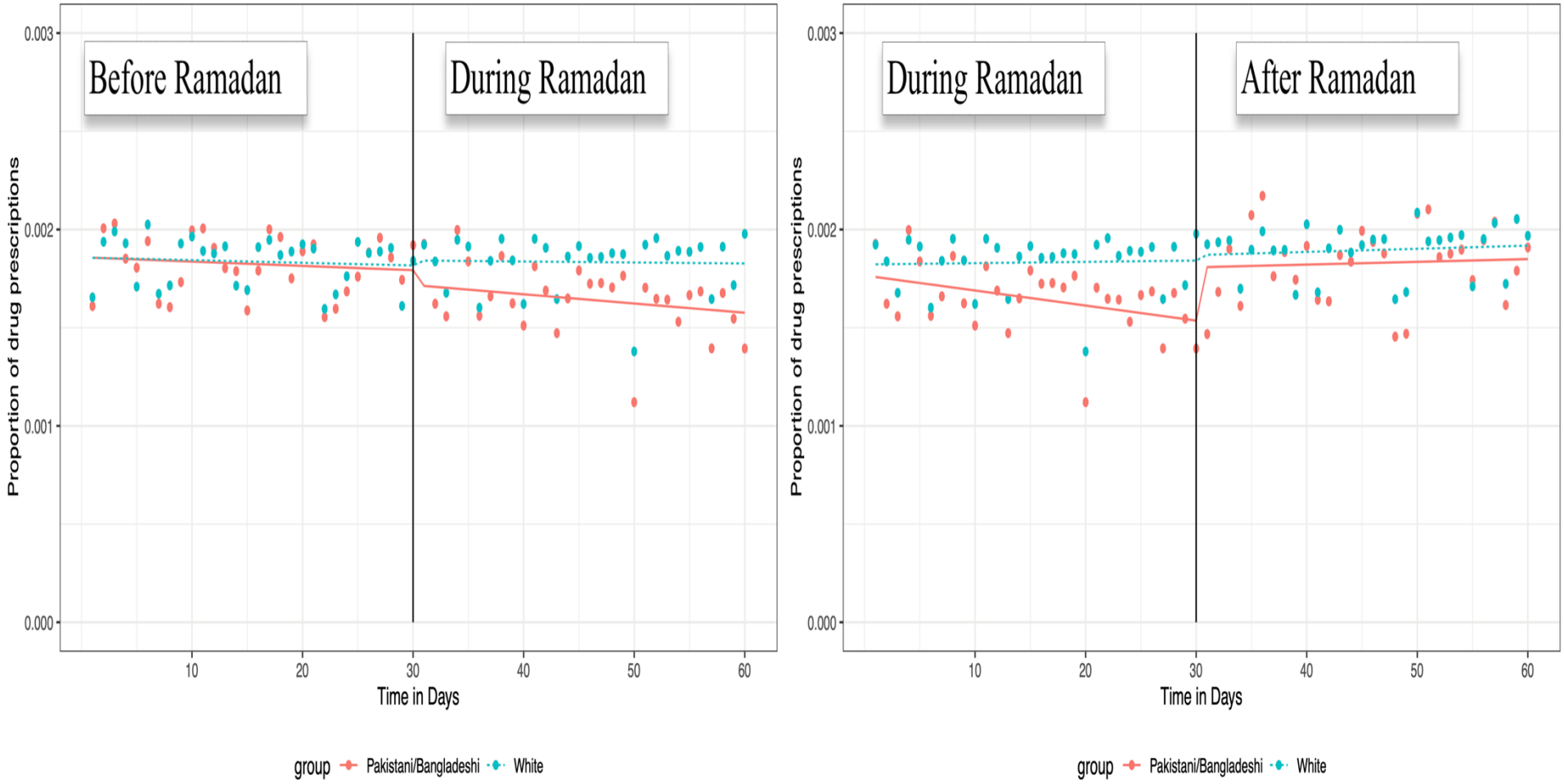

Figure 3: Daily antibiotic prescription patterns in (CITS)*

**Proportion = Number of antibiotic prescriptions/total number of people in that period*

Table 3: Findings from the SITS and CITS analyses for the general population

Parameter	SITS	P-value	Parameter	CITS	P-value
	Incidence Rate Ratio (95% CI)			Incidence Rate Ratio (95% CI)*	
Difference in trend changes before/during Ramadan (Pakistani/Bangladeshi) - $\beta 3$	0.995 (95% CI: 0.990–1.001)	0.089	Difference in trend changes between the two groups before/during Ramadan - $\beta 7$	0.994 (95% CI: 0.988-1.001)	0.082
Difference in trend changes before/during Ramadan (White)- $\beta 3$	1.001 (95% CI: 0.997–1.006)	0.54			
Difference in trend changes during/after Ramadan (Pakistani/Bangladeshi)- $\beta 3$	1.007 (95% CI: 1.001–1.013)	0.025	Difference in trend changes between the two during/after Ramadan - $\beta 7$	1.006 (95% CI :0.999, 1.013)	0.082
Difference in trend changes during/after Ramadan (White)- $\beta 3$	1.001 (95% CI: 0.996–1.005)	0.78			

*IRR (95%CI) in the Pakistani/Bangladeshi population controlled for the background rate in the white population

5.4.4 Stratified analysis using CITS:

Fig 4 shows the IRR (95% CI) for the stratified groups in the Pakistani/Bangladeshi population, controlled for the background rate in the white population. Females showed a significant decrease in antibiotic prescriptions during Ramadan compared to before (IRR: 0.991; 95% CI: 0.985–0.998). However, females showed an increase in prescriptions after Ramadan compared to during (IRR: 1.010; 95% CI:1.004–0.018). We observed no changes in prescription pattern for men during Ramadan (IRR: 0.998; 95% CI: 0.991–1.006) or after Ramadan (IRR: 1.000; 95% CI: 0.992–1.007). No significant change in antibiotic prescription patterns was identified in patients with diabetes during Ramadan (IRR: 0.996; 95% CI: 0.988–1.005) or after Ramadan (IRR:1.003, 95% CI: 0.994 –1.012).

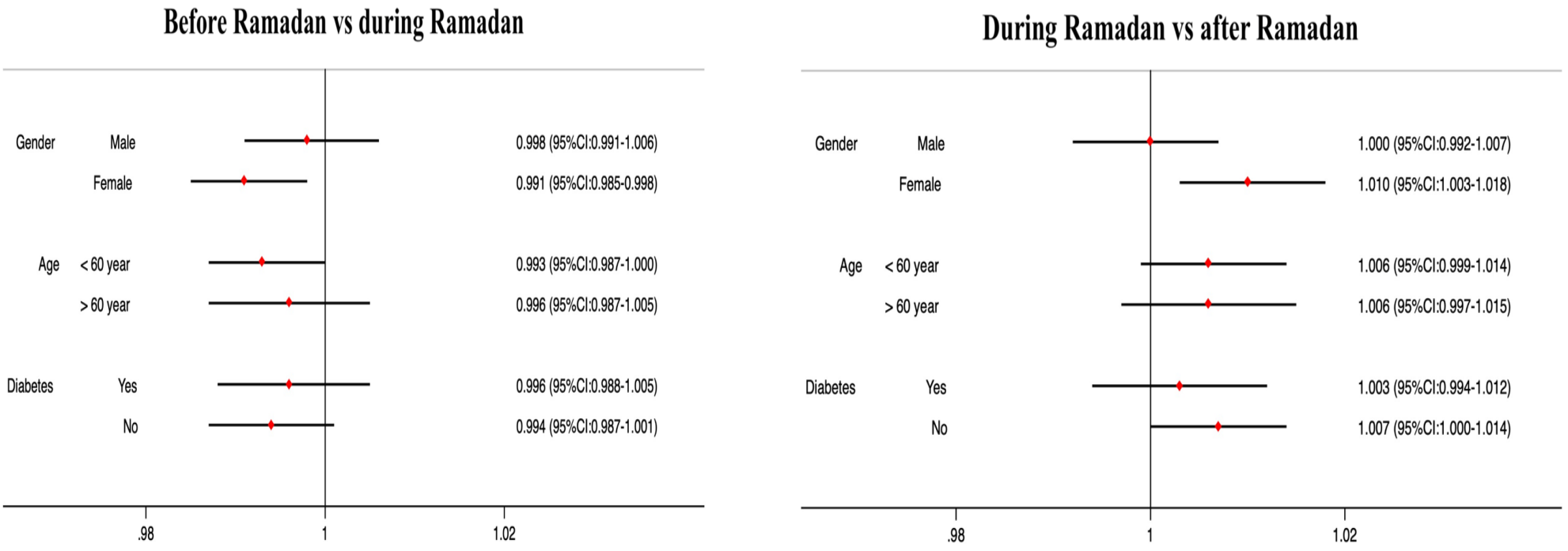

Figure 4: Incidence rate ratios with 95% confidence intervals for the stratified groups in the Pakistani/Bangladeshi population, controlled for the background rate in the white population

5.5 Discussion:

To our knowledge, this is the first study carried out to determine patterns of antibiotic prescriptions before, during, and after Ramadan for a predominantly Muslim community in the UK. In this large population-based study, we have demonstrated that there was an increase in antibiotic prescribing following Ramadan (compared to during Ramadan) among people of Pakistani or Bangladeshi origin within the UK; however, this did not remain significant when corrected for antibiotic prescriptions in the white population. Importantly, the Ramadan period was not associated with altered prescription patterns among older adults (>60) or among those with diabetes, the two groups with the greatest potential infection risk. It would be expected that female would have higher risk of infection, particularly UTI due to the prolonged fasting and the potential dehydration. Interestingly, female had lower antibiotics prescriptions during Ramadan compared to before Ramadan, and higher prescriptions after Ramadan compared to Ramadan. It is not clear what is the reason of this. Some studies suggested that Ramadan fasting strengthen the immune system against microbial agents[30,31], this could explain the decreases prescriptions during Ramadan. Another possible explanation is that the impact of fasting and the potential detrimental effects may started to appear by the end of Ramadan, which may explain the increase after Ramadan.

The effects that fasting during Ramadan exerts on the immune system have been previously studied using indices of basal inflammation and its potential to respond to infection. However, these studies have typically observed only small samples of healthy individuals, yielding conflicting results; this may be partially explained by the timing and methods used for assess-

ment.[3,4] The significance of transient changes in basal inflammation is not clear, and the response to infection during Ramadan fasting has not been widely studied. However, in vitro assays from small numbers of people have demonstrated a continued, and possibly increased, ability to respond to infection during Ramadan fasting.[32,33]

The important finding that older adults (over 60 years old) and people with diabetes were not affected by the Ramadan period should be interpreted with caution. Behavioural modifications, such as reducing the number of fasting days or not observing the fast due to pre-existing conditions, may explain the absence of an effect. Indications that diabetics who have additional comorbidities are avoiding fasting is supported by hospital data.[34] However, other studies reported that the majority of diabetic Muslims are participating in Ramadan fasting.[16,35] The effects of diabetes[36] and age[37] on the immune system are well-established, including increased susceptibility to infection, especially severe infection. Nevertheless, any potential modulation of this effect by Ramadan fasting is unknown. Extrapolating data from non-Ramadan fasting (as undertaken by diabetics to achieve weight loss) is difficult, given the potential for significant confounders such as exercise modulation, caloric reduction, differences in hydration status, and other health-promoting behaviours that may be part of a weight-loss strategy. Further investigations are warranted on the effects of Ramadan fasting on the older and diabetic Muslim population.

While we did not demonstrate a significant difference in antibiotic prescribing during or after Ramadan among those who observe and those who do not observe, we considered the possibility that prescriptions of antibiotics during Ramadan may decrease due to fewer primary care visits for mild illnesses during that period. However, this is not supported by a large US-

based study on primary care visits[38] that actually showed an increase during the Ramadan period.

Our epidemiological approach to the question of whether Ramadan fasting is associated with an increased risk of bacterial infection has advantages over previously published work, in that we focus on clinically significant bacterial infections requiring antibiotic therapy. Further strengths of our study include the extensive study period, large sample size, and the use of a control group that does not typically observe Ramadan. Another key strength of this study is our use of interrupted time series analysis on routinely collected data, which allowed for tracking changes during the different periods.

Some limitations existed in our study. One of the limitations was that our analyses did not account for seasonal change. Ramadan moves 11 days forward every year, and it can take up to 33 years to occur in all seasons. Our study used ten years of data, during which Ramadan occurred in summer and autumn (June to mid-October). Including data from years where Ramadan took place in other months could have aided our understanding of whether temperature, hours of daylight, and hours of sleep play a role in the risk of infection. Another limitation was that we could not confirm who in our exposed group definitely took part in Ramadan fasting, leading to ecological fallacy. Our assumption of fasting within the Pakistani and Bangladeshi populations compared to the broader UK population was based on estimates that more than 90% of people from these ethnic backgrounds are Muslims.[39] According to a Pew Research Centre survey of more than 38,000 Muslims around the world, most Muslims practise fasting during Ramadan.[10] Therefore, we assume that our exposed group accurately

represented practising Muslims. Given that we only investigated the Pakistani and Bangladeshi population in the UK, the results from our study may not reflect other Muslim communities within the country. Moreover, the generalisability of the results is limited due to variations in the prevalence of pre-existing conditions, such as diabetes, and of infectious agents circulating in Muslim populations in other countries. Generalisability is also affected by different fasting rituals, cultural traditions, daylight hours, and temperatures in other countries during Ramadan.

The use of any antibiotic prescriptions as an outcome of the study is another issue. This may broaden the scope of the study and may obscure any true causal associations. Limiting the antibiotics to those prescribed only for UTI (which is hypothesised that it may increase in Ramadan due to prolonged infection and resulted dehydration) or diagnosis of specific infection could be more appropriate as an outcome. Moreover, antibiotic prescriptions are influenced by both patients and clinician behaviour[40,41], thus antibiotic prescriptions are not always true indication of true bacterial infection.

Another issue that needs to be acknowledge is that sample size calculation was not done. The purpose of estimating the appropriate sample size is to produce studies capable of detecting clinically relevant differences. Sample size refers to the number of participants or observations included in a study. The size of a sample influences two statistical properties: 1) the precision of the estimates and 2) the power of the study to draw conclusions. There is a concern of that the small sample size may risk the study of failing in type II errors. Type II errors refers to the chance of incorrectly accepting the null hypothesis and concluding that there is no significant effect, when in fact the null hypothesis is false and there really is a difference.

This research has thrown up few ideas for future research. A natural progression of this work is to investigate the risk of individual infectious diseases such as UTI using diagnosis as outcome. Future research should consider the impact of different length of fasting on dehydration and potential risk of UTI through comparing the risk between different geographical locations. Another possible area of future research would be to investigate the effect of Ramadan fasting of risk of Covid-19.

The absence of a clear effect is encouraging in terms of the safety of fasting, although at-risk groups should note that additional risks may remain, including complications from diabetes and cardiovascular disease, which were beyond the scope of this study. Currently, there is no evidence that Ramadan fasting itself increases the risk of contracting bacterial infections within the studied population, although the generalisability to other populations (including in warmer climates) is uncertain. Further research on this topic in other communities and countries is necessary, in order to account for factors such as Ramadan season, age, gender, and comorbidity.

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6 Chapter six: The effect of Ramadan fasting on cardiovascular diseases

Ischemic Heart Disease Risk in Pakistani and Bangladeshi Populations: Findings from Controlled Interrupted Time Series Analysis in University Hospitals Birmingham, UK

6.1 Abstract:

Background: It is speculated that changes such as mealtime and sleeping pattern that occur during Ramadan could lead to circadian dysfunction, which can increase the risk of cardiovascular disease (CVD). However, there is a lack of information on the effect of Ramadan fasting on the risk of CVD. This study examines hospitalisation patterns for ischemic heart disease (IHD) before, during and after Ramadan in the Pakistani and Bangladeshi populations in the UK, most of whom are Muslims, compared to patterns among those who do not observe Ramadan.

Method: Retrospective controlled interrupted time series (CITS) analysis using anonymised data obtained from the University Hospitals Birmingham (UHB). The study consists of two groups comprising Pakistanis/Bangladeshis and white individuals. The inclusion criteria were all hospitalisations for Pakistani, Bangladeshi, and white patients with IHD as first diagnosis (ICD-10 codes I20–I25) a month before Ramadan, the month of Ramadan and a month after Ramadan. For each group, we constructed a series of aggregated daily data from 2009 to 2018 for the 30 days before, during and after Ramadan.

Findings: Controlling for the admission rate in the white population, there was no evidence of increased IHD-related admissions in the Pakistani/Bangladeshi population during Ramadan compared to before Ramadan (IRR: 0.999, 95% CI: 0.975–1.023, p=0.930) or after Ramadan (IRR: 0.999, 95% CI: 0.972–1.025, p=0.913).

Interpretation: The findings of the study suggest that Ramadan fasting is not associated with an increased risk of IHD.

6.2 Introduction:

Ramadan is the ninth month in the Islamic calendar. Muslims observing this month abstain from food and drinks as well as oral medications from sunrise to sunset. Ramadan fasting is associated with significant changes in daily routines. This includes changes in mealtimes, sleeping patterns and physical activity levels [1-3], which can be associated with changes in metabolism and circadian rhythms.[4,5] The resulting changes in insulin resistance as well as multiple neurohormonal changes, including the activation of the hypothalamic-pituitary axis and increased catecholamine levels, can lead to endothelial dysfunction and an increased number of cardiovascular events.[5-7]

Some studies reported that the daylight saving time transition, i.e. the practice of turning clocks forward by an hour in spring, was associated with an increased risk of acute myocardial infarction (MI).[8-10] It is speculated that sleep deprivation has adverse effects on cardiovascular health. Adverse effects include a predominance of sympathetic activity and an increase in proinflammatory cytokine levels.[11] Studies on sleep and Ramadan reported that sleep is disturbed during Ramadan.[2,12,13] Changes in sleep patterns include delayed sleep, decreased sleep cycles times, decreased rapid eye movement sleep. [2,14,15]

Dehydration is another possible trigger of cardiovascular disease (CVD) in Ramadan. The increased blood viscosity that could be induced by dehydration may increase the risk of thrombosis, and thereby, the risk of CVD.[16,17] A small study in Iran reported that Ramadan was associated with a significant increase in cerebral venous sinus thrombosis compared to the other months. [18] The study speculated that this increase was due to dehydration.

In the UK, Muslims represent 5% of the population. Two-thirds of them are Asian, and Pakistanis and Bangladeshis comprise the largest Muslim ethnic groups, representing 38% and 15% of Muslims in the UK, respectively. [19] These populations have a high burden of chronic disease, in particular, diabetes and CVD. [20] The current evidence suggests that Ramadan is not associated with an increased incidence of CVD. [21,22] However, the effect of Ramadan on CVD has not been investigated extensively, and a few comprehensive reviews have shown that this is a research-deficient area. [22,23] Moreover, we recently conducted a systematic review that revealed a lack of studies investigating the effects of fasting on patterns of hospital admissions and complications in patients with diabetes. [24] To address the gap in the literature regarding the effects of prolonged fasting on ischemic heart disease (IHD), we aimed to examine IHD-related hospitalisation patterns before, during, and after Ramadan in a predominantly Muslim population compared to one which does not observe Ramadan, in the University Hospitals Birmingham (UHB), UK.

6.3 Methods:

6.3.1 Study design and data source:

We performed a retrospective controlled interrupted time series study using anonymised data obtained from the UHB, which is a large, approximately 1200-bed teaching hospital trust in England. The data were extracted from the Prescribing Information and Communications System (PICS), which is an electronic medical record system at the University Hospitals Birmingham NHS Foundation Trust. The data included data from both admitted patient care and A&E data. Birmingham is one of the UK's most diverse cities. The Office for National Statistics (ONS) estimates that Birmingham's resident population was 1,141,800 in 2019. [25] Birmingham is the largest local authority district and is home to around 20% of the residents in the West

Midlands [26], with an ethnic composition that is 57.9% white, 13.5% Pakistani, 6% Indian, 4.4% Caribbean, 3.0% Bangladeshi, 2.8% African, 1.2% Chinese and 11.1% other ethnicities.[27] It is estimated that Muslims represent about 7.5% of the population in Birmingham, making Islam the second-largest religion in Birmingham.[26] Therefore, Birmingham was selected as the location for this study.

6.3.2 Study period:

The study period consisted of the time before, during, and after Ramadan each year from 2009 to 2018. We only included three months in each year. As Ramadan is based on the lunar calendar, in which calendar months can last for 29 or 30 days depending on the sighting of the moon, we standardised months to 30 days for this study. We identified the start of Ramadan each year and identified 30 days before, during and after Ramadan based on that date.

6.3.3 Population:

The study consisted of two groups. The first targeted group comprised Pakistanis and Bangladeshis, who represent the Muslim population in this study. The second group was the control group consisting of white individuals who do not observe Ramadan. Ethnicity in the hospital information system is coded based on the census classification on ethnicity. A subpopulation of patients with diabetes was also identified using the International Classification of Diseases (ICD)-10 codes for diabetes (E11–E11.9). Patients with the outcome of interest, i.e. IHD, were also identified based on the ICD-10 codes (I20–I25).

6.3.4 Analysis:

We used descriptive statistics to summarise the basic features of the data from before, during and after Ramadan. We investigated the frequency of IHD-related hospital admission using interrupted time series (ITS) analysis, which is a quasi-experimental design that can evaluate

an intervention effect using longitudinal data. ITS analysis requires data on continuous or counted outcome measures, summarised at regularly spaced time intervals. This model often uses before-and-after comparisons for underlying trends; it is particularly useful for assessing the impacts of policies or healthcare initiatives. It can provide information on any changes that could have occurred due to the intervention/exposure, whether immediately or over time. Single ITS (SITS) analysis elucidates changes within a group before and after the exposure. Controlled ITS (CITS) analysis, which includes a control group, helps separate the effect of the exposure from other confounding effects that could have occurred at the same time.[28,29]

For each group, we developed a series of 90 days of data (30 days each before, during and after Ramadan) consisting of aggregated daily data from 2009 to 2018. We performed two analyses, ITS and CITS. We then explored effect modification via the following factors: sex, age (< 60 years and > 60 years) and diabetes status. In the stratified analysis, due to the low numbers of events in some of the factors and to avoid zero events, we aggregated data from 5 days.

Interrupted time series (ITS) analysis requires a minimum of three variables[30]:

- T is the time since the start of the study (e.g., day, month, or year);
- X_t is a dummy (indicator) variable representing the intervention (pre-intervention periods equal 0, otherwise 1); and
- Y_t is the aggregated outcome variable measured at each equally spaced time point t.

The following segmented regression model is used for standard ITS analysis[30]:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \varepsilon_t$$

where β_0 represents the baseline level at T = 0; β_1 represents the change in outcome associated with a time unit increase (representing the underlying pre-intervention trend); β_2 is the level of change following the intervention; β_3 indicates the change in slope pre- and post-intervention; ε_t is an error term.

Controlled interrupted time series (CITS) analysis requires a minimum of four variables[30]:

- T is the time since the start of the study (e.g., day, month, or year);
- X_t is a dummy (indicator) variable representing the intervention (pre-intervention periods equal 0, otherwise 1);
- Z_t is a dummy variable to denote the cohort assignment (treatment or control); and
- Y_t is the aggregated outcome variable measured at each equally spaced time point *t.*

The controlled interrupted time series model is indicated by the following equation[30]:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \beta_4 Z_t + \beta_5 Z_t T + \beta_6 Z_t X_t + \beta_7 Z_t T X_t + \varepsilon_t$$

where β_0 to β_3 represents the control group, and β_4 to β_7 represents the treatment group. β_4 represents the difference in level between treatment and control prior to the intervention. β_5 represents the difference in the slope between treatment and control prior to the intervention. β_6 represents the difference in level between treatment and control in the period immediately following the intervention initiation. β_7 represents the difference between the treatment and control in the slope after the intervention was initiated, compared to the pre-intervention period; ε_t is an error term.

6.4 Results:

A total of 1,031,962 hospital admissions were included in the study from 1st January 2009 to 30th September 2018. We identified 22,305 IHD-related admissions and included 4,670 IHD-related admissions in the analysis, 460 admissions among Pakistanis/Bangladeshis and 4,210 among white individuals (Figure 1). The proportion of males was higher in both groups across the study period. The Pakistani/Bangladeshi group in all periods (before, during, after) were younger than the white group and had a higher proportion of patients with diabetes (Table 1).

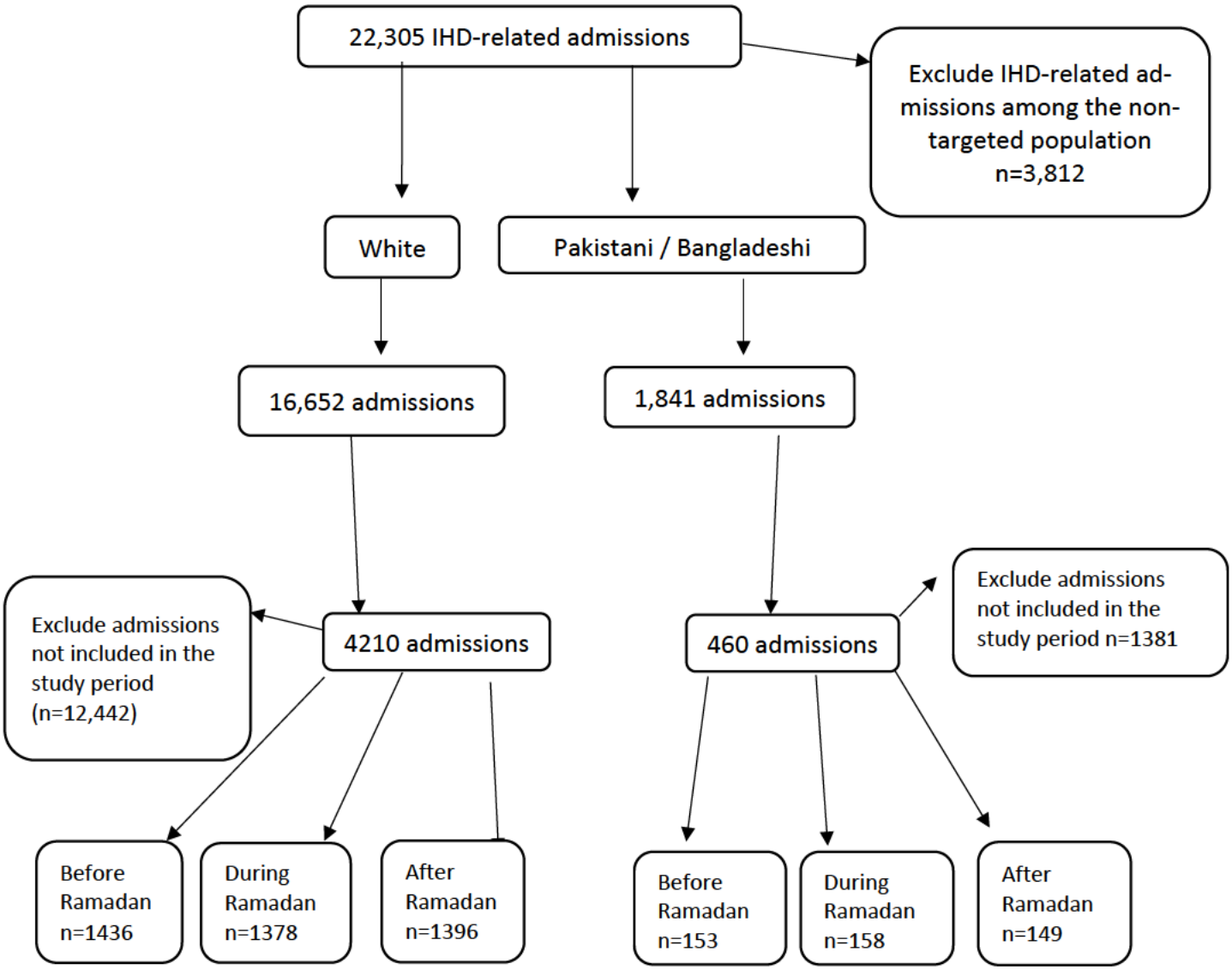

Figure 1: Flow diagram of the study data

Table 1: Characteristics of the aggregated IHD-related admissions data from before, during and after Ramadan each year from 2009 to 2018

	White (4,210 IHD-related admissions)			Pakistani/Bangladeshi (460 IHD-related admissions)		
	Before Ramadan (1,436)	During Ramadan (1,378)	After Ramadan (1,396)	Before Ramadan (153)	During Ramadan (158)	After Ramadan (149)
No. of contributing patients	1,375	1,314	1,319	137	153	143
Sex						
Male	987 (68.73%)	986 (71.55%)	982 (70.34%)	110 (71.90%)	117 (74.05%)	105 (70.47%)
Female	449 (31.27%)	392 (28.45%)	414 (29.66%)	43 (28.10%)	41 (25.95%)	44 (26.53%)
Age (year), mean (SD)						
All	66.90 (12.02)	67.32 (11.91)	66.89 (1.95)	62.08 (13.19)	63.35 (13.37)	63.85 (12.37)
Male	65.41 (11.44)	65.84 (11.20)	65.40 (11.14)	61.09 (13.63)	62.51 (13.08)	64.31 (13.27)
Female	69.18 (12.63)	71.01 (12.83)	70.42 (13.02)	64.62 (11.77)	65.75 (14.05)	62.77 (9.96)
Comorbidities						
Diabetes	280 (19.50%)	273 (19.81%)	285 (20.42%)	73 (47.71%)	82 (51.90%)	73 (48.99%)
Hypertension	102 (33.77%)	103 (34.11%)	97 (32.12%)	840 (33.82%)	817 (32.89%)	827 (33.29%)

6.4.1 SITS analysis:

The time series analysis did not identify any significant trend change in IHD-related admissions during Ramadan (as compared to before Ramadan; IRR: 1.000, 95% CI: 0.978–1.023, p=0.975) or after Ramadan (compared to during Ramadan; IRR: 0.995, 95% CI: 0.971–1.019,0.671) in the Pakistani/Bangladeshi group. Similarly, there was no change observed in IHD-related admission patterns in the white population during Ramadan (IRR: 1.001, 95% CI: 0.994–1.009, p=0.716) or after Ramadan (IRR: 0.996, 95% CI: 0.988–1.005, p=0.996; Figure 2, Table 2).

6.4.2 CITS analysis:

Controlling for the background IHD-related admission patterns in the white population did not alter our findings when admissions during Ramadan in the Pakistani/Bangladeshi group were compared to those before Ramadan (IRR: 0.999, 95% CI: 0.975–1.023, p=0.930) or after Ramadan (IRR: 0.999, 95% CI:0.972–1.025, p=0.913; Figure 3, Table 2).

6.4.3 Stratified analysis:

Figure 4 shows the IRR (95% CI) for the stratified groups in the Pakistani/Bangladeshi population controlled for the background rate in the white population (CITS analysis). There was no difference in IHD-related admissions observed when the population was stratified by age. Similarly, no significant change in IHD-related admissions was observed during Ramadan compared to the period before in both males (IRR: 1.010, 95% CI: 0.838–1.219) and females (IRR: 0.939, 95% CI: 0.747–1.180). After Ramadan, females showed an insignificant increase in IHD-related admissions compared to the period during Ramadan (IRR: 1.217, 95% CI: 0.973–1.524), while there was no notable difference in men (IRR: 0.904, 95% CI: 0.763–1.070). No

significant change in IHD-related admission patterns was identified in patients with diabetes during Ramadan (IRR: 0.998, 95% CI: 0.832–1.197) or after Ramadan (IRR: 1.001, 95% CI: 0.845–1.187). Similarly, we did not observe any changes in incident IHD in patients with hypertension during Ramadan compared to before Ramadan (IRR: 0.894, 95% CI: 0.751–1.064) or after Ramadan (IRR: 1.138, 95% CI: 0.991–1.308) compared to during Ramadan. However, we observed a significant decrease in IHD-related admission patterns after Ramadan (compared to during Ramadan) in patients without hypertension (IRR: 0.781, 95% CI: 0.627–0.973).

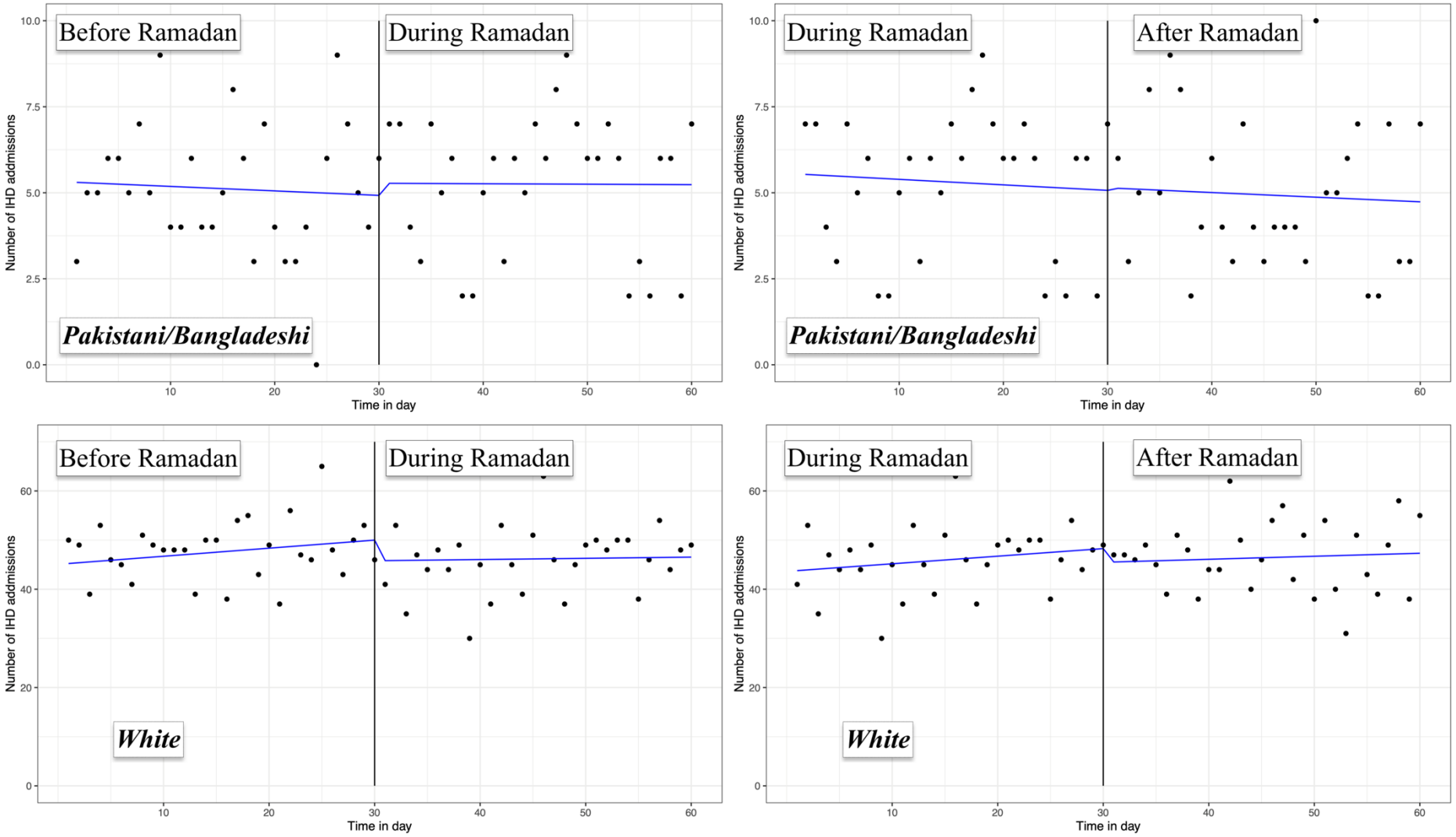

Figure 2: Daily IHD-related admission patterns (SITS)

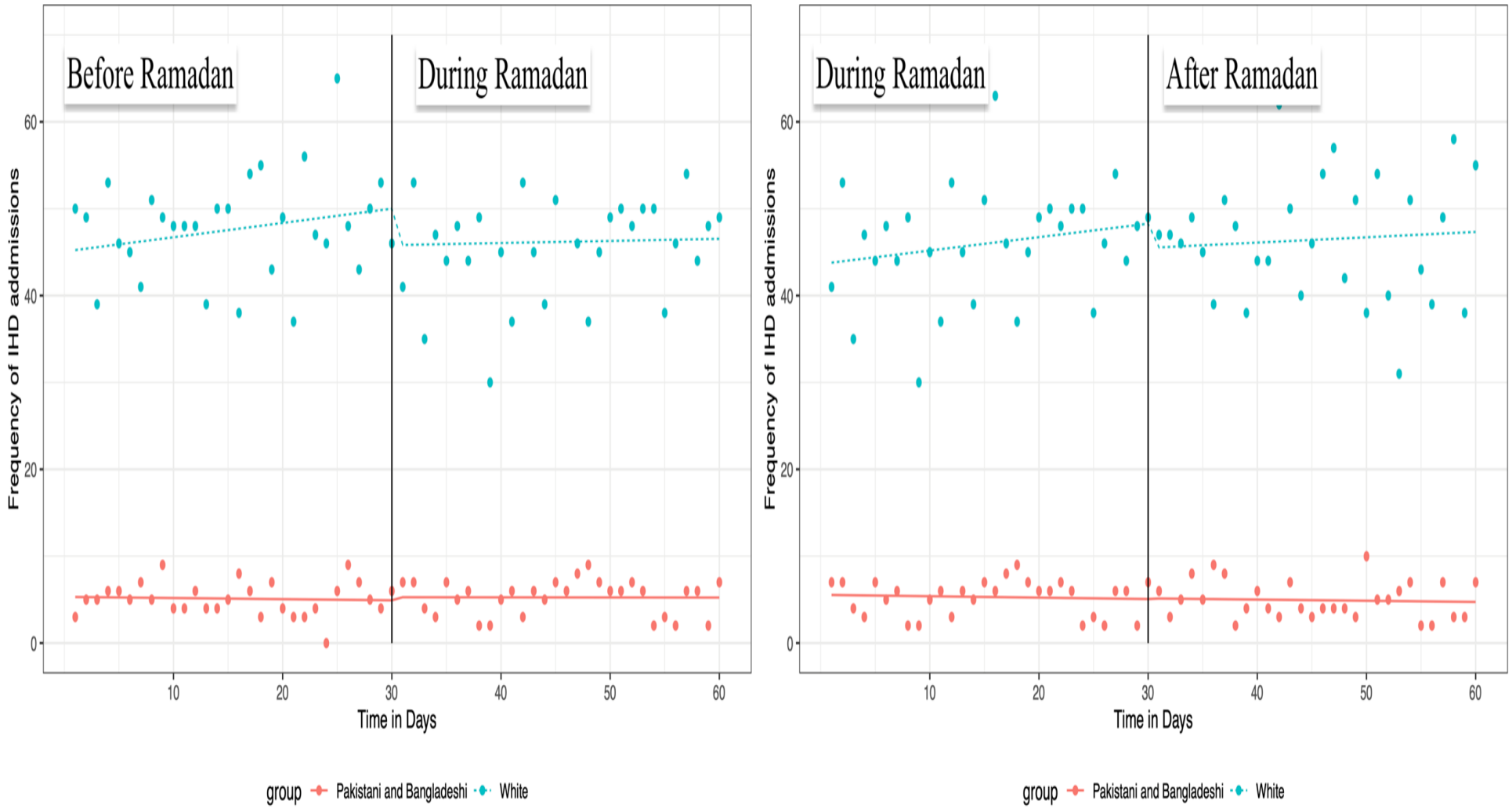

Figure 3: Daily IHD-related admission patterns (CITS)

Table 2: Findings from the SITS and CITS analyses

Parameter	SITS	P-value	Parameter	CITS	P-value
	IRR (95% CI) *			IRR (95% CI)*	
Difference in trend changes before/during Ramadan (Pakistani/Bangladeshi) - $\beta 3$	1.000 (95% CI: 0.978–1.023)	0.975	Difference in trend changes between the two groups before/during Ramadan - $\beta 7$	0.999 (95% CI: 0.975–1.023)	0.930
Difference in trend changes before/during Ramadan (white) - $\beta 3$	1.001 (95% CI: 0.994–1.009)	0.716			
Difference in trend changes during/after Ramadan (Pakistani/Bangladeshi) - $\beta 3$	0.995 (95% CI: 0.971–1.019)	0.671	Difference in trend changes between the two during/after Ramadan - $\beta 7$	0.999 (95% CI: 0.972–1.025)	0.913
Difference in trend changes during/after Ramadan (white) - $\beta 3$	0.996 (95% CI: 0.988–1.005)	0.996			

* IRR (95% CI) in the Pakistani/Bangladeshi population controlled for the background rate in the white population

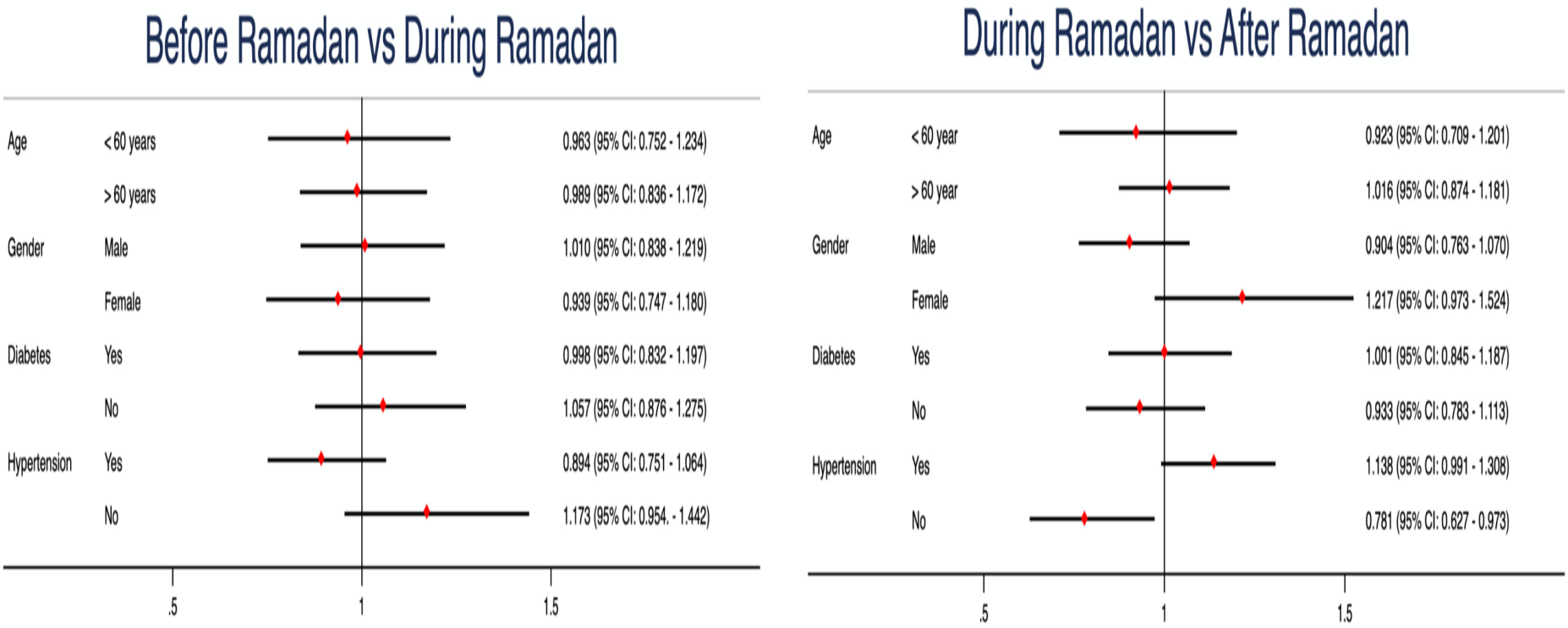

Figure 4: IRR with 95% confidence intervals for the stratified groups in the Pakistani/Bangladeshi population controlled for the background rate in the white population

6.5 Discussion:

This study aimed to assess patterns of IHD-related hospitalisation before, during and after Ramadan in a predominantly Muslim population in the UK. We found no significant differences in the pattern of hospitalisation during and after Ramadan in the Pakistani/Bangladeshi population. Another important finding was that Ramadan fasting was not associated with altered hospitalisation patterns among older adults (> 60), those with diabetes and those with hypertension—groups with the greatest potential risk.

These findings further support the idea that Ramadan fasting does not increase the risk of IHD. The findings of the current study are consistent with those of another hospital study conducted in Turkey between 1991 and 1997 [31], which suggested that Ramadan fasting does not increase the risk of IHD events. Similar to our findings, there was no significant effect of age and gender in the study.[31] These findings are also in accordance with a large population-based study that was conducted in Qatar over a 10-year period. The study did not find any significant differences in the incidence of acute MI or unstable angina before, during and after Ramadan.[32] Clinical characteristics of patients such as age, smoking status, hypertension, diabetes and pre-existing cardiac disease did not show any significant difference.[32]

It is speculated that Ramadan fasting could have a cardio-protective effect on CVD patients. Ramadan fasting does not exacerbate IHD symptoms. Mousavi, Mirkarimi [33] reported that symptoms such as chest pain and dyspnoea in the fasting group were not significantly different from those in the non-fasting group. Another small study in Saudi Arabia found that fasting was significantly associated with shorter hospitalisation after acute MI compared to the

those who did not fast.[34] However, it was not reported if the non-fasting group were more ill or not , which could explain why where not fasting.

Studies on daylight savings time proposed that even mild changes in sleeping patterns increase the risk of acute MI.[8,9] A meta-analysis that included more than 100,000 participants reported that the weeks following spring and autumn daylight savings were significantly associated with an increased risk of acute MI.[10] Changes in lifestyle that occur in Ramadan may contribute to the disruption of the circadian rhythm. Such changes include sudden shifts in mealtimes and sleep patterns. It is suggested that during Ramadan, sleep duration is reduced significantly by about one hour and diurnal sleepiness increases.[14] These changes could lead to circadian dysfunction. Circadian rhythm dysfunction causes impaired cardiometabolic function, which can lead to an increased risk of CVD.[35] However, the current evidence suggests that Ramadan is not associated with an increased risk of CVD.[21,22,36] This could be because of the favourable changes in CVD risk factors reported in Ramadan.[36] The literature suggests that Ramadan fasting could induce favourable changes in healthy individuals which could reduce the risk of CVD [37-39] [40], including improvements in lipid profile, blood pressure and anthropometric parameters such as weight, body mass index (BMI) and waist circumference.

To our knowledge, this is the first study to investigate patterns of IHD hospitalisation before, during and after Ramadan in a predominantly Muslim community in the UK. A key strength of this study is the use of CITS analysis, which allows tracking of changes within a group across different periods. Further strengths of our study include the extensive study period and use of a control group that does not typically observe Ramadan. However, several limitations

need to be acknowledged. This was a single-centre study; therefore, the finding may not represent all Pakistani/Bangladeshi communities or other Muslim communities in the UK. We could not also confirm patients were fasting or not. Our assumption of fasting within the Pakistani/Bangladeshi populations was based on estimates that more than 90% of people from these ethnic backgrounds are Muslims and that most Muslims practice fasting.[41,42] The results of our study may not reflect other Muslim communities within the UK as different communities may have differing fasting rituals and cultural traditions that could affect the results. Another issue is the lack of sample size calculation. Due to the small sample size, there is an increased chance of type II errors, where the study found that there is not a significant effect, when there is an effect. Thus, caution must be applied, as the findings might not be transferable to other Muslim communities. Moreover, the scope of this study was limited in terms of the consideration of other types of CVD in the analysis; due to the limited number of cases, we only considered IHD in the study. Additionally, the analysis did not account for seasonal changes. Ramadan moves 11 days forward every year, thus complicating the analysis.

At present, there is no evidence that fasting itself increases the risk of IHD. However, the data available in this area is sparse, which limits the strength of any recommendations. More research is needed to better understand the impact of fasting on the risk of CVD. Large multicentre observational studies could provide more definitive evidence. It will be interesting to investigate this area in other Muslim communities and countries and consider other forms of CVD. This will provide more information to establish evidence-based recommendations for patients wishing to fast Ramadan. Further studies are needed to explore gaps in knowledge around fasting and its impact on CVD to help refine current recommendations.

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7 Chapter seven: Discussion

7.1 Contents of Chapter 7

The final chapter of this thesis summarises the key findings in relation to the aims of the thesis, how the findings fit into the context of the current literature, the strengths and limitations of overall thesis, the challenges of research on Ramadan fasting, recommendations, personal reflections and suggestions for future work. As the thesis has been written in an alternate format, it is worth noting that there is a detailed discussion section within each of the manuscripts. Therefore, there may be some overlaps and repetitions.

7.2 Summary of key findings

As described in Chapter 1, the aims of this thesis were to assess the impact of Ramadan fasting on different aspects of health and to strengthen the available evidence on the effect of Ramadan fasting on health using robust methods that have not previously been applied in Ramadan research.

I intended to achieve the aims of the thesis through the following steps: (1) describe the cardiometabolic profile of a predominantly Muslim population in the UK, (2) review the literature on Ramadan and CVD risk in patients with diabetes, (3) assess the risk of infection before, during and after Ramadan in a predominantly Muslim population in the UK and (4) estimate the incidence of hospital admissions for IHD before, during and after Ramadan in a predominantly Muslim population in the UK.

7.2.1 Cardiometabolic profile of a predominantly Muslim population in the UK

As pointed out in Chapter 1, this thesis focuses on a Pakistani/Bangladeshi population as it represents the largest predominantly Muslim community in the UK. Before conducting my

research on Ramadan, I described the health profile of this population. In Chapter 3, I described the conduct of a controlled, population-based cohort study aiming to explore the cardiometabolic profile of this population. Differences in health outcomes across ethnic groups have been documented in the UK.[19-21] Although South Asians (SAs) may be divided into different ethnic groups, they tend to be studied as one group. Thus, findings from previous studies may not represent the complete picture of SA subgroups.

Overall, SA patients were at increased risk of developing T2DM, HTN, IHD and HF, with a lower risk of AF. The findings of this study suggest that there are variations in health outcomes depending on the subgroup being explored. The study showed that, compared to their matched white controls, Bangladeshis had the highest risk of diabetes with a more than fivefold increase in risk (aHR 5.30, 95% CI: 4.62–6.09), followed by Pakistanis with a more than threefold increase in risk (aHR 3.51, 95% CI: 3.23–3.82) and Indians (aHR 2.67, 95% CI: 2.52–2.83). However, these should be interpreted with caution as my study did not directly compare between SA subgroups. This was consistent with the findings of Hippisley-Coxet.al [22], who reported that Bangladeshis had a higher hazard ratio than Pakistanis and Indians compared to the white population.

The increased prevalence of diabetes in SAs has been associated with an increased risk of CVD in this group.[23] Compared to their matched white controls, the risk of IHD was higher in Bangladeshis (aHR 2.03, 95% CI: 1.95–2.61) and Pakistanis (aHR 2.09, 95% CI: 1.83–2.39), followed by Indians (aHR 1.53, 95% CI: 1.39–1.68).

The three subgroups had a higher risk of hypertension compared to white controls. Bangladeshis had the highest risk of hypertension with aIRR 1.47, 95% CI: 1.28–1.68 (Indians: aIRR 1.35, 95% CI: 1.29–1.42; Pakistanis: aIRR 1.32, 95% CI: 1.22–1.43). Agyemanget.al [24] pointed out that blood pressure levels and the prevalence of hypertension varies across SA subgroups in the UK compared to the white population. In this study we found that compared to their white control the highest risk was found in Indians, and the lowest was found in Bangladeshis.

The SA population has consistently been shown to have a lower prevalence of AF despite the high prevalence of AF risk factors in the population.[25-27] Compared to their matched white controls, all three SA subgroups had lower risk of AF at follow-up (Bangladeshis: aHR 0.41, 95% CI: 0.26–0.64; Indians: aHR 0.54, 95% CI: 0.48–0.61; Pakistanis: aHR: 0.51, 95% CI: 0.41–0.63). Similar to the findings of Owusu Adjahet.al [28], there was no significant difference in the risk of stroke between the SA and white populations. It would be expected that as the risk AF is lower in SA that the risk of stroke would be lower (as AF is risk factor for stroke). This could be due to underdiagnosis of AF in SA.

Differing risk factor profiles between SA communities have not been examined extensively to explain the heterogeneity in risks. It is not clear why Bangladeshi seems to have the worst health profile. It is suggested that the variation in risk between groups could be attributed to the heterogeneity of genotypes, cultures, health behaviours, belief systems, education , socio-economic status, migration patterns and risk factors encompassed among different SA immigrant communities.[29] Thus more studies are needed to explain why Bangladeshi seems to have the worst health profile among SA subgroups even after accounting for key risk factors.

The heterogeneity across the SA subgroups could be explained by the heterogeneity of health behaviours. Although these groups share the same ethnicity, there are different risk factors associated with each one.[30] For example, smoking is known to be more prevalent amongst Bangladeshi men than Indians and Pakistanis.[31,32]

Religion is another factor that has been discussed in the literature to explain the variation in health outcomes between groups. it is proposed that religion can influence health.[33-35] Most Pakistanis and Bangladeshis in the UK are Muslims and the majority of Indians are Hindus.[36] Williams [29] found that although SAs share the same background and culture, CVD risk factors were heterogeneous within the different SA religious subgroups. Indian Sikhs show a high rate of heavy drinking, while most SAs from a Muslim background, such as those from Pakistan and Bangladesh, abstain from alcohol for religious reasons.[37]

Ramadan fasting can be considered a potential challenge for Muslim health. As pointed out in Chapter 1, the impact of Ramadan fasting on health is an area of recent interest. The current understanding of health disparities could be enhanced by an appreciation of ethnicity and religion.[38] Unlike race and ethnicity, the effect of religion on health is underinvestigated. There is a lack of quantitative studies assessing the impact of religion on health and the extent to which faith could impact health outcomes.[39]

7.2.2 Impact of Ramadan on health

Ramadan and CVD in patients with diabetes

As described in Chapter 4, I conducted a systematic review on the effect of Ramadan fasting on CVD in patients with diabetes. The review included 22 studies, five of which reported CVD events and 17 of which reported changes in cardiovascular risk factors. Based on the included studies, the review did not identify any association between Ramadan fasting and the risk of CVD events in people with diabetes. However, the findings were inconsistent in terms of CVD risk factors as some favoured Ramadan and others did not.

Ramadan fasting and risk of infection

As described in Chapter 1, much uncertainty still exists regarding the risk of infection in the Muslim population in Ramadan. In reviewing the literature, no previous study was found to have been conducted to explore the risk of infection during Ramadan in the Muslim population. Therefore, I conducted a study to describe the risk of bacterial infection in the Pakistani/Bangladeshi population in the UK based on an evaluation of prescriptions for antibiotics (see Chapter 5). In this large, population-based study, an interrupted time series analysis demonstrated that there was no significant change in the prescribing pattern during Ramadan (compared to before Ramadan) among the Pakistani/Bangladeshi population (IRR: 0.995, 95% CI: 0.990–1.001, p = 0.089). However, there was an increase in the prescription of antibiotics following Ramadan (compared to during Ramadan) among this population (IRR: 1.007, 95% CI: 1.001–1.013, p = 0.025). Interestingly, this observation did not remain statistically significant once antibiotic prescriptions in the white population were corrected for (IRR: 0.999, 95% CI: 0.972–1.025, p = 0.913). Importantly, the Ramadan period was not associated with altered

prescription patterns among older adults (> 60 years) or among those with diabetes, the two groups with the greatest potential risk of infection.

Ramadan Fasting and IHD hospitalisation

The study in Chapter 6 was designed to describe IHD-related hospitalisation patterns before, during and after Ramadan in the UK-based Pakistani/Bangladeshi population using data from UHB. An interrupted time series analysis did not identify any significant trend change in IHD-related admissions during Ramadan (compared to before Ramadan; IRR: 1.000, 95% CI: 0.978–1.023, p = 0.975) or after Ramadan (compared to during Ramadan; IRR: 0.995, 95% CI: 0.971–1.019, p = 0.671) in the Pakistani/Bangladeshi group.

Controlling for the background IHD-related admission pattern in the white population did not change our findings when IHD-related admissions during Ramadan were compared to those before Ramadan (IRR: 0.999, 95% CI: 0.975–1.023, p = 0.930) or after Ramadan (IRR: 0.999, 95% CI: 0.972–1.025, p = 0.913) in the Pakistani/Bangladeshi group. Another important finding of this study is that Ramadan fasting was not associated with an increased risk of IHD-related hospitalisation in patients > 60 years or patients with diabetes or hypertension.

7.3 Results in relation to the current literature on Ramadan and health

Below, I outline the areas where the studies contributing to this thesis support or contradict the current literature. In this section, I will not include Chapter 3 in the discussion as it has been discussed earlier (7.2.1). I will be focusing on the work on Ramadan (Chapters 4–6) as they are the focus of the thesis.

7.3.1 Ramadan fasting and CVD risk in patients with diabetes

One of my areas of interest was the effect of Ramadan fasting on CVD in patients with diabetes. Several studies have attempted to explore the impact of Ramadan fasting on the risk of CVD. However, the systematic review in this thesis is the first to focus on the associations between Ramadan fasting, CVD events and risk factors in patients with diabetes. Based on the systematic review, there is insufficient evidence to make clear conclusions on the association of fasting during Ramadan with the risk of CVD events in people with diabetes. However, the findings of this review are consistent with those of Salim [13] and Turinet.al [40] in term that there is no evidence of that Ramadan fasting is associated with increased risk of CVD events. The literature suggests that Ramadan fasting could induce favourable changes in healthy individuals which could reduce the risk of CVD [13-15] [16], including improvements in lipid profile, blood pressure and anthropometric parameters such as weight, BMI and waist circumference. However, the findings of this review were inconsistent in terms of risk factors as some favoured Ramadan and others did not. The review highlighted the scarcity of quality research in this area.

The inconsistent findings of Ramadan fasting studies could be attributed to different reasons, including variations in geographical locations, climate conditions, fasting duration and diversity in dietary and sleeping habits. Another possible explanation for the discrepancies is differences in methodological approaches between studies, namely the time points of baseline measurement, duration of follow-up, patient eligibility and exclusion criteria and timing of blood sampling of participants. Risk of bias between studies was mainly affected by confounding factors and participants selection. Though some studies reported collecting some clinical information from their participants, none of them accounted for the potential confounders

in their analysis. Moreover, It is need to be noted that some studies did not report any clinical data. Having these data would provide better understanding on the effect of Ramadan fasting on CVD and its risk factors in patients with diabetes by considering the impact of potential confounders. Lack of accounting of potential confounder could bias the results. It is not clear if there was an effect if was truly due to the fasting process or any other confounders. Participant selection is another source of bias of the studies. In many studies the recruitments were opportunistically, which led to imbalance in the characteristics of the samples. Another noted issue is that some studies excluded those with comorbidities or diabetes complications, smokers, and those were on insulin. This led to a concern of the representation of the sample to the targeted population.

Due to the degree of heterogeneity in key aspects of Ramadan and diabetes studies, comparisons across studies remain challenging.[41] Hence, although a variety of guideline documents have been published offering recommendations on managing diabetes during Ramadan, there is no gold-standard guideline with evidence-based recommendations.[42]

7.3.2 Ramadan fasting and the risk of infection

The study described in Chapter 5 of this thesis relates to antibiotic prescription patterns before, during and after Ramadan in a predominantly Muslim population in the UK. I conducted this study to explore the risk of infection in Ramadan using primary health care records. In this large, population-based study, I applied a unique method that has never been used before in Ramadan studies, i.e., CITS analysis. The study found no evidence that Ramadan fasting is associated with an increased risk of infection. This result conflicts with the findings of Joachimet.al [43], who reported that Ramadan fasting is associated with an increased risk of

acute sialadenitis during Ramadan compared to the other months when fasting does not take place. They speculated that the increase in risk was caused by dehydration due to fasting.

The effects of Ramadan fasting on the immune system have previously been studied using indices of basal inflammation and the immune system's potential to respond to infection. Although there are some claims that Ramadan fasting could adversely impact the immune system, more recent evidence refutes these claims.[44] Nevertheless, much uncertainty exists regarding the effect of Ramadan fasting on the immune system and very little was found in the literature on the impact of Ramadan fasting on immunity and the risk of infection. In the context of the ongoing COVID-19 pandemic, there has been increased interest in delineating the impact of Ramadan fasting on the risk of infection.[44-46] Unfortunately, there has been no investigation of the impact of Ramadan fasting on COVID-19 incidence, and such an analysis was out of the scope of the work in this thesis. However, the available evidence suggests that Ramadan fasting does not negatively impact the immune system, with indications that it may even be beneficial to the immune system.[44 47]

7.3.3 Ramadan fasting and cardiovascular disease

The available evidence suggests that Ramadan fasting is not associated with an increased risk of cardiovascular events in Ramadan.[10,11] The findings of the study detailed in Chapter 6 of this thesis support the current evidence, matching those of previous studies. A hospital study conducted in Turkey between the years 1991 and 1997 speculated that Ramadan fasting does not increase the risk of IHD events.[1] This statement is supported by a large, population-based study conducted in Qatar over a 10-year period, which reported that there were no significant differences in the number of hospitalisations for IHD during Ramadan compared to the rest of the year.[48]

CVDs are the leading cause of death in the world.[49] As stated earlier, Ramadan is associated with a sudden change in daily routines including eating and sleeping patterns as well as physical activity levels.[50,51] Circadian rhythm dysfunction causes impaired cardiometabolic function which can lead to an increased risk of cardiovascular disease [9]. However, the current evidence suggests that Ramadan is not associated with increased incidence of CVD [10-12]. This could be because of the favourable changes in CVD risk factors reported in Ramadan, particularly lipid profile.[12]

Factors such as hypertension, diabetes and age increase the risk of developing CVD [52]. The findings of this study show that the risk of CVD in patients with these risk factors was not affected by the Ramadan period. Nematyet.al [53] reported improvements in the CVD risk factors in patients with history of CVD during Ramadan. Elbarshaet.al [54] investigated hospital admissions in Ramadan among patients with diabetes. There was no significant variation in the reasons for admission between Ramadan and the non-fasting period. However, admissions for CVD were significantly higher among those who were fasting compared to those who did not fast. Those who did not fast were high-risk patients. A recent study found that the risk of stroke increased significantly during Ramadan. The association was significant in the first half of Ramadan but not in the second half. However, this association was absent when compared to a non-Muslim population.[55] A multi-centre study that explored the effect of fasting on patients with acute HF reported that Ramadan fasting did not worsen the signs and symptoms in patients hospitalised with HF.[56]

With a significantly high and increasing prevalence of CVD in Muslim communities, including in the UK as suggested by the findings of Chapter 3, healthcare professionals (HCPs) are likely to come across inquiries from patients regarding their suitability for Ramadan fasting. Therefore, there is a need for evidence-based recommendations that help HCPs in dealing with those who plan to fast. However, there is a lack of evidence supporting such recommendations.

7.4 Strengths and limitations

The strengths and limitations of each of the studies' methods have been discussed in detail in Chapters 3–6. Therefore, in this section, I will mainly focus on the general themes that run throughout the thesis.

7.4.1 Strength of evidence

The present thesis makes several noteworthy contributions to the growing body of literature on the impact of Ramadan fasting on health. To the best of my knowledge, the areas that have been explored in the studies contributing to this thesis have not been previously explored. One of the main issues in Ramadan studies that I aimed to address through this work is improving the quality of evidence. Evidence-based guidelines are extremely important to support HCPs dealing with patients wishing to fast for Ramadan safely. Unfortunately, most of the available evidence and guidelines are based on small observational studies that lacked a robust design, or on experts' opinions.[57] Therefore, I used CITS design in this thesis (see Chapters 5 and 6), which is considered to be one of the strongest quasi-experimental designs for evaluating the longitudinal effects of interventions/exposures. To my knowledge, this is the first time this method has been used in Ramadan studies. One of the advantages of this

design is that it can detect secular trends which occur before, during and after the exposure (in this case Ramadan month). Moreover, the previous research in this area tended to lack a control group, which threatens the validity of the result. However, the unique method that I applied in this thesis allowed me to add a control group that does not observe Ramadan. Adding control groups can separate the effect of the exposure from other confounding effects that could have occurred at the same time. Taking these points together, the evidence provided in this thesis may be considered robust.

7.4.2 Generalisability of findings

The generalisability of the findings of this thesis is subject to certain limitations. It is unfortunate that the thesis did not include all Muslim communities in the UK. Throughout this thesis, I took the Pakistani/Bangladeshi population as representative of Muslims in the UK. However, this predominantly Muslim community may not reflect all Muslim communities in the UK. Muslim communities in the UK vary in terms of ethnicity and culture, with different Ramadan traditions, such as food choices. Moreover, these findings may not represent those outside the UK, as they may observe different fasting conditions (length of fasting, food choices, etc.)

7.4.3 Ecological fallacy

The ecological nature of the aggregated data could lead to ecological fallacy. I could not determine if individuals included in the study practise Islam or if they were fasting or not. My assumption that Pakistani and Bangladeshi populations in the UK are Muslims is based on estimates that > 90% of people from these ethnicities are Muslims.[17] According to a Pew Research Centre survey of more than 38,000 Muslims around the world, most Muslims practice fasting during Ramadan, with a median of 93%[58], therefore I believe the findings are robust.

7.4.4 Sample size

The number of antibiotics prescriptions and IHD-related hospitalisations in the Pakistani/Bangladeshi population was relatively small compared with the white population. This could be explained by the fact that Pakistanis/Bangladeshis represent only 3% of the population, so a low number in this group compared with the white population is to be expected.[59] The small sample size could be a reason for not achieving statistically significant results, which limit the attainment of a conclusive inference.[60] It is need to be pointed out that sample size calculation was not performed in any of the studies. A sample size that is too small (as in chapter 6) increases the likelihood of a type II error which is the failure to reject a false null hypothesis. This leads to the conclusion that an effect or relationship doesn't exist when it really does.

7.5 Challenges of Ramadan and health studies

Although there is increasing interest in the impact of Ramadan fasting on health, studies in this field are still limited and tend to be small and lacking robust designs. Through the conduction of this thesis work, I identified some issues that make research on Ramadan fasting challenging. Recruiting participants for Ramadan studies is not easy. Ramadan occurs once a year, which necessitates the planning of a recruiting stage sufficiently in advance of Ramadan. However, some patients tend to avoid consulting their doctors [61] for fear of being advised to avoid fasting; therefore, it is not surprising that potentially invasive studies have been difficult to conduct, leading to a relative paucity of direct evidence regarding the physiological effects of Ramadan fasting, particularly in those with comorbidities. The difficulty in recruiting par-

ticipants from minorities or predominantly Muslim communities for research has been discussed in the literature.[62-65] Barriers to recruitment include unfamiliarity with medical research, lack of interest, religious or cultural factors, poor understanding of research intentions, mistrust of research, fear of side effects, length and requirements of the study and concerns about privacy and confidentiality.

An additional issue is the difficulty of dividing participants into fasting and non-fasting groups to compare findings between groups. Finding a control group that is not fasting from the same population could be challenging. It is likely that those who do not fast are exempted due to health issues, which could bias the findings if they were recruited and compared to a fasting, most probably healthy, group. Moreover, in retrospective studies, it is difficult to confirm if individuals included in the study were fasting or not. When conducting such a study in a non-Muslim-dominant country, it could also be difficult to differentiate Muslims from non-Muslims, particularly if the study is based on electronic health records.

There are many confounders that need to be addressed when conducting research on the impact of Ramadan on health. As Ramadan follows the lunar calendar, it can occur in any season, causing variations in weather and the length of the fast in different locations. Moreover, lifestyle changes in Ramadan including food choices and exercise and sleep patterns could have an impact on research outcomes. Compliance with fasting and medication use are other factors that need to be considered. When recruiting women for Ramadan studies, it is expected that some of them may have to break the fast for a few days, as menstruating women are exempted from fasting.

7.6 Implications and recommendations

The findings of this thesis (Chapters 4–6) suggest that there is no evidence that Ramadan fasting is associated with negative effects on health, at least in the areas explored in this thesis. There is currently no epidemiological evidence that Ramadan fasting associated with detrimental effect on health. Most of the available evidence and guidelines regarding Ramadan fasting are based on experts' opinions and small observational studies that lacked robust designs.[57,66] Evidence-based guidelines are extremely important to support HCPs dealing with patients who wish to fast safely during Ramadan. Further studies using a standardised protocol and controlling for potential confounders are required to study the impact of Ramadan fasting on health.

The work in this thesis can facilitate evidence-based recommendations as it used more validated data and a stronger method. However, the results were not conclusive, and more research is needed. Using primary care and hospital data to explore the health consequences and epidemiology of Ramadan fasting could be an alternative to the small observational studies that have been conducted thus far in Ramadan and health research. Another way of improving the current practice methodologically is applying ITS design rather than the before-and-after study approach that is used more frequently.

There is abundant room for further research in this field as many questions have not been answered, and because of the scarcity of well-designed studies. Most of the studies investigating the consequences of fasting have been related to diabetes management. However, other health conditions such CVDs, endocrine and metabolic disorders, chronic kidney disease, gastrointestinal and liver disorders, autoimmune diseases, infectious diseases, and

chronic obstructive pulmonary disease (COPD) should be considered in future studies. Hence, future studies should include more elderly individuals with different comorbidities to make more specific recommendations. It is important that future studies consider the role of different medications and polypharmacy as it could influence health risks that could be associated with Ramadan fasting. Different medications to treat diabetes have varying levels of complication risks. For example, the risk of hypoglycaemia may be greater in those taking oral hypoglycaemic medications such as gliclazide, where those taking medications such as vildagliptin could be at lower risk of hypoglycaemia. [67]

Large-scale observational studies are required in order to improve the generalisability of the findings. Future research should consider collaboration between different institutes nationally and internationally to join efforts and resources. Moreover, it would be interesting to assess the impact of Ramadan fasting on different populations under different fasting circumstances. More prospective studies should be considered. Additionally, further research is needed to fully characterise fasting practices among people with different medical conditions during Ramadan.

More qualitative research is needed to better understand the challenges and needs of patients fasting during Ramadan to inform future research and educational programmes. Moreover, qualitative studies can be conducted to investigate the barriers and/or facilitators to adopting a healthy lifestyle during that month.

7.7 Personal reflections

In thinking about the last few years spent on doing this research, I realised that, although the journey was neither easy nor smooth, I gained much more than just a doctoral degree. Although it was sometimes difficult to motivate myself to do the work, I found myself enjoying the PhD journey on the whole. I learned a lot on this journey. The broad mix of methods learned in the undertaking of this thesis has expanded my knowledge and experience of different techniques and methods that I may use in my future work.

The PhD taught me to be flexible and to be able to prepare alternate plans. Throughout this journey I faced many challenges, leading me to rethink my plans and find other ways to continue the project. In the beginning, receiving rejections from journals made me think that I am the problem and that I do not deserve to be in this position or have the skills to continue my work. I later realised that rejections from journals are normal and expected in academia and are sometimes necessary to improve our plans. I try to apply this learning in every aspect of my life. Rejection is not the end of the world; it is redirection. Now, I appreciate all research endeavours, whether small or big, as I know that the process of conducting research is not always smooth and does not always proceed as planned. Time management is an important skill that I gained during this journey. Having to conduct more than one project with different tasks and the need to respond to journal deadlines improved my prioritisation skills.

The PhD increased my confidence. As English is not my first language, writing is not one of my strengths and I sometimes find it difficult to translate my thoughts into words. I also used to underestimate myself and my work. I tended to feel that I am not capable of continuing this PhD and that I do not deserve this place or am not good enough for it. However, receiving

encouraging feedback from my supervisors and publishing my work in peer-reviewed journals made me regain confidence in my work and my skills as a researcher.

I used to think that I will be an expert after completing my PhD and will know everything about research. Now I realise that a PhD is just the beginning, and it opens doors for me to learn more. I now consider the process of doing a PhD to be a course on learning how to be a researcher.

The thesis itself provided me with the opportunity to develop as an independent researcher. After completing my PhD, I will return to Saudi Arabia to work as an academic at King Faisal University. I hope to continue my research in this area and to explore other fields there using the skills and experience I gained at the University of Birmingham. It is encouraging that there is increased interest in research in Saudi Arabia. I hope to start a collaboration with the University of Birmingham to improve the public health department and create research opportunities within King Faisal University.

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8 Appendices

Appendices for chapter 3

Supplementary table 1: adjusted Hazard ratios (HR) and 95% confidence intervals (95% CI) for White Europeans (WE) and south Asians (SA) using interaction terms.

Outcome	aHR (95% CI)
T2DM	5.50 (95%CI:4.67-6.48)
HTN	1.63 (95%CI:1.41-1.89)
IHD	1.85 (95%CI:1.40-2.45)
Stroke/TIA	0.82 (95%CI:0.57-1.19)
HF	1.03 (95%CI:0.60-1.177)
AF	0.53 (95%CI:0.33-0.86)

Supplementary Table 2: Baseline characteristics of Indian and White participants

Characteristic	Indian (n=49,249)	White (n= 98,498)
Male, n (%)	25,374 (51.52%)	50,748 (51.52%)
Age, year ,median (IQR)	41 (35 to 54)	41 (35 to 54)
BMI, mean (SD)	25.95 (4.6)	26.97 (5.6)
BMI category		
18.5-25 kg/m2	10,854 (22.04%)	34,426 (34.95%)
25-30 kg/m2	18,824 (38.22%)	29,487 (29.94%)
>30 kg/m2	13,413 (27.24%)	20,114 (20.42%)
Missing	6,158 (12.50%)	14,471 (14.69%)
Smoking, n (%)		
Non-smoker	39,351 (79.90%)	47,860 (48.59%)
Smoker	4,590 (9.32%)	26,203 (26.60%)
Ex-smoker	4,143 (8.41%)	21,892 (22.23%)
Missing	1,164 (2.36%)	2,543 (2.58%)
Townsend, n (%)		
1	6,588 (13.38%)	13,176 (13.38%)
2	6,039 (12.26%)	12,078 (12.26%)
3	10,353 (21.02%)	20,706 (21.02%)
4	10,011 (20.33%)	20,022 (20.33%)
5	6,011 (12.21%)	12,022 (12.21%)
Missing	10,247 (20.81%)	20,494 (20.81%)
Lipid profile		
Total cholesterol (mean (SD))	4.9(1.04)	5.1 (1.08)
Triglycerides(med an (IQR))	1.3 (0.94 to 1.90)	1.32 (0.93 to 1.95)
HDL(mean (SD))	1.3 (0.36)	1.4 (0.42)
Blood pressure, (mean±SD)		
Systolic	124.67 (16.21)	127.08 (15.63)
Diastolic	76.9 (9.86)	77.41 (9.72)
Comorbidities, n (%)		
Type 2 diabetes	5,425 (11.02%)	4,414 (4.48%)
Hypertension	7,925 (16.09%)	12,659 (12.85%)
IHD	2,184 (4.43%)	1,628 (1.65%)
Stroke or TIA	671 (1.36%)	3,266 (3.32%)
Heart failure	295 (0.60%)	549 (0.56%)
Atrial fibrillation	244 (0.50%)	1,086 (1.10%)

Supplementary Table 3: Baseline characteristics of Pakistani and White participants

Characteristic	Pakistani (n= 22,353)	White (n= 44,706)
Male, n (%)	11, 888 (53.18 %)	23,776 (53.18%)
Age, years, median (IQR)	40 (35 to 51)	40(35 to 51)
BMI, mean (SD)	27.17 (5.1)	26.98 (5.7)
BMI category, n (%)		
18.5-25 kg/m2	3,693 (16.52%)	15,826 (35.40%)
25-30 kg/m2	7,613 (34.06%)	13,091(29.28%)
>30 kg/m2	8,219 (36.77%)	9,245 (20.68%)
Missing	2,828 (12.65%)	6,544 (14.64%)
Smoking, n (%)		
Smoker	16,484 (73.74%)	20,702 (46.31%)
Ex-smoker	3,473 (15.54%)	13,247 (29.63%)
Non-smoker	1,891 (8.46%)	9,581 (21.43%)
Missing	505 (2.26%)	1,176 (2.63%)
Townsend, n (%)		
1	2,005 (8.97%)	4,010 (8.97%)
2	2,315 (10.36%)	4,630 (10.36%)
3	3,424 (15.32%)	6,848 (15.32%)
4	5,275 (23.60%)	10,550 (23.60%)
5	4,606 (20.61%)	9,212 (20.61%)
Missing	4,728 (21.15%)	9,456 (21.15%)
Lipid profile		
Total cholesterol (mean (SD))	4.8 (1.05)	5.09 (1.1)
Triglycerides (med an (IQR))	1.5 (1.01 to 2.1)	1.3(0.91 to 1.99)
HDL (mean (SD))	1.2 (0.3)	1.4 (0.4)
Blood pressure, (mean, (SD))		
Systolic	123.5 (16.1)	126.5 (15.5)
Diastolic	76.4 (9.9)	77.3 (9.7)
Comorbidities, n (%)		
Type 2 diabetes	3,145 (14.07%)	1,911 (4.27%)
Hypertension	153 (0.68%)	207 (0.46%)
IHD	1,074 (4.80%)	1,331 (2.98%)
Stroke or TIA	356 (1.59%)	695 (1.55%)
Heart failure	153 (0.68%)	207 (0.46%)
Atrial fibrillation	120 (0.54%)	435 (0.97%)

Supplementary Table 4: Baseline characteristics of Bangladeshi and white participants

Characteristic	Bangladeshi (n=7,678)	White (n=15,356)
Male, n (%)	4,500 (58.61 %)	9,000 (58.61 %)
Age, years, median (IQR)	39(35 to 50)	39(35 to 50)
BMI, mean (SD)	25.77 (4.27)	27.1 (5.83)
BMI category, n (%)		
18.5-25 kg/m2	1,640 (21.36%)	5,251 (34.20%)
25-30 kg/m2	3,136 (40.84%)	4,461 (29.05%)
>30 kg/m2	1,982 (25.81%)	3,206 (20.88%)
Missing	920 (11.98%)	2,438 (15.88%)
Smoking, n (%)		
Smoker	4,957 (64.56%)	6,670 (43.44%)
Ex-smoker	1,703 (22.18%)	5,109 (33.27%)
Non-smoker	298 (3.88%)	1,016 (6.62%)
Missing	720 (9.38%)	2,561 (16.68%)
Townsend, n (%)		
1	393 (5.12%)	786 (5.12%)
2	605 (7.88%)	1,210 (7.88%)
3	994 (12.95%)	1,988 (12.95%)
4	1,569 (20.44%)	3,138 (20.44%)
5	2,832 (36.88%)	5,664 (36.88%)
Missing	2,570 (16.74%)	1,285 (16.74%)
Lipid profile		
Total cholesterol (mean (SD))	4.8 (1.09)	5.08 (1.10)
Triglycerides (med an (IQR))	1.57 (1.1 to 2.20)	1.37 (0.96-2.00)
HDL (mean (SD))	1.1 (0.3)	1.34 (0.4)
Blood pressure, (mean, (SD))		
Systolic	121.9 (15.71)	126.6 (15.6)
Diastolic	76.05 (9.86)	77.4 (9.84)
Comorbidities, n (%)		
Type 2 diabetes	1,249 (16.27%)	705 (4.59%)
Hypertension	1,163 (15.15%)	1,691 (11.01%)
IHD	336 (4.38%)	452 (2.94%)
Stroke or TIA	93 (1.21%)	259 (1.69%)
Heart failure	47 (0.61%)	90 (0.59%)
Atrial fibrillation	22 (0.29%)	155 (1.01%)

Appendices for chapter 6

Assumptions:

Interrupted time series design's validity rests on the following assumptions[1]:

- **Assumption 1:** The expectation of the pre intervention level and trend would be the same irrespective of whether the sample received the treatment

We checked this assumption through applying single interrupted time series to the targeted group (Pakistani/Bangladeshi) and compared it to the control group (white) that were not exposed to Ramadan.

The slops in both models were similar. However, levels were different. This is expected as the size of the two populations is different.

Before vs during Ramadan

Model parameters	Pakistani/Bangladeshi	White
level	513.45 (95%CI:481.73-547.27)	32799.25 (95%CI:31116.01-34573.54)
Slop	1.00 (95%CI:0.99-1.00)	0.99 (95%CI:0.99-1.00)

During vs after Ramadan

Model parameters	Pakistani/Bangladeshi	White
level	502.72 (95%CI:466.45-541.82)	32119.015(95%CI:30451.88-33877.40)
Slop	0.99 (95%CI:0.99-0.99)	1.000 (95%CI:0.99-1.0)

1. Baicker K, Svoronos T. Testing the Validity of the Single Interrupted Time Series Design. *ERN: Hypothesis Testing (Topic)* 2019.

- **Assumption 2:** In the absence of the intervention, the post intervention trendline would have been equivalent in expectation to an extrapolated pre intervention trend.

  We checked this assumption through comparing Intercepts and slops in the different time series (before, during and after Ramadan) in the control group (white) that were not exposed to Ramadan. Both intercepts and slops are similar in all period.

  There are 3 different types of models we have fitted:

  Model A: **Before Ramadan series (30 days)**

  Model B: **During Ramadan series (30 days)**

  Model C: **After Ramadan (30 days)**

Model parameters	**Model A**	**Model B**	**Model C**
level	32799.25 (95%CI: 31223.73-34454.27)	32119.01 (95%CI: 30363.24-33976.31)	33008.978 (95%CI: 31417.44-34681.14)
slop	0.999 (95%CI: 0.996 - 1.002)	1.0 (95%CI: 0.99- 1.004)	1.001 (95%CI: 0.99-1.004)

Sensitivity analysis

We conducted a sensitivity analysis with incorporating for seasonality (daily temperature) for selected years and found that temperature did not affect the results significantly.

Before vs during Ramadan

a. the model results without incorporating for seasonality

Year	Model parameters	Pakistani/Bangladeshi	White
2007	level	0.96 (95%CI:0.48-1.93)	0.90 (95%CI:0.45-1.79)
	Slop	0.997(95%CI:0.95-1.03)	1.01 (95%CI:0.97-1.05)
2008	level	1.37 (95%CI:0.65-2.9)	1.35 (95%CI:0.66-2.78)
	Slop	1.00 (95%CI:0.96-1.04)	1.00 (95%CI:0.96-1.04)
2009	level	0.75 (95%CI:0.37-1.53)	0.79 (95%CI:0.39-1.61)
	Slop	0.98 (95%CI:0.94-1.03)	0.99 (95%CI:0.95-1.03)
2010	level	0.91 (95%CI:0.45-1.82)	1.01 (95%CI:0.52-1.98)
	Slop	1.01 (95%CI:0.97-1.05)	1.01 (95%CI:0.97-1.05)
2011	level	1.42 (95%CI:0.69-2.90)	1.32 (95%CI:0.66-2.65)
	Slop	0.98 (95%CI:0.94-1.03)	0.98 (95%CI:0.94-1.03)

b. the model results with incorporating for seasonality (daily temperature)

Year	Model parameters	Pakistani/Bangladeshi	White
2007	level	1.29 (95%CI:0.58-2.87)	1.21 (95%CI:0.56-2.64)
	Slop	1.00 (95%CI:0.96-1.04)	1.02 (95%CI:0.97-1.05)
2008	level	1.30 (95%CI:0.59-2.83)	1.32 (95%CI:0.62-2.80)
	Slop	1.00 (95%CI:0.96-1.04)	1.00 (95%CI:0.96-1.04)
2009	level	0.74 (95%CI:0.35-1.55)	0.80 (95%CI:0.38-1.67)
	Slop	0.98 (95%CI:0.94-1.03)	0.99 (95%CI:0.95-1.04)
2010	level	0.88 (95%CI:0.43-1.76)	0.96 (95%CI:0.49-1.87)
	Slop	1.01 (95%CI0.97-1.05)	1.00 (95%CI:0.96-1.04)
2011	level	1.55 (95%CI:0.73-3.29)	1.45 (95%CI:0.70-3.0)
	Slop	0.98 (95%CI:0.94-1.03)	0.98 (95%CI:0.95-1.03)

<u>During vs after Ramadan</u>

a. the model results without incorporating for seasonality

Year	Model parameters	Pakistani/Bangladeshi	White
2007	level	1.00 (95%CI:0.48- 2.11)	0.81 (95%CI:0.41-1.61)
	Slop	1.00 (95%CI:0.96-1.04)	0.98 (95%CI:0.94-1.02)
2008	level	1.17 (95%CI:0.60-2.29)	1.08 (95%CI:0.56-2.06)
	Slop	0.99 (95%CI:0.96-1.03)	1.00 (95%CI:0.96-1.04)
2009	level	1.77 (95%CI:0.86-3.64)	1.28 (95%CI:0.63-2.56)
	Slop	0.99 (95%CI:0.95-1.03)	0.99 (95%CI:0.95-1.03)
2010	level	0.94 (95%CI:0.47-1.88)	0.92 (95%CI:0.46-1.81)
	Slop	0.99 (95%CI:0.96-1.04)	1.00 (95%CI:0.96-1.04)
2011	level	1.48 (95%:CI:0.72-3.00)	1.218 (95%CI:0.62-2.39)
	Slop	1.02 (95%CI:0.98-1.06)	1.017 (95%CI:0.98-1.05)

b. the model results with incorporating for seasonality (daily temperature)

Year	Model parameters	Pakistani/Bangladeshi	White
2007	level	1.03 (95%CI:0.49-2.16)	0.82 (95%CI:0.41-1.65)
	Slop	1.01 (95%CI:0.96-1.05)	0.99 (95%CI:0.95-1.03)
2008	level	1.08 (95%CI:0.54-2.17)	1.02 (95%CI:0.52-2.01)
	Slop	0.99 (95%CI:0.95-1.03)	1.00 (95%CI:0.96-1.03)
2009	level	1.72 (95%CI:0.82-3.61)	1.24 (95%CI:0.60-2.55)
	Slop	0.98 (95%CI:0.94-1.03)	0.99 (95%CI:0.94-1.03)
2010	level	0.92 (95%CI:0.46-1.85)	0.90 (95%CI:0.45-1.79)
	Slop	1.00 (95%CI:0.96-1.04)	1.00 (95%CI:0.96-1.04)
2011	level	1.58 (95%CI:0.76-3.31)	1.01 (95%CI:0.98-1.05)
	Slop	1.02 (95%CI:0.98-1.06)	0.97 (95%CI:0.93-1.03)

Supplementary Table 2: Structure of dataset variables used in the analysis for SITS

1. Pakistani/Bangladeshi before vs during Ramadan

T	X	XT	X1	antibi-otics
1	0	0	No Intervention	451
2	0	0	No Intervention	562
3	0	0	No Intervention	569
4	0	0	No Intervention	519
5	0	0	No Intervention	506
6	0	0	No Intervention	544
7	0	0	No Intervention	455
8	0	0	No Intervention	450
9	0	0	No Intervention	486
10	0	0	No Intervention	560
11	0	0	No Intervention	563
12	0	0	No Intervention	534
13	0	0	No Intervention	506
14	0	0	No Intervention	501
15	0	0	No Intervention	445
16	0	0	No Intervention	502
17	0	0	No Intervention	561
18	0	0	No Intervention	550
19	0	0	No Intervention	491
20	0	0	No Intervention	530
21	0	0	No Intervention	540
22	0	0	No Intervention	436
23	0	0	No Intervention	448
24	0	0	No Intervention	474
25	0	0	No Intervention	495
26	0	0	No Intervention	530
27	0	0	No Intervention	551
28	0	0	No Intervention	523
29	0	0	No Intervention	491
30	0	0	No Intervention	541
31	1	1	Intervention	543
32	1	2	Intervention	457
33	1	3	Intervention	439
34	1	4	Intervention	564
35	1	5	Intervention	519
36	1	6	Intervention	441
37	1	7	Intervention	469
38	1	8	Intervention	527

39	1	9	Intervention	459
40	1	10	Intervention	427
41	1	11	Intervention	512
42	1	12	Intervention	477
43	1	13	Intervention	416
44	1	14	Intervention	466
45	1	15	Intervention	507
46	1	16	Intervention	488
47	1	17	Intervention	489
48	1	18	Intervention	482
49	1	19	Intervention	499
50	1	20	Intervention	317
51	1	21	Intervention	482
52	1	22	Intervention	466
53	1	23	Intervention	465
54	1	24	Intervention	433
55	1	25	Intervention	471
56	1	26	Intervention	477
57	1	27	Intervention	395
58	1	28	Intervention	471
59	1	29	Intervention	438
60	1	30	Intervention	395

Supplementary Table 2: Structure of dataset variables used in the analysis for CITS

T	X	XT	Z	ZT	ZX	ZTX	X1	group	antibiotics
1	0	0	1	1	0	0	No Int-V	Pakistani/Bangladeshi	451
2	0	0	1	2	0	0	No Int-V	Pakistani/Bangladeshi	562
3	0	0	1	3	0	0	No Int-V	Pakistani/Bangladeshi	569
4	0	0	1	4	0	0	No Int-V	Pakistani/Bangladeshi	519
5	0	0	1	5	0	0	No Int-V	Pakistani/Bangladeshi	506
6	0	0	1	6	0	0	No Int-V	Pakistani/Bangladeshi	544
7	0	0	1	7	0	0	No Int-V	Pakistani/Bangladeshi	455
8	0	0	1	8	0	0	No Int-V	Pakistani/Bangladeshi	450
9	0	0	1	9	0	0	No Int-V	Pakistani/Bangladeshi	486
10	0	0	1	10	0	0	No Int-V	Pakistani/Bangladeshi	560
11	0	0	1	11	0	0	No Int-V	Pakistani/Bangladeshi	563
12	0	0	1	12	0	0	No Int-V	Pakistani/Bangladeshi	534
13	0	0	1	13	0	0	No Int-V	Pakistani/Bangladeshi	506
14	0	0	1	14	0	0	No Int-V	Pakistani/Bangladeshi	501
15	0	0	1	15	0	0	No Int-V	Pakistani/Bangladeshi	445
16	0	0	1	16	0	0	No Int-V	Pakistani/Bangladeshi	502
17	0	0	1	17	0	0	No Int-V	Pakistani/Bangladeshi	561
18	0	0	1	18	0	0	No Int-V	Pakistani/Bangladeshi	550
19	0	0	1	19	0	0	No Int-V	Pakistani/Bangladeshi	491
20	0	0	1	20	0	0	No Int-V	Pakistani/Bangladeshi	530
21	0	0	1	21	0	0	No Int-V	Pakistani/Bangladeshi	540
22	0	0	1	22	0	0	No Int-V	Pakistani/Bangladeshi	436
23	0	0	1	23	0	0	No Int-V	Pakistani/Bangladeshi	448
24	0	0	1	24	0	0	No Int-V	Pakistani/Bangladeshi	474
25	0	0	1	25	0	0	No Int-V	Pakistani/Bangladeshi	495
26	0	0	1	26	0	0	No Int-V	Pakistani/Bangladeshi	530
27	0	0	1	27	0	0	No Int-V	Pakistani/Bangladeshi	551
28	0	0	1	28	0	0	No Int-V	Pakistani/Bangladeshi	523
29	0	0	1	29	0	0	No Int-V	Pakistani/Bangladeshi	491
30	0	0	1	30	0	0	No Int-V	Pakistani/Bangladeshi	541
31	1	1	1	31	1	1	Int-V	Pakistani/Bangladeshi	543
32	1	2	1	32	1	2	Int-V	Pakistani/Bangladeshi	457
33	1	3	1	33	1	3	Int-V	Pakistani/Bangladeshi	439
34	1	4	1	34	1	4	Int-V	Pakistani/Bangladeshi	564
35	1	5	1	35	1	5	Int-V	Pakistani/Bangladeshi	519
36	1	6	1	36	1	6	Int-V	Pakistani/Bangladeshi	441
37	1	7	1	37	1	7	Int-V	Pakistani/Bangladeshi	469

38	1	8	1	38	1	8	Int-V	Pakistani/Bangladeshi	527
39	1	9	1	39	1	9	Int-V	Pakistani/Bangladeshi	459
40	1	10	1	40	1	10	Int-V	Pakistani/Bangladeshi	427
41	1	11	1	41	1	11	Int-V	Pakistani/Bangladeshi	512
42	1	12	1	42	1	12	Int-V	Pakistani/Bangladeshi	477
43	1	13	1	43	1	13	Int-V	Pakistani/Bangladeshi	416
44	1	14	1	44	1	14	Int-V	Pakistani/Bangladeshi	466
45	1	15	1	45	1	15	Int-V	Pakistani/Bangladeshi	507
46	1	16	1	46	1	16	Int-V	Pakistani/Bangladeshi	488
47	1	17	1	47	1	17	Int-V	Pakistani/Bangladeshi	489
48	1	18	1	48	1	18	Int-V	Pakistani/Bangladeshi	482
49	1	19	1	49	1	19	Int-V	Pakistani/Bangladeshi	499
50	1	20	1	50	1	20	Int-V	Pakistani/Bangladeshi	317
51	1	21	1	51	1	21	Int-V	Pakistani/Bangladeshi	482
52	1	22	1	52	1	22	Int-V	Pakistani/Bangladeshi	466
53	1	23	1	53	1	23	Int-V	Pakistani/Bangladeshi	465
54	1	24	1	54	1	24	Int-V	Pakistani/Bangladeshi	433
55	1	25	1	55	1	25	Int-V	Pakistani/Bangladeshi	471
56	1	26	1	56	1	26	Int-V	Pakistani/Bangladeshi	477
57	1	27	1	57	1	27	Int-V	Pakistani/Bangladeshi	395
58	1	28	1	58	1	28	Int-V	Pakistani/Bangladeshi	471
59	1	29	1	59	1	29	Int-V	Pakistani/Bangladeshi	438
60	1	30	1	60	1	30	Int-V	Pakistani/Bangladeshi	395
1	0	0	0	0	0	0	No int-C	White	29114
2	0	0	0	0	0	0	No int-C	White	34076
3	0	0	0	0	0	0	No int-C	White	35015
4	0	0	0	0	0	0	No int-C	White	33942
5	0	0	0	0	0	0	No int-C	White	30061
6	0	0	0	0	0	0	No int-C	White	35616
7	0	0	0	0	0	0	No int-C	White	29437
8	0	0	0	0	0	0	No int-C	White	30177
9	0	0	0	0	0	0	No int-C	White	33937
10	0	0	0	0	0	0	No int-C	White	34582
11	0	0	0	0	0	0	No int-C	White	33291
12	0	0	0	0	0	0	No int-C	White	33048
13	0	0	0	0	0	0	No int-C	White	33721
14	0	0	0	0	0	0	No int-C	White	30171
15	0	0	0	0	0	0	No int-C	White	29786
16	0	0	0	0	0	0	No int-C	White	33625
17	0	0	0	0	0	0	No int-C	White	34268
18	0	0	0	0	0	0	No int-C	White	32913
19	0	0	0	0	0	0	No int-C	White	33225

20	0	0	0	0	0	0	No int-C	White	33874
21	0	0	0	0	0	0	No int-C	White	33486
22	0	0	0	0	0	0	No int-C	White	28098
23	0	0	0	0	0	0	No int-C	White	29396
24	0	0	0	0	0	0	No int-C	White	31044
25	0	0	0	0	0	0	No int-C	White	34116
26	0	0	0	0	0	0	No int-C	White	33122
27	0	0	0	0	0	0	No int-C	White	33270
28	0	0	0	0	0	0	No int-C	White	33585
29	0	0	0	0	0	0	No int-C	White	28378
30	0	0	0	0	0	0	No int-C	White	32437
31	1	1	0	0	0	0	Int-C	White	33886
32	1	2	0	0	0	0	Int-C	White	32384
33	1	3	0	0	0	0	Int-C	White	29562
34	1	4	0	0	0	0	Int-C	White	34353
35	1	5	0	0	0	0	Int-C	White	33743
36	1	6	0	0	0	0	Int-C	White	28255
37	1	7	0	0	0	0	Int-C	White	32451
38	1	8	0	0	0	0	Int-C	White	34437
39	1	9	0	0	0	0	Int-C	White	32480
40	1	10	0	0	0	0	Int-C	White	28568
41	1	11	0	0	0	0	Int-C	White	34415
42	1	12	0	0	0	0	Int-C	White	33612
43	1	13	0	0	0	0	Int-C	White	29007
44	1	14	0	0	0	0	Int-C	White	32819
45	1	15	0	0	0	0	Int-C	White	33803
46	1	16	0	0	0	0	Int-C	White	32741
47	1	17	0	0	0	0	Int-C	White	32831
48	1	18	0	0	0	0	Int-C	White	33173
49	1	19	0	0	0	0	Int-C	White	33098
50	1	20	0	0	0	0	Int-C	White	24362
51	1	21	0	0	0	0	Int-C	White	33956
52	1	22	0	0	0	0	Int-C	White	34550
53	1	23	0	0	0	0	Int-C	White	32943
54	1	24	0	0	0	0	Int-C	White	33401
55	1	25	0	0	0	0	Int-C	White	33305
56	1	26	0	0	0	0	Int-C	White	33770
57	1	27	0	0	0	0	Int-C	White	29088
58	1	28	0	0	0	0	Int-C	White	33804
59	1	29	0	0	0	0	Int-C	White	30347
60	1	30	0	0	0	0	Int-C	White	34962

Parameter estimates

1) Single interrupted time series (Pakistani/Bangladeshi)

a) Before vs during Ramadan

Parameter	Interpretation	Estimation (95%CI)
β_0	Intercept	513.459 (95%CI: 481.731-547.276)
β_1	Pre-trend	1.000 (95%CI:0.996-1.003
β_2	Post-level change	0.990 (95%CI: 0.905-1.083)
β_3	Post-trend change	0.995 (95%CI:0.990-1.001)

b) During vs during Ramadan

Parameter	Interpretation	Estimation (95%CI)
β_0	Intercept	502.725 (95%CI:466.451-541.820)
β_1	Pre-trend	0.995 (95%CI:0.991-0.999)
β_2	Post-level change	1.165 (95%CI:1.050-1.292)
β_3	Post-trend change	1.007 (95%CI:1.001-1.013)

2) Single interrupted time series (white)

a) Before vs during Ramadan

Parameter	Interpretation	Estimation (95%CI)
β_0	Intercept	32799.253 (95%CI:31116.019-34573.543)
β_1	Pre-trend	0.999 (95%CI:0.996-1.002)
β_2	Post-level change	1.005 (95%CI:0.934-1.081)
β_3	Post-trend change	1.001 (95%CI:0.997-1.006)

b) During vs during Ramadan

Parameter	Interpretation	Estimation (95%CI)
β_0	Intercept	32119.015 (95%CI:30451.889-33877.409)
β_1	Pre-trend	1.000 (95%CI:0.997-1.003)
β_2	Post-level change	1.014 (95%CI:0.943-1.091)
β_3	Post-trend change	1.001 (95%CI:0.996-1.005)

3) Controlled interrupted time series

a) Before vs during Ramadan

Parameter	Interpretation	Estimation (95%CI)
β_0	Intercept	32801.625 (95%CI:31086.900-34610.933)
β_1	Control pre-trend	0.999 (95%CI: 0.996-1.002)
β_2	Control post level change	1.005 (95%CI: 0.933- 1.083)
β_3	Post-trend change	1.001 (95%CI: 0.997- 1.006)
β_4	Treatment/control pre-trend difference	0.016 (95%CI: 0.014-0.017)
β_5	Treatment/control pre-level difference	1.001 (95%CI: 0.996 -1.005)
β_6	Treatment/control post level difference	0.985 (95%CI: 0.879-1.104)
β_7	Treatment/control change in slope	0.994 (95%CI: 0.988-1.001)

b) During vs during Ramadan

Parameter	Interpretation	Estimation (95%CI)
β_0	Intercept	32120.057 (95%CI: 30321.572-34025.218)
β_1	Control pre-trend	1.000 (95%CI: 0.997-1.004)
β_2	Control post level change	1.015 (95%CI: 0.937-1.098)
β_3	Post-trend change	1.001 (95%CI: 0.996-1.005)
β_4	Treatment/control pre-trend difference	0.016 (95%CI: 0.014-0.017)
β_5	Treatment/control pre-level difference	0.995 (95%CI: 0.990-1.000)
β_6	Treatment/control post level difference	1.148 (95%CI: 1.017-1.297)
β_7	Treatment/control change in slope	1.006 (95%CI: 0.999-1.013)