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The efficacy of fasting regimens on health outcomes: a systematic overview

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INDEX

ABSTRACT

BACKGROUND

Fasting involves limiting or decreasing the intake of food and drink for a specific period. There are various fasting methods, such as Ramadan fasting, intermittent fasting, and Christian Orthodox fasting. This overview aims to offer a comprehensive overview of the beneficial effects and potential harms of different fasting regimens and to discuss how these non-medicinal methods might improve human health.

STUDY DESIGN

I conducted a systematic search using databases such as MEDLINE (PubMed), Embase, Cochrane Library, and CINAHL. The review included systematic reviews (SRs) that examined the impact of various fasting regimens on health. The selection of SRs, data extraction, and quality assessment were performed using AMSTAR tool.

RESULTS

A total of 21 SRs were reviewed, identifying 97 health outcomes. Among these, heart-related risk indicators were the most commonly analyzed. Ramadan fasting was linked to significant improvements in body weight, visceral lean mass, and high-density lipoprotein cholesterol (HDL-c), as well as reductions in low-density lipoprotein cholesterol (LDL-c) and total cholesterol (T-chol), especially in cardiac patients. Similarly, reviews on intermittent and Orthodox fasting demonstrated benefits for weight, BMI, lipid and glucose profiles, and inflammatory markers.

CONCLUSIONS

Fasting regimens appear to offer potential benefits for various health indicators in adults. However, evidence regarding certain health aspects, such as cognitive function, well-being, and quality of life, remains limited. Future research, including randomized controlled trials (RCTs) and cohort studies with robust methodologies and larger sample sizes, is needed to better understand the biological mechanisms and multidimensional health benefits associated with fasting.

1. INTRODUCTION

1. Introduction:

Fasting, practiced since ancient times, is a dietary pattern characterized by partial or total abstinence from solid food and drinks, with little or no daily caloric intake, for a defined and restricted period. This practice has been observed in various cultural, religious, and spiritual traditions worldwide, often associated with rituals and periods of reflection. Recent evidence suggests that fasting could be a promising non-pharmacological intervention that can improve health, increase longevity, and manage various chronic diseases and health conditions, such as diabetes, cardiovascular diseases, and obesity. Studies indicate that fasting can enhance metabolic health, reduce inflammation, and promote cellular repair processes through mechanisms like autophagy. Consequently, there is significant interest in the health implications of this dietary practice, leading to numerous scientific investigations aimed at understanding its benefits and potential risks. The growing body of research highlights the need for well-designed clinical trials to further elucidate the effects of different fasting protocols and to establish evidence-based guidelines for their safe and effective implementation.

1.1 Fasting regimens:

The most studied fasting strategies include intermittent fasting (IF) and religious fasting, such as Ramadan fasting and Christian Orthodox fasting. While religious fasting is typically practiced for spiritual purposes and is not always based on scientific evidence, therapeutic fasting methods (e.g., complete alternate-day fasting, time-restricted feeding, caloric restriction) are designed as medical interventions aimed at reducing energy intake and metabolic expenditure. These therapeutic approaches focus on leveraging the body's physiological responses to periods of reduced caloric intake to promote health benefits,

including weight loss, improved metabolic health, and reduced risk factors for chronic diseases. Research in these areas seeks to understand the underlying mechanisms of fasting and its potential to serve as a viable, non-pharmacological strategy for enhancing overall health and longevity.

1.2 In-vivo studies on fasting regimens:

In vivo studies conducted on animals have revealed that when rodents and mice undergo fasting and caloric restriction they experience an increase, in lifespan and a decrease in the occurrence of various age related diseases like cancer, diabetes and heart disease. The lowered risk of illnesses in these animal subjects is attributed to a series of biological processes triggered by fasting, such as stress response, autophagy, apoptosis and changes in homeostasis.

While there is growing evidence supporting the safety and positive effects of fasting in animal studies the data regarding its benefits for human health outcomes and biological mechanisms are still lacking. The safety and effectiveness of fasting in humans are uncertain due to conflicting results from past reviews (SRs) and meta analyses. Currently there is a lack of assessments on the pros and cons of fasting well as its practical implications, for clinical use.

2. THE OBJECTIVE OF THE THESIS

The main aim of this overview is to offer a summary of the existing evidence regarding the benefits and risks associated with popular fasting routines. Additionally, it aims to discuss the mechanisms by which this non-pharmacological approach may improve human health. Furthermore, our secondary purpose is to identify needs, uncertainties, and priorities for future systematic reviews. This will help to provide more specific information to patients, clinicians, and policymakers, ensuring that the evidence base is robust enough to inform clinical practice and public health guidelines.

Evidence Acquisition

An overview of systematic reviews (SRs) on the potential beneficial impact on health of the most commonly practiced fasting regimens was conducted. The final report was written in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. This methodology ensures a comprehensive and rigorous approach to synthesizing the existing evidence, facilitating a clear understanding of the potential health benefits and risks associated with different fasting strategies.

3. MATERIALS AND METHODS

3.1 Eligibility criteria:

Systematic reviews (SRs) were selected for inclusion in this overview based on the following eligibility criteria:

- **Population**: Eligible participants included healthy individuals or those with a prevalent diagnosis of disease who sought medical attention at study entry.
- **Interventions**: The overview considered religious or therapeutic fasting regimens involving a reduction in daily caloric intake, measured in kcal/day.
- **Studies**: Included SRs needed to report on the associations between fasting dietary patterns and health outcomes. SRs were eligible if they included at least one randomized controlled trial (RCT) or one observational study, had clinically relevant health outcomes, and clearly defined eligibility criteria for the studies identified.
- **Outcomes**: The overview focused on indicators related to the overall dimensions of health status, aligning with the WHO's 1948 definition of health concept.
- **Period**: Papers published from January 1st, 1980, to March 31st, 2024, were considered.
- **Setting**: Studies conducted in any type of setting were included without limitation.
- **Language**: Only SRs published in English were included in this overview.

These criteria ensured a comprehensive and systematic approach to reviewing the literature, aiming to capture relevant evidence on the health effects of fasting across diverse populations and settings.

3.2 Search strategy

For this study, databases including Medline (PubMed), Embase, CINHAL Complete, and the Cochrane Library were systematically searched. The literature search was conducted collaboratively by two reviewers (A.S. and M.F.), with any conflicts or disagreements resolved through discussion with a third author (D.C.), who is an expert in methodology and epidemiology.

To identify potentially relevant papers, a comprehensive search strategy was employed using a combination of MeSH terms and specific keywords related to fasting, including "fasting," "alternate day fasting," "intermittent fasting," "Ramadan fasting," "Christian Orthodox fasting," and "human." Three distinct search strings were developed, each tailored to capture studies on the three fasting regimens of interest.

The search was conducted up to March 2024, and articles were restricted to those written in English or Italian. Additionally, potential eligible studies were identified using a snowballing approach, which involved screening the reference lists of all selected papers to ensure comprehensive coverage of relevant literature.

This systematic approach ensured that a broad range of relevant studies on fasting and its health impacts were considered, enhancing the robustness and completeness of the overview.

3.3 Selection of studies

Records identified through our search strategy were compiled into an Excel spreadsheet. After removing duplicates, two authors of the overview (A.S. and M.F.) independently evaluated the

titles and abstracts of potentially eligible studies. Subsequently, the selected papers underwent a full-text review. The entire process of study selection was documented in a flowchart, including reasons for excluding papers. Any disagreements or discrepancies were resolved through consensus or consultation with a third party (P.A.B.), and further discussion within the broader team if necessary (M.P., P.A.B., A.N.).

3.4 Data extraction and management

Data from the selected systematic reviews (SRs) were extracted by two overview authors (A.N. and P.A.B.) using a predefined extraction form database. This extraction process was carefully monitored and cross-checked by a third reviewer (M.P.) to ensure accuracy in data extraction, entry, and management. For each included SR, the following information was systematically collected:

- Author and year of publication
- Number and type of studies included in the SR
- Number of participants included in the SR
- Description of results and data reported

This structured approach to data extraction and management ensured that all relevant information from the selected SRs was captured accurately, facilitating a comprehensive synthesis of findings related to fasting and its health implications

3.5 Assessment of methodological quality of included reviews

The methodological quality of the systematic reviews (SRs) included in our overview was evaluated using the AMSTAR tool. This assessment aimed to identify potential biases in the

review process and quantify their impact on the reported effect estimates. Two overview authors (AN. and P.A.B.) independently analyzed the included papers in a blinded manner. Any disagreements or discrepancies in the assessment were documented and resolved through discussion between the reviewers and, if necessary, within the wider team.

It's important to note that we did not reassess the quality of the individual randomized controlled trials (RCTs) or observational studies included within the SRs that were considered potentially eligible for our overview. Our focus remained on evaluating the methodological rigor of the SRs themselves to ensure reliability and validity in synthesizing the evidence on fasting and its health effects. This structured approach to quality assessment ensured that our overview relied on systematically reviewed and robustly analyzed SRs, enhancing the reliability of our conclusions regarding the impact of fasting regimens on health outcomes.

3.6 Prioritization of study findings

In my overview, we designated primary/major outcomes as all risk factors for diseases, such as anthropometric body measures and cardiovascular risk factors. Secondary/minor measures included well-being, quality of life, mood and mental disorders, as well as nutritional and dietary parameters.

3.7 Data synthesis

Following a preliminary qualitative assessment of study findings and efficacy trials of the three fasting regimens analyzed (Ramadan fasting, Christian Orthodox fasting, Intermittent fasting), we synthesized the main findings of the included systematic reviews (SRs) into a narrative summary. These findings were categorized within a framework organized by the health status

of enrolled participants. The overview authors, with support from nutrition experts, decided not to report the study results separately for each individual dietary intervention in the final paper. Instead, findings were integrated across fasting regimens to provide a cohesive overview of the effects on health outcomes. Furthermore, we critically assessed and discussed limitations in the evidence base, including the overall methodological quality of the identified reviews. These considerations informed recommendations for future research directions aimed at strengthening the evidence base on fasting and its health impacts. This approach ensured a comprehensive synthesis of available evidence while addressing methodological rigor and potential biases in the reviewed literature, thereby enhancing the reliability and applicability of our findings.

4. Results

4.1 Description of studies

In this systematic overview, a total of 21 systematic reviews (SRs) met the inclusion criteria and were included. The initial search across PubMed, Embase, CINHAL Complete, and the Cochrane Library yielded 5239 records. After removing duplicates, 3688 unique records remained. Following screening based on title and abstract, 2170 records were excluded due to inconsistency with the inclusion criteria. Subsequently, 1518 full-text articles were assessed, with 1,497 being excluded primarily due to study design criteria. The selection process is summarized in a PRISMA flowchart (Figure 1), available in Supplementary Digital Material 1. Specifically, five of the included SRs incorporated randomized controlled trials (RCTs), while the remaining reviews included cohort studies. The search dates for the reviews ranged from 2012 to February 2019. Among the 543 studies included in these SRs, only a small proportion involved children or adolescents. This comprehensive approach ensured that the overview captured a broad spectrum of evidence on fasting regimens and their impact on health outcomes, providing a solid foundation for synthesizing findings and drawing conclusions.

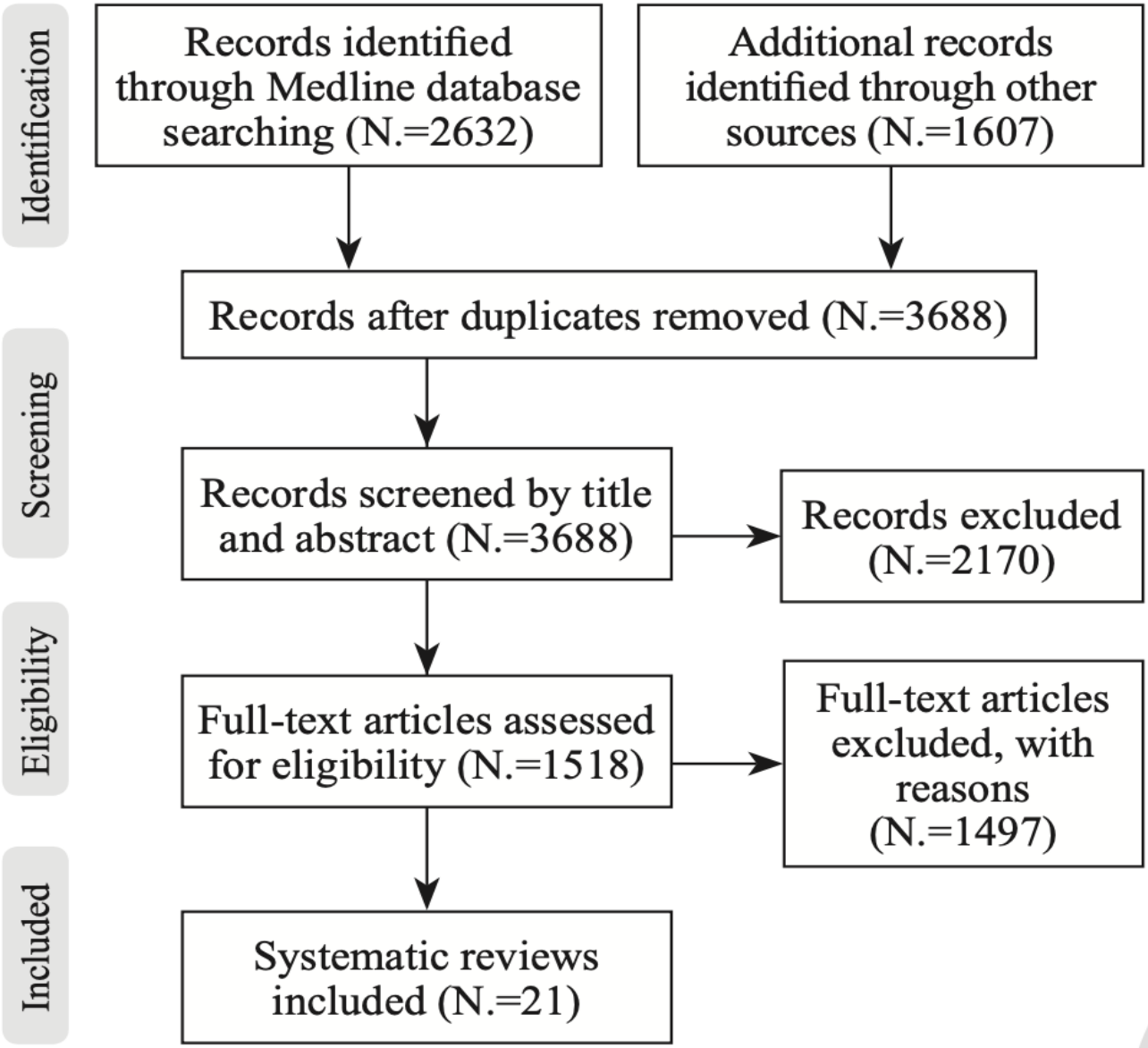

Figure 1.—PRISMA flow diagram adapted for a systematic overview. The flow chart summarizes and describes the se- lection process of SRs, from the identification of records to the final inclusion phase.

4.2 Methodological quality of included systematic reviews

The methodological quality of the included reviews (Table I) reveals a notable number of issues related to selection and critical methodological assessment. Among the 21 included systematic reviews (SRs), only one, which focused on the impact of Ramadan fasting, exhibited significant methodological limitations. The remaining 20 selected reviews displayed minor limitations. While a few reviews had some limitations regarding the comprehensiveness of the search, most included SRs exhibited weaknesses in terms of study selection and the analysis of emerged evidence.

4.3 Narrative Synthesis of Results

We observed heterogeneous and diverse study findings. Cumulatively, 97 health outcomes were identified. Among them, cardiovascular risk factors were the most frequently analyzed and reported, with 33 observations concerning this health variable. Other study findings included renal diseases (12 outcomes), gastrointestinal diseases (8 outcomes), inflammation and oxidative stress (12 outcomes), and dietary and nutritional aspects. Infectious diseases were measured less frequently, with only seven outcomes assessed by a few studies. Well-being, quality of life, and mood disorders were not evaluated in any identified systematic review. Table II provides details of the studies included, while a brief narrative synthesis is presented in Table III. Herein, we report the most significant emerged results, organized by health status of participants.

TABLE I.—*AMSTAR score (class) for each included systematic reviews (SRs). AMSTAR is a measurement tool to assess the methodological quality of the included SRs. AMSTAR ranges from 0 (low quality) to 11 (optimal quality).*

15-35

Study	Year	Fasting regimen analyzed	N. of participants	AMSTAR score (class)	AMSTAR class
Lazarou *et al.*[26]	2010	Orthodox Fasting	724	4.5	2
Sadeghpour *et al.*[18]	2012	Ramadan	10735	4.5	2
Sadeghirad *et al.*[31]	2012	Ramadan	1258	8.5	4
Salim *et al.*[15]	2013	Ramadan	NA	3.5	2
Kul *et al.*[25]	2014	Ramadan	1476	9.5	4
Bragazzi *et al.*[30]	2014	Ramadan	2521	3.5	2
Barnosky *et al.*[20]	2014	Intermittent	861	3.5	2
Horne *et al.*[23]	2015	Intermittent	796	3.5	2
Seimon *et al.*[34]	2015	Intermittent	1765	5.5	2
Bragazzi *et al.* [19]	2015	Ramadan	NA	2.5	1
Mazidi *et al.*[32]	2015	Ramadan	NA	4.5	2
Bragazzi *et al.*[17]	2015	Ramadan	NA	3.5	2
Turin *et al.*[27]	2016	Ramadan	NA	8.5	4
Alhamdan *et al.*[33]	2016	Intermittent	1193	7.5	3
Lettieri-Barbato *et al.*[29]	2016	Intermittent	NA	8.5	4
Koufakis *et al.* [24]	2017	Orthodox Fasting	2661	5.5	2
Adawi *et al.*[16]	2017	Ramadan	1704	3.5	2
Faris *et al.*[35]	2018	Ramadan	311	7.5	3
Harris *et al.*[21]	2018	Intermittent fasting	400	8.5	4
Fernando *et al.*[22]	2019	Ramadan	2947	9.5	4
Glazier *et al.*[28]	2019	Ramadan	31374	10.5	4

Table II characteristics of the studies in the review.

N		Title	Year of publication	Type of included studies	Number of included studies	Participants	At risk / ill /healthy	Intervention description
1	Lazarou C.	A critical review of current evidence, perspectives and research implications of diet-related traditions of the Eastern Christian Orthodox Church on dietary intakes and health consequences	2010	Five prospective studies, three cross-sectional studies, and three case–control studies	11	NA	Healthy	Orthodox fasting
2	Koufakis T.	Effects of Orthodox religious fasting on human health: a systematic review	2017	Nine studies were prospective, whereas only one was cross-sectional	10	NA	Healthy	Orthodox fasting
3	Sadeghirad S.	Islamic fasting and weight loss: a systematic review and meta-analysis	2012	Observational prospective studies	35		Healthy	Ramadan fasting
4	Sadeghpour S.	Ramadan fasting and digestive disorders: SEPAHAN systematic review No. 7	2012	Observational prospective studies	23	10735	Healthy or people diagnosed with digestive disorders	Ramadan fasting
5	Kul S.	Does Ramadan Fasting Alter Body Weight and Blood Lipids and Fasting Blood Glucose in a Healthy Population? A Meta-analysis	2014	Observational prospective studies	23	1476	Healthy	Ramadan fasting
6	Bragazzi NL.	Ramadan fasting and chronic kidney disease: A systematic review	2014	Observational prospective studies	26	2521	Ill people diagnosed with kidney diseases	Ramadan fasting
7	Barnosky AR.	Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings	2014	Randomized control trials and nonrandomized trials	19	861	Overweight and obese adults.	Intermittent Fasting, Alternate day Fasting, Calorie restriction
8	Horne B.D.	Health effects of intermittent fasting: hormesis or harm? A systematic review	2015	Randomized controlled clinical trials	7	796	Healthy	Intermittent Fasting
9	Mazidi M.	Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials	2015	Observational	25	NA	Patients diagnosed with stable cardiac disease	Ramadan fasting

10	Seimon RV.	Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials	2015	Randomized clinical trial	40	1765	Obese or overweight	Intermittent Fasting
11	Bragazzi NL.	Ramadan fasting and infectious diseases: a systematic review	2015	Observational	51	NA	Adults diagnosed with infectious diseases	Ramadan fasting
12	Bragazzi NL.	Ramadan fasting and chronic kidney disease: does estimated glomerular filtration rate change after and before Ramadan? Insights from a mini meta-analysis.	2015	Observational	6 studies	362	Chronic kidney disease	Fasting of Ramadan
13	Alhamdan BA.	Ramadan fasting in not usually associated with the risk of cardiovascular events: a Systematic review and meta-analysis	2016	Observational	10 studies	1193	NA	Fasting on alternate days
14	Turin TC.	Ramadan fasting in not usually associated with the risk of cardiovascular events: a Systematic review and meta-analysis	2016	Observational	16 studies	NA	Healthy subjects	Fasting of Ramadan
15	Lettieri-Barbato D.	Effects of dietary restriction on adipose mass and biomarkers of healthy aging in human	2016	Unrandomized, Randomized or Controlled, Randomized and Controlled, Cross-Sectional	43 studies	NA	Healthy subjects or people with metabolic pathologies	Dietary restriction regimens (intermittent fasting (4 studies), low calorie diet or calorie restriction)
16	Salim I.	Impact of Religious Ramadan Fasting on Cardiovascular Disease: a Systematic Review of the Literature	2013	Observational studies	36 studies	NA	Healthy subjects and in subjects with acute heart disease	Fasting of Ramadan
17	Adawi M.	Ramadan fasting exerts immunomodulatory effects: insights from a systematic review	2017	Case–control study, prospective cohort study	45 studies	1704	Healthy subjects / affected by autoimmune, cardiac or other diseases / athletes / pregnant women	Fasting of Ramadan

18	Mo'ez Al-Islam. E.Faris.	Impact of diurnal intermittent fasting during Ramadan on inflammatory and oxidative stress markers in healthy people: Systematic review and meta-analysis	2018	Observational studies	12 studies	311	Healthy subjects	Fasting of Ramadan
19	Harris L.	Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis	2018	Randomized and pseudo-randomized controlled trials.	6 studies	400	Obese or overweight non-hospitalized subjects	Intermittent fasting: consumption <800kcal in at least 1 day a week but not more than 6 days.
20	Fernando HA.	Effect of Ramadan fasting on weight and body composition in healthy non-athlete adults: a systematic review and meta-analysis	2019	NA	70 studies	2947	Healthy non-athletic subjects	Fasting of Ramadan
21	Glazier J.	The effect of Ramadan fasting during pregnancy on perinatal outcomes: a systematic review and meta-analysis	2019	Observational studies	22 studies	31374	Pregnant women	Fasting of Ramadan

Table III. Narrative synthesis of included studies.

Orthodox fasting				
N	**Author**	**Intervention**	**Outcomes**	**Results**
1	Lazarou et al. 2010	Orthodox fasting	Dietary quality, nutrient intake adequacy, blood pressure levels, blood lipid levels, body mass, and metabolic health	Compared with non-fasters, adult and child fasters showed better dietary quality and healthier blood lipid profiles. In general, adult and child fasters showed a good lipid profile (total cholesterol, low density lipoprotein [LDL], triglyceride [TG], and high-density lipoprotein [HDL] values are within or closer to acceptable/recommended values) compared with non-fasters presumably due to modification in lipid intake. Furthermore, in contrast with expectations, fasters revealed higher mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) than controls
2	Koufakis et al. 2010	Orthodox fasting	Dietary analysis Lipidic and glucose profile Body mass index (BMI) and body weight Arterial blood pressure Iron status and relative hematological parameters	The results are limited. Orthodox fating (OF) is characterized by a reduction in total energy and fat intake; an increase in carbohydrate and fiber consumption An improvement in lipids profile was observed; to be more specific, the authors found an optimal reduction of total cholesterol and LDL-C levels (up to 17.8 and 31.4%, respectively). However, the impact of this dietary pattern on HDL-C is not clear. Data on the impact on body weight and glucose homeostasis are limited. Lastly, among potential negative aspects of, the authors cited a reduction in dietary intake of vitamin D and B12 and minerals (mainly calcium).

Ramadan fasting				
3	Sadeghirad et al. 2012	Ramadan fasting	Body weight, BMI, average daily nutrient consumption (i.e. intakes of carbohydrate, protein and fat) and total daily energy intake	Fasting during Ramadan determined a relevant reduction in weight. Nevertheless, the weight lost was regained within some weeks after Ramadan. Only a modest decrease in body weight was observed in the following weeks after the end of fasting. Weight loss during Ramadan was greater among Asian populations; Africans and Europeans showed little weight changes. In three included studies, the total daily energy intake did not show changes. The number of studies with increased total daily energy intake was equal to the number of studies with decreased total daily energy intake during Ramadan. For this reason, it is not possible to draw definite conclusions. The most relevant findings were represented by the increase of total average daily energy intake during Ramadan month. This total energy intake continued to increase even after Ramadan (9923 (SD 1818) kJ/d). The intakes of carbohydrate were larger than protein and fat consumption before, during and after Ramadan. The percentage of energy intake from protein and fat during Ramadan did not change considerably compared with before or after the month of Ramadan.
4	Sadeghpour S et al. 2012	Ramadan fasting	Digestive disorders RC:R[3]C	Ramadan fasting seems to increase peptic ulcer complications (e.g. peptic ulcer perforation and bleeding). While the authors observe a deteriorating effect on patients with chronic peptic ulcer diseases on drug therapy, they did not find a similar impact on duodenal ulcer patients on treatment. Healthy individuals show minor GI symptoms; indeed, they did not show serious complications. Results about the incidence of acute appendicitis and peptic ulcer diseases are discordant, but acute mesenteric ischemia, hyperemesis gravidarum and primary small bowel volvulus seem to increase during Ramadan. No increase in idiopathic intussusception was observed during Ramadan and people diagnosed with an inflammatory bowel did not show serios adverse effects.
5	Kul et al. 2014	Ramadan fasting	Body weights. Blood levels of lipids and fasting blood glucose serum levels.	After Ramadan fasting, low-density lipoprotein (SMD = -1.67, 95 % CI = -2.48 to -0.86) and fasting blood glucose levels (SMD = -1.10, 95 % CI = -1.62 to -0.58) were decreased in both male and female. To be more specific, in the female subgroup, body weight (SMD = -0.04, 95 % CI = -0.20, 0.12), total cholesterol (SMD = 0.05, 95 % CI = -0.51 to 0.60), and triglyceride levels (SMD = 0.03, 95 % CI = -0.31, 0.36)did not change, while HDL levels (SMD = 0.86, 95 % CI = 0.11 to 1.61, p = 0.03) showed a significant increase. In males, the authors observed a relevant weight loss (SMD = -0.24, 95 % CI = -0.36, -0.12, p = 0.001). Also, a substantial reduction in total cholesterol (SMD = -0.44, 95 % CI = -0.77 to -0.11) and LDL levels (SMD = -2.22, 95 % CI = -3.47 to -0.96) and a small decrease in triglyceride levels (SMD = -0.35, 95 % CI = -0.67 to -0.02) were reported in males.
6	Bragazzi NL et al. 2014	Ramadan fasting	Kidney diseases	During Ramadan, the concentration of immunosuppressive drugs tends to remain stable, and biochemical parameters do not change significantly in recipients of kidney allograft. Furthermore, no organ rejection or deterioration of kidney functions were observed. Ramadan fasting does not seem to deteriorate health condition in subjects with renal colic, does not cause hypercalciuria and does not increase lithogenic promotors (that is to say, oxalate, calcium, uric acid, phosphates) and inhibitors (citrate, magnesium). Ramadan does not generate severe adverse effects in patients suffering from severe renal failure.

7	Bragazzi NL et al. 2015	Ramadan fasting	Complications of Ramadan fasting on patients with infectious diseases or at risk of developing an infectious complication (appendicitis, diarrhea, diabetes, meningitis, HIV, active ulcers, eye infectious, hepatitis, and tropical infectious)	Diabetic ppatients with a moderate risk of infectious complications should not practice Ramadan fasting Ramadan fasting showed a little effect on patients suffering from diarrhea Ramadan fasting did not show an impact on the effectiveness of anti-helminthic medications Fasting should not be recommended to patients diagnosed with active ulcers should not fast due to higher probability of developing complications and adverse effects.
8	Turin TC et al 2016	Ramadan fasting	Incidence of congestive heart failure, acute myocardial infarction and stroke. GFR	No significant difference in the incidence of cardiovascular disease. No significant difference in GFR during fasting.
9	Bragazzi NL 2015	Ramadan fasting	Number of cardiovascular events and hospitalizations, effect on cardiovascular risk factors (Weight, BMI, total cholesterol, LDL, VLDL, HDL, triglycerides (TG), PAD and PAD, Apo A1 and Apo B).	Improvement in lipid levels, No change in the number of cardiovascular events.
10	Salim I et.al 2013	Ramadan fasting	Immunological and inflammatory markers.	Immune markers slightly modified in healthy and athletes. No fetal and maternal risks during pregnancy. Improvement of the lipid profile and ↓ of oxidative stress in subjects with heart disease. Safe fasting in HIV and autoimmune diseases. Immunological markers unchanged in asthma and increased in schizophrenia.
11	Adawi M. et al 2017	Ramadan fasting	Weight, BMI, body composition changes (percentage of fat mass, absolute fat mass, lean mass).	↓ significant in weight, fat mass and lean mass. The higher the starting BMI, the greater the loss of weight and fat mass.
12	Fernando HA et.al 2019	Ramadan fasting	Weight, BMI, body composition changes (percentage of fat mass, absolute fat mass, lean mass).	↓ significant in weight, fat mass and lean mass. The higher the starting BMI, the greater the loss of weight and fat mass.
13	Glazier JD et al. 2019	Ramadan fasting	Perinatal mortality, risk of premature birth and small infant by gestational age (EMS), newborns born dead, neonatal mortality, maternal mortality, gestational hypertension, gestational diabetes, congenital anomalies, neonatal morbidity, placental weight and weight of the infant at birth.	Birth weight not affected by fasting. Significantly reduced placental weight. Risk of premature birth not affected by fasting. Absence of data on perinatal mortality.

14	Mo'ez Al-Islam E. Faris et al. 2018	Ramadan fasting	Inflammatory markers (IL-1 / β, IL-6, TNF-α, CRP / hs-CRP) and oxidative stress markers (MDA)	Modest reduction of TNF-α and IL-6, Very modest reduction of IL-1β, MDA and CRP / hs-CRP
15	Mazidi M et Al., 2015	Ramadan fasting	Cardiovascular outcomes (myocardial infarction, stroke, heart failure and cardiac revascularization) and cardiometabolic risk factors (BMI, waist circumference, blood pressure (BP) and lipid profile	Unchanged incidence of cardiovascular disease during fasting Effects on cardiovascular risk factors not relevant (only some studies report an improvement in lipid profile or BMI)
Intermittent fasting				
16	Alhamandam et al. 2016	Fasting on alternate days.	Body weight, BMI, fat mass, lean mass.	Alternating fasting appears to be better than VLCD for better compliance, greater loss of fat mass and preservation of lean mass.
17	Barnosky AR et al. 2015	Intermittent fasting, alternate day fasting, calorie restriction	Body weight, body composition, glucose and insulin levels	The authors reported a superior decrease in body weight in calorie restriction regimen, in comparison with intermittent fasting and alternate day fasting. Similar reductions in visceral fat mass, fasting insulin, and insulin resistance were observed in obese adults. None of the interventions produced clinically significant reductions in glucose levels.
18	Horne BD et al. 2015	Intermittent fasting	Weight loss Lipidic profile Brain-derived neurotrophic factor Coronary artery disease Diabetes Mood disorders	The authors found relevant improvements in weight and other risk-related outcomes (e.g. lipidic serum levels). Fasting was associated with a lower prevalence of CAD or diabetes diagnosis.
19	Lettieri – Barbato D. et al. 2016	Dietary restriction regimens (intermittent fasting (4 studies), low calorie diet or calorie restriction).	Fat mass, adipokines (adiponectin and leptin), insulinemia, inflammatory markers (TNF-α, IL-1, IL-6, PCR), HOMA index, DHEA, IGF-1, IGFBPs (IGFBP-1, -2, -3).	Caloric restriction regimens reduce total and visceral fat mass and improve adiponectin / leptin ratio and cytokine inflammatory profile. There are also improvements in insulin levels, IGF-1 and IGFBP-1,2.
20	Harris et al. 2018	Intermittent fasting: consumption <800kcal in at least 1 day a week but not more than 6 days.	Body weight, fat mass, lean body mass, waist circumference, PAS and PAD, blood sugar, insulinemia, total cholesterol, HDL, LDL, triglycerides.	Intermittent fasting and continuous calorie restriction reduce weight in the same way. Intermittent fasting, on the other hand, is more useful than no treatment. Moderate improvement also in the other parameters.
21	Seimon Rv et al. 2015	Intermittent fasting	Weight change Anthropometric changes Effects on glucose homeostasis	Iintermittent fasting seems to be similar to continuous energy restriction to reduce body weight, fat mass, fat-free mass and improve glucose homeostasis, and may reduce appetite The authors stated also that this dietary pattern appears to mitigate responses to energy restriction or improve weight loss efficiency. Intermittent fasting represents a valid dietary strategy, not superior, to continuous energy restriction for weight loss.

4.3.1 Effects of Fasting on Outcomes of Disease

A total of nine systematic reviews (SRs) assessed the effect of fasting regimens as non-pharmacological management of illnesses. Study findings varied; while significant improvements were observed in 23 out of the 97 identified outcomes, selected studies indicated a negative or non-significant impact of this dietary intervention on other health measures.

i.) Cardiovascular Risk Factors

Several SRs examined the impact of Ramadan fasting on the incidence of cardiovascular disease and lipid profiles in patients with stable cardiac conditions. Although fasting did not appear to affect the incidence of acute cardiac illness during Ramadan fasting, significant improvements were noted in high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and total cholesterol (T-chol) levels among cardiac patients. Additionally, therapeutic fasting was found to be an effective non-pharmacological therapy for weight loss among subjects with prevalent cardiac disease seeking medical attention.

ii.) Kidney Diseases

One SR analyzed the correlation between fasting and kidney diseases. Ramadan fasting did not significantly decrease health outcomes in patients with renal colic or renal transplant recipients. Similarly, fasting did not result in severe adverse effects or significant changes in glomerular filtration rate among patients with chronic kidney disease (CKD).

iii.) Digestive Disorders

Limited data were available on the impact of fasting on digestive disorders. One SR reported increased peptic ulcer complications during Ramadan fasting, particularly among patients under pharmacological treatment.

iv.) Infectious Diseases

An SR on the clinical impact of Ramadan fasting among patients with infectious diseases found limited effects on diarrheal patients and a protective effect against urinary tract infections in urological patients. Additionally, no significant changes were observed in treatment adherence or clinical parameters among HIV patients.

v.) Inflammation

A review assessed the influence of Ramadan fasting on immune system regulation in patients with stable cardiac illnesses, asthma, and schizophrenia. The dietary intervention was found to be safe and beneficial, particularly in reducing oxidative stress.

vi.) Hormonal and Metabolic Homeostasis

Two SRs reported positive effects of fasting on hormonal and metabolic homeostasis in pre-diabetic and obese patients. Intermittent fasting (IF) and alternate-day fasting (ADF) led to decreases in serum glucose concentrations and fasting insulin levels, along with improvements in insulin sensitivity.

4.3.2 Effects of fasting on healthy participants

Among 15 systematic reviews focusing on fasting in healthy participants, findings were mixed. While some studies showed improvements in 31 out of 97 outcomes, others reported

either negative impacts or no significant effects. This highlights the need for further research to clarify when fasting may be beneficial or detrimental to health.

i.) Anthropometric body measurements

Several systematic reviews included in this overview examined the relationship between different fasting regimens and anthropometric body measurements. Two meta-analysis, conducted in order to ascertain the impact of Ramadan fasting on body composition in healthy population, reported a weight loss statistically significant in enrolled males (SMD=-0.24, 95% CI: -0.36, -0.12, P=0.001), but not in women (SMD=-0.04, 95% CI: -0.20, 0.12). While no change in fat percentage between pre-Ramadan and post-Ramadan in people with normal weight (-0.41% [-1.45% to 0.63%], P=0.436) was reported, on the other hand loss of fat-free mass was significant between pre-Ramadan and post-Ramadan, but was about 30% less than loss of absolute fat mass. These findings were transient; after the end of Ramadan, participants typically returned to their pre-Ramadan values. Similar beneficial effects on anthropometric body composition measurements have been observed in systematic reviews and meta-analyses investigating the effectiveness of intermittent fasting for weight loss. One quantitative meta-analytic analysis showed that the pooled change in body weight, fat mass and fat-free mass was 4.30 kg (95% CI: 3.41, 5.20), 4.06 kg (95% CI: 2.99, 5.13) and 0.72 kg (95% CI: -0.07, 1.51), respectively. By contrast, the overall impact of Christian Orthodox fasting (COF) on body weight is still unclear because of conflicting results.

ii.) Cardiovascular risk factors

A meta-analysis included in this overview demonstrated a reduction in serum levels of low-density lipoprotein (LDL) cholesterol (SMD=-1.67, 95% CI: -2.48 to -0.86) and fasting blood

glucose levels across both sexes following Ramadan fasting compared to pre-fasting levels. Specifically, in males, Ramadan fasting led to a significant decrease in total cholesterol (SMD=-0.44, 95% CI: -0.77 to -0.11) and LDL cholesterol (SMD=-2.22, 95% CI: -3.47 to -0.96), with a slight reduction in triglyceride levels (SMD=-0.35, 95% CI: -0.67 to -0.02). Similar improvements in lipid profiles were observed in systematic reviews evaluating the health effects of Christian Orthodox fasting (COF) and intermittent fasting (IF) regimens. These reviews consistently reported reductions in total cholesterol and LDL cholesterol levels.

Regarding the incidence of cardiovascular diseases, fasting did not appear to affect the occurrence of acute cardiac events during Ramadan fasting, as evidenced by the literature reviewed. These findings suggest that fasting, particularly during Ramadan and with other fasting regimens, may contribute to favorable changes in cardiovascular risk factors, specifically lipid profiles, without influencing acute cardiac illness incidence.

iii.) Inflammation

A systematic review and meta-analysis examined the potential beneficial effects of Ramadan fasting on immune system regulation, particularly in reducing inflammation and oxidative stress markers. Diurnal fasting was associated with small reductions in IL-1 (Hedge's g=0.016), CRP/hs-CRP (Hedge's g=0.119), MDA (Hedge's g=0.219), TNF-α (Hedge's g=0.371), and IL-6 (Hedge's g=0.407).

These findings suggest that Ramadan fasting may offer protective effects against inflammation and oxidative stress, which are implicated in various chronic diseases. This highlights a

potential mechanism through which fasting regimens could contribute to improved health outcomes beyond weight management and metabolic health.

iv.) Pregnancy

Glazier conducted a systematic review and meta-analysis to assess the impact of Ramadan fasting during pregnancy on perinatal outcomes among pregnant Muslim women. A significant finding from this meta-analysis was a decrease in placental weight in fasting pregnant mothers (SMD=-0.94, 95% CI: -0.97 to -0.90). It's important to note that this result was predominantly supported by data from a single observational study. No data regarding perinatal mortality outcomes were reported in the review.

These findings suggest a potential concern regarding placental health during Ramadan fasting among pregnant women, although further research, particularly through robust prospective studies, is needed to better understand the implications for perinatal health and mortality.

v.) Hormonal and metabolic homeostasis

Three studies included in this overview analyzed the relationship between various fasting regimens and hormonal and metabolic outcomes. One meta-analysis focused on the influence of Ramadan fasting reported a reduction in fasting blood glucose serum concentrations (SMD: -1.10, 95% CI: -1.62 to -0.58) compared to pre-Ramadan levels, potentially attributed to changes in body weight and composition. Similarly, improvements in metabolic markers were observed in healthy subjects following intermittent fasting. Another meta-analysis indicated significant reductions in insulin (SDM=-1.019; 95% CI: -1.362 to -0.675; P<0.000) and IGF-1 levels (SDM=-0.546; 95% CI: -0.750 to -0.342; P<0.000). Additionally, increased insulin

sensitivity was noted among fasting subjects, with a significant reduction in the HOMA Index after the dietary intervention (SDM=-0.837; 95% CI: -0.990 to -0.750; P<0.000). These findings suggest that both Ramadan fasting and intermittent fasting may positively impact hormonal and metabolic homeostasis, potentially offering benefits for individuals in managing conditions related to insulin resistance and glucose metabolism.

5. Discussion

This systematic overview was conducted to provide a comprehensive update on the current literature regarding the association between fasting and health outcomes in the general population.

Caloric restriction (CR) is a dietary pattern characterized by a reduction in daily caloric intake without a deficiency in essential nutrients. Numerous in vivo and in vitro studies have demonstrated a strong correlation between CR and increased lifespan. This correlation is evidenced by longer life expectancy in both animal and human models. Moreover, previous experimental and observational studies have confirmed a significant reduction in the incidence of many non-communicable diseases in animals and humans on a CR diet. The reduction in daily caloric intake triggers complex biological and chemical mechanisms contributing to these benefits.

Previous systematic reviews (SRs) have evaluated the potential beneficial impact of fasting on specific health predictors. However, this review aimed to summarize all findings on this topic to draw more definitive conclusions about the safety and efficacy of fasting.

Our search identified 21 SRs reporting data from 543 randomized controlled trials (RCTs) and observational studies. In this overview, we emphasized the three most widely studied fasting interventions: Ramadan fasting, Christian Orthodox fasting (COF), and intermittent fasting (IF).

Fasting appears to induce encouraging changes in various health dimensions in both healthy and ill subjects, such as anthropometric body composition measurements, inflammation, cardiovascular risk factors, insulin sensitivity, and the incidence of acute cardiac illnesses. These outcomes are considered strong indicators of longevity and healthy aging.

The most consistent results include reductions in body measurements (e.g., body weight and visceral lean mass) and cardiovascular risk factors (e.g., lipid profile, blood pressure). Many of the included SRs reported significant weight loss and improvements in lipid profiles after a limited period of fasting in both healthy participants and individuals with stable cardiac diseases. However, these benefits are often not lasting. After Ramadan, participants typically returned to their pre-Ramadan weight, possibly due to overeating following periods of food deprivation and reduction. It is also important to note that such nutritional patterns can be challenging for individuals who need to eat frequently due to metabolic changes induced by their medications (e.g., diabetes).

Fasting interventions (IF, Ramadan fasting, and COF) also bring significant improvements in fasting insulin and insulin sensitivity, likely due to a potential hyperplasia of pancreatic islet B cells triggered by these dietary patterns.

The magnitude and clinical importance of improvements in body measures and cardiometabolic outcomes suggest the potential use of fasting regimens in the non-pharmacological treatment of several chronic diseases (e.g., diabetes, cancer, cardiovascular diseases) and lifestyle-related issues (e.g., obesity, overweight). Thus, our study supports the idea that fasting may effectively postpone the onset of aging and prevent diseases, reducing the adverse effects of chronic pharmacological treatments.

Fasting regimens also positively affect inflammatory status by reducing the serum concentration of inflammatory markers such as IL-6, homocysteine, and CRP. These findings suggest the potential clinical application of fasting as a non-genetic modulator in treating patients with dysregulation of the inflammatory apparatus.

However, fasting also has drawbacks and adverse effects. For example, Ramadan fasting may increase the risk of peptic ulcer complications (e.g., perforation, bleeding), acute mesenteric ischemia, hyperemesis gravidarum, and primary small bowel volvulus in patients with peptic ulcers undergoing treatment. Additionally, fasting may increase the risk of ocular infectious diseases. Notably, no studies included in the SRs assessed well-being, quality of life, and social functionality, preventing definitive conclusions on fasting's impact on all health aspects per the World Health Organization's 1948 definition of health status.

6. Limitations of the Study

This systematic overview has several limitations that need to be acknowledged. Firstly, many of the included systematic reviews (SRs) were conducted on specific populations: observational studies on Ramadan fasting were primarily conducted in Islamic countries, while randomized controlled trials (RCTs) on intermittent fasting (IF) were predominantly carried out in America. Consequently, the generalizability of results to global populations may be limited.

Secondly, meta-analyses could not be performed for all identified outcomes due to insufficient reported data necessary for statistical and quantitative analysis. This limitation prevented comprehensive synthesis across all variables and outcomes, potentially leading to varied interpretations.

Thirdly, there was a lack of studies specifically focusing on cognitive functionality, well-being, quality of life, and social functionality related to fasting. This gap in research limits the ability to conclusively recommend fasting as a method for improving these important health parameters.

Fourthly, while some selected SRs showed good methodological quality according to the AMSTAR tool, many reviews did not adhere to robust study designs. This inconsistency in methodological quality across studies raises concerns about the reliability of the results. Consequently, the findings of this overview should be interpreted cautiously.

Lastly, there was a scarcity of studies reporting data on the impact of fasting in children, elderly individuals, and underweight individuals, which limits the applicability of findings across diverse demographic groups.

Despite these limitations, strengths of this work include a comprehensive search strategy using multiple sources to retrieve relevant studies, and independent selection and data extraction by two authors, which helps mitigate potential selection bias.

In conclusion, while this systematic overview provides valuable insights into the effects of fasting on various health parameters, its limitations underscore the need for further well-designed studies across diverse populations and outcomes to strengthen the evidence base and inform clinical practice effectively.

7. Conclusions

In adult populations, fasting regimens show potential beneficial effects on several health indicators and risk factors (e.g., fasting insulin, insulin sensitivity, body weight, lipid profile) for non-communicable chronic diseases. Despite some findings not being of relevant clinical interest and some adverse effects, fasting interventions result in improvements in functional outcomes such as inflammatory status and hormonal and metabolic parameters. However, some specific health dimensions (cognitive function, well-being, quality of life) were not assessed by the included SRs. Therefore, further RCTs or cohort studies with good methodological quality and larger sample sizes are needed to better understand the health benefits of fasting and the underlying biological mechanisms.

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