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The Effects of Intermittent Fasting on Chronic Disease in Adults: A Systematic Review

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The Effects of Intermittent Fasting on Chronic Disease in Adults:

A Systematic Review

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Abstract

This systematic review investigated thirteen primary and secondary research studies from the past 20 years to determine the effects of intermittent fasting on chronic disease in adults through evaluation of biological markers pertaining to inflammation, oxidative stress, and the cardiovascular system. The dependent variables examined included heart rate, blood pressure, and cholesterol levels for cardiovascular risk; leptin and TNF-α for inflammatory risk; and F_2-Isoprostanes and free radicals for oxidative stress biomarkers. The reviewed studies found that there was a decrease in resting heart rate, systolic and diastolic blood pressure, blood LDL and total cholesterol levels, inflammatory cells, like leptin, TNF-α, and insulin, and oxidative stress (isoprostanes and free radicals); and an increase in HDL cholesterol levels and insulin sensitivity in human and animal subjects engaged in various forms of intermittent fasting. The reviewed effects in both human and animal trials point to beneficial health effects of intermittent fasting in preventing and resisting chronic disease risk factors. In the short-term, it can be implicated that intermittent fasting could be successful in preventing chronic disease from a holistic perspective. This review is limited due to its narrow examination of only thirteen studies, minimal intervention time, and small population size for tested subjects.

Keywords: intermittent fasting, intermittent energy restriction, caloric restriction, chronic disease, inflammation, oxidative stress, cardiovascular system

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The Effects of Intermittent Fasting on Chronic Disease in Adults: A Systematic Review

Chronic diseases combined, which is a general term for any disease that lasts for three or more months and is generally incurable and ongoing, were recently labeled as a leading cause of death in the United States (Buttorff, Ruder, and Bauman, 2017). These detrimental diseases included diabetes, cardiovascular disease, hypertension, stroke, metabolic diseases, pulmonary conditions, and even cancer (Roberts and Barnard, 2005). Since chronic disease is a wide-encompassing term for a multitude of diseases, it is important to categorize them into objective categories. Chronic inflammation, oxidative stress, and cardiovascular disease were chosen as subheadings that were considered origins of chronic diseases.

According to the Center for Chronic Disease Control (Buttorff, Ruder, and Bauman, 2017), 60% of the 247.5 million adults living in the United States were inflicted with a chronic disease. Statistically, this led to a staggering 7 out of 10 Americans dying from issues complicated by a chronic disease. Within healthcare, $1.65 trillion was spent annually treating patients with one or more chronic diseases, which accounted for more than 75% of the $2.2 trillion that the U.S. spent on health care (Erdam, Prada, and Haffam, 2013). Even with these astonishing statistics, chronic disease is a preventable epidemic that some say is being neglected. According to (Horton, 2005):

> “The reduction of chronic disease is not a Millennium Development Goal (MDG). While the political fashions have embraced some diseases—HIV/AIDS, malaria, and tuberculosis, in particular—many other common conditions remain marginal to the mainstream of global action on health. Chronic diseases are among these neglected conditions.” (p.1514)

Statistically, chronic diseases are hurting the financial status of the US healthcare system and leaving Americans with a 70% chance of dying from complications.

Implementing an intervention plan to reduce the impact of chronic diseases could have multiple positive impacts on society. The keys to any intervention are prevention and reduction of any negative health consequences (Partnership to Fight Chronic Disease, 2007). Risk of chronic diseases may be reduced by lifestyle modifications and early detection. The CDC reported that the leading determinants of chronic disease risk derived from a lack of exercise, poor nutrition, and tobacco/alcohol use, all of which are relatively modifiable ("Power of Prevention," 2009). Thus, regulations of modifiable risk factors have been identified as key in chronic disease prevention strategies (CDC, 2009).

The most common approaches to modifying chronic disease risk factors involve instruction to stop the causes at the source such as: reduce or abstain from alcohol consumption, cease tobacco products, monitor caloric consumption with an eye toward energy balance (Willett et al. 2006). Success at adopting these lifestyle interventions has been limited (Abramson, 2005). Abramson (2005) stated that people failed in their exercise and diet protocol because of their lack of understanding of the different niches of fitness and nutrition such as the financial and time commitments of gym memberships, nutritional plans, meticulous cooking, and shopping for healthy foods (Roa, et al, 2013).

For instance, many dieting fads have a start and end date; however, when considering chronic diseases prevention, modifying risk factors has been shown to require less acute approaches (Willett et al., 2006). Investigating attainable and sustainable lifestyle interventions shown to have positive effects on the reduction of chronic disease is an important and necessary endeavor (Abramson, 2005).

Adopting a healthy diet, in conjunction with regular physical activity, has been shown to improve health in humans (Coe, 2012). Feig and Lowe (2017) found that dietary consistency and compliance was key to maintaining weight and remaining healthy. Lemstra (2016) reported that finding a dietary plan that was easily adoptable and consistently followed was a challenge.

Though consistency was identified as a challenge, Wegman and colleagues (2015) found that an alternate-day fasting protocol was easily followed and dietary compliance was only an issue when subjects were told to overeat. Intermittent fasting has been readily adopted over the last ten years (Collier, 2013). Intermittent fasting has been shown to be realistic, attainable, and sustainable solution to prevent modifiable risks of chronic diseases (Lay, 2014). Varady and Hellerstein (2007) found that intermittent fasting not only helped adults lose weight, but also helped decrease chronic disease risk through a myriad of secondary health benefits.

Intermittent Fasting

In the past decade, interest in new popular dieting fads have steadily led the general public toward intermittent fasting (Collier, 2013). (Research has shown intermittent fasting works to reduce overall body mass and body fat percentage in overweight and obese adults, as well as a way to maintain full-body health in active, nonobese adults, according to Ganesan, Habboush, and Sultan (2018)). Intermittent fasting is an umbrella term for short-term caloric restriction for periods shorter than 24 hours, which leaves room for different protocols for participating in an intermittent fasting regimen (Patterson et al., 2015). There are three main regimens of intermittent fasting for health benefits: complete alternate-day

fasting (ADF), modified weekly fasting regimens (MIF), and time-restricted feeding (TRF; Patterson et al., 2015).

Complete alternate-day fasting involves one day of zero caloric intake or energy-producing ingestion followed by another day of feeding *ad libitum*, or as willed (Varady & Hellerstein, 2007). Modified weekly fasting regimens involve the popular 5:2 diet, which involves caloric restriction by consuming only 20-25% of needed energy calories for two consecutive days and then eating *ad libitum* for the other five days of the week (Patterson et al., 2015). Finally, time-restricted feeding involves a lack of energy consumption for a majority of each day (Patterson et al., 2015). For example, the 16:8 or 18:6 time-restricted feeding protocol would involve neither eating nor consuming calories for 16-18 hours and then eating *ad libitum* for 6-8 hours of the day.

According to Collier (2013), intermittent fasting is an anomaly when it comes to most dietary plans because of its simple and straightforward constraints. Intermittent fasting plans allow participants to consume the types of foods they like, unlike most diet plans. The only difference between intermittent fasting and other diet plans is that participants are only allowed to eat for a few select hours of the day or on select days of the week, while most diet plans ask for the user to eat small meals all the time, reduce calorie intake, or eat special meals.

Intermittent fasting works by decreasing the overall caloric consumption period in one's week, or by restricting the time an individual is allowing themselves to eat. By reducing the consumption period, the non-consumption time is also increased. By reducing the eating time, an individual reduces his or her caloric intake measured in kilocalories or

calories consumed by an individual in a defined amount of time, measured in calories consumed per day (Varady, Bhutani, Church, and Klemptel, 2009).

The majority of health benefits accrued from intermittent fasting originate from the fasting period, which permits the body to predominately use stored fatty acids instead of macronutrients the user is consuming (Byrne, Sainsbury, King, Hills, Wood, 2018). Not only has this been shown to decrease excess body fat, but because fat is more difficult for the body to consume than carbohydrates, the body burns more calories by consuming stored fat (Hayward et al., 2014), This short-interval fat utilization method has had a significant impact on weight loss and favorable body composition changes (Ganesan, Habboush, and Sultan, 2018). Increased stored fat utilization and weight loss aid are not the only benefits intermittent fasting has been shown to produce. Intermittent fasting has been found to have positive effects on inflammatory biomarkers, improved cardiovascular system efficiency, increased insulin sensitivity, reduction in oxidative stress levels, as well as improvement in the neurological system, the immune system and the lifespan (Collier, 2013).

Biomarkers.

Strimbu and Tavel (2010) defined a biomarker broadly as a biological sign, an objective indication of a medical state that can be measured accurately and quantified from outside of the patient. In terms of this review, biomarkers for inflammation included insulin, leptin and TNF-α (Tumor Necrosis Factor Alpha); F_2-Isoprostanes and free radicals for the investigation of oxidative stress; and resting heart rate, blood pressure, and cholesterol blood levels for cardiovascular measures (Collier, 2013).

It is important to note that the effects of biomarkers have not been researched heavily in humans. Mayeux (2004) stated that the reason for this lack of human research was related

to the invasiveness of biomarker-testing in humans, causing ethical limitations to the studies. Even though there is lack of research in this area, intermittent fasting has been used as a way to reduce possibly harmful secondary biomarkers and improve beneficial secondary biomarkers (Aly, 2014).

Intermittent fasting and oxidative stress. Oxidative stress, cellular inflammation, and insufficient cardiac activity are additional factors identified to lead to chronic disease (Khansari, Shakiba, and Mahmoudi, 2009). Roberts and Barnard (2005) found intermittent fasting helped decrease oxidative stress and cellular inflammation, as well as improve the health of the cardiovascular system. Oxidative stress derives from an imbalance in the ratio between the input into chemically reactive oxygen-containing chemical species and the output of these species by detoxifying and damage repairing tools, which occurs through the antioxidant defense system (Burton and Jauniaux, 2011). Oxidative stress is suspected to be linked to the development of neurodegenerative diseases, cardiovascular diseases, and even cancer (Khansari, Shakiba, and Mahmoudi, 2009).

Free radicals. Free radicals are molecules that have an unpaired valence electron that is unstable. Biologically, they result from metabolic processes and are regulated by the antioxidant mechanisms. In excess, they can be harmful to the body and can cause various diseases, including Parkinson's disease, Schizophrenia, and Alzheimer's (Collier, 2013). Free radicals are not just dangerous by themselves, but can form other dangerous compounds, isoprostanes (Milne, Yin, Hardy, Davies, and Roberts, 2011).

Isoprostanes are compounds formed in vivo from a reaction with free radicals. High levels of isoprostanes are suspected to increase risk of myocardial infarction and have been used as biomarkers for oxidative stress in research subjects (Montuschi, Barnes, and Roberts,

2004). Free radicals have been found to be detrimental by increasing the risk of neurodegenerative diseases and the risk of heart attacks (Montuschi, Barnes, and Roberts, 2004). Collier (2013) reported that even though free radical studies remain minimal, evidence points to a reduction in free radicals throughout the body after a short-term bout of intermittent fasting protocol.

Intermittent fasting and inflammation. Inflammation is a natural, biological response to harmful stimuli and serves as the body's protective reaction to damaged cells or irritants (Johnson, Summer and Cutler, 2006). While beneficial in acute injuries, chronic inflammation has been found to lead to a number of life-altering diseases, including cancer, cardiovascular disease, neurodegenerative diseases, respiratory diseases, etc. (Kunnumakkara et al, 2018).

Biological markers of inflammation include TNF-α and leptin, as well as insulin (Johnson, Summer and Cutler, 2006). Leptin is a naturally-occurring hormone produced by adipose cells to help regulate energy balance in the body by inhibiting hunger. Leptin has also been found to be involved in the regulation of the inflammatory response. Chronically increased levels of leptin have been found to be associated with inflammatory-related diseases (Mattson and Wan, 2015). TNF-α (Tumor Necrosis Factor) is a cell-signaling protein, activated by white blood cells called macrophages, that is involved in inflammation in the body. While beneficial in acute inflammation, TNF-α also plays a part in many autoimmune disorders found to be related to chronic inflammation (Shojaie, Ghanbari, Shojaie, 2017). Both leptin and TNF-α have been used as biological markers of chronic diseases and can be used to track the onset of a possible inflammatory-based chronic disease (Shojaie, Ghanbari, Shojaie, 2017).

Insulin resistance has been shown to cause an increase in chronic inflammation at a cellular level (Khansari, Shakiba, and Mahmoudi, 2009). Insulin, a hormone naturally-occurring in the body, is secreted by beta cells, found in the pancreas, in order to regulate the metabolism of carbohydrates, fats, and proteins by increasing the use of carbohydrates as energy (McArdle, Katch, and Katch, 2015).

Diabetes Mellitus Type 2, commonly referred to as Type 2 Diabetes, is a metabolic disorder that involves the body's increased insulin resistance, according to Kharroubi and Darwish (2015). Type 2 diabetes has been found to result from an increase of insulin resistance, which can be caused by obesity, lack of exercise, and genetic risks (Kharroubi and Darwish, 2015). Obesity and a lack of exercise can increase the risk of developing type 2 diabetes, and certain genes can cause an increased risk of developing type 2 diabetes as well (Kharroubi and Darwish, 2015). In most cases, Type 2 diabetes can be managed by lowering cardiovascular risk factors, losing weight, exercising, and maintaining normal blood glucose levels (Mitchell, Catenaci, Wyatt, and Hill, 2011).

Insulin sensitivity, TNF-α, and leptin have been investigated in relation to intermittent fasting (Sutton et al., 2018). Because of intermittent fasting's proposed chronic anti-inflammatory effects, there is evidence that intermittent fasting may lead to a decrease in these inflammatory biomarkers, therefore improving chronic cellular inflammation chronic diseases (Shojaie, Ghanbari, and Shojaie, 2017).

Intermittent fasting and the cardiovascular system. The cardiovascular system, comprised of the heart, blood vessels, and its contained blood, is the organ system of the body that allows blood to circulate and transport nutrients, hormones, and blood cells carrying oxygen and carbon dioxide. Cardiovascular system variables include resting blood

pressure and heart rate, as well as total cholesterol levels (Varady, Bhutani, Church, and Klemptel, 2009). Heart rate is measured in beats of the heart per minute (McArdle, Katch, and Katch, 2015). Blood pressure is the pressure of circulating blood on the walls of arterial and venous blood vessels (McArdle, Katch, and Katch, 2015). It is measured in millimeters of mercury above the surrounding atmospheric pressure and is comprised of systolic and diastolic blood pressure. Systolic blood pressure is the maximum pressure during one heartbeat, while diastolic blood pressure is the minimum pressure between two heart beats. A normal resting blood pressure is usually a 120 mmHg systolic pressure over a 80 mmHg diastolic pressure (McArdle, Katch, and Katch, 2015). A heightened blood pressure and heart rate suggest a heart that is working harder than it needs to because of an underlying issue, according to McArdle, Katch, and Katch (2015).

In addition to the concerns raised with an unhealthy blood pressure and heart rate, cholesterol, a fatty substance that is found in the blood, can also be problematic if levels rise. Cholesterol is an organic molecule characterized by a waxy-like texture that is found naturally in the body (Varaday, Bhutani, Church, and Klempel, 2009). It is vital to the body to make and maintain membranes in the body; however, excess amounts of cholesterol can lead to heart attacks, stroke, or various vascular diseases (Varaday et al., 2009). Low-density lipoproteins (LDL) and high-density lipoproteins (HDL) are two common biomarkers found in health studies. LDL is sometimes referred to as the “bad type” of cholesterol because an increased level of LDL can lead to a buildup of cholesterol in arterial walls, leading to heart attacks and stroke (Varaday et al., 2009).

Heightened heart rate, blood pressure, and cholesterol levels generally means there is something wrong going on in the body. In order to combat these issues, health professionals

recommend exercise and special dieting plans when encountering these issues in patients, according to the American Heart Association. Although these instructions are helpful and have been proven to aid in cholesterol levels, resting heart rate, and blood pressure levels, there are hypotheses about whether or not intermittent fasting could play a major role in helping reduce these cardiovascular biological markers even without the aid of exercise (Francis, Young, and Lara, 2017).

Purpose

The purpose of this review was to explore the biological effects of intermittent fasting in human adults, beside the effect on weight, that can lead to chronic disease. This systematic review also worked to explore the effects of intermittent fasting on chronic disease biomarkers in patients who already had been previously diagnosed. This systematic review synthesizes completed research on intermittent fasting, effects on the cardiovascular system (heart rate, blood pressure, cholesterol levels), inflammation (leptin and TNF-α), and oxidative stress biomarkers (f_2-isoprostanes and free radicals). While intermittent fasting is theorized to cause weight loss by a combination of reduced caloric intake and burning of stored body fat, it has led to benefits like an increase in insulin and leptin sensitivity, as well as a decrease in cholesterol levels, inflammation, free radicals, and resting blood pressure and heart rate.

This review evaluated the clinical evidence that fasting is beneficial in humans. Clinical evidence has involved randomized controlled trials of the effects of fasting on relevant surrogate outcomes (e.g. cholesterol, inflammatory biomarkers, etc.) as well as the actual clinical endpoints (e.g. diabetes, cardiovascular disease, etc.) and any other studies of other supporting clinical outcomes. In addition, this study will include and discuss results

taken from animal studies to use as supporting evidence; however, no conclusive remarks will be made based on them.

Methods

The review of participating studies followed a systematic procedure, which included particular inclusion criteria during searches and data extraction. The primary aim of these searches were to 1) identify randomized clinical trials of intermittent fasting in which a standard diet or control group was used, 2) find studies that tested for the listed biomarkers in humans, and 3) find studies that observed the desired clinical endpoints in humans. Searches were also used to analyze animal studies meeting this criteria, in areas with little research.

Inclusion and Exclusion Criteria

Study designs included in this review were both human and animal clinical trials, with emphasis on use of human trials. These trials were randomized controlled trials and pilot studies. Original research studies and review articles were included, but case studies, surveys, and abstracts were excluded from review. To be included for this review, studies had to use human subjects of any age or BMI that would undergo an intermittent fasting or alternate-day feeding protocol. Studies researching Ramadan fasting were excluded because of their differing eating patterns from standard intermittent fasting protocols. Studies that did and did not include a control or comparable group were included to give a broader perspective of intermittent fasting research; however, studies with control groups were primarily used for data analysis.

No limit was placed on the duration of the intermittent fasting of subjects. Studies were excluded if participants were taking medication designed to induce weight loss or

reduce blood pressure, if participants were on a given diet (not *ad libitum* feeding), were diagnosed with cancer, were adolescent, elderly, or pregnant.

To be included for this systematic review, studies needed to measure one or more variables prior to the commencement of the intermittent fasting diet and following the cessation of the intermittent fasting period that the study investigated. Studies investigating parameters during the course of the intermittent fast program were favored.

Search Strategy

A systematic review of the literature was conducted by searching computerized databases for scholarly, peer-reviewed articles that had been published between January 1998 and December 2018, with limitations to the English language. Computerized data bases that were used included Bulldog One Search, found through the Gardner-Webb Library home page, Google Scholar, and PubMed/MEDLINE. Search engine requests included the terms, "Intermittent fasting", "energy restriction," and "caloric restriction," when researching intermittent fasting studies; "Inflammation," "oxidative stress," and "cardiovascular system," as well as their sub-terms: "blood pressure," "heart rate," "leptin," "TNF-α," "Insulin," "isoprostanes," and "free radicals" were used to research the affected variables in studies. In addition, the reference list of articles found in the search articles were examined for other trials and studies to ensure that all relevant studies were found.

Multiple searches were conducted with variations of the searched phrases, which included one of the primary "intermittent fasting" phrases and at least one of the sub-terms listed above.

Data Analysis

The titles and abstracts of the studies identified through use of the search strategy were screened prior to data analysis to ensure that they met the inclusion criteria. The full texts of the approved relevant studies were retried and then screened again with a full read through, analyzing the inclusion and exclusion criteria. Studies discussed in the investigated research articles that were possibly relevant to this review were investigated and prepared according to this same system. If the studies did not abide by the inclusion/exclusion criteria, they were discarded.

Results

Search Results and Study Characteristics

After a thorough search of the search engines, a total of 343 studies were found to be relevant towards the objectives of this review. Of these 343 studies, abstracts of these were read and analyzed. Thirteen were found fit, after reviewing inclusion and exclusion criteria, to be discussed in this review. A total of thirteen studies were included in this review, with eight of the studies pertaining to inflammatory biomarkers, three of the studies examining oxidative stress biomarkers, and eight of the studies examining cardiovascular chronic disease biomarkers. Of these 13 studies, seven of them used human subjects, while two of them used rats as subjects, and four were review studies looking at both human and animal trials. The intermittent fasting regimens varied across studies, with some including alternate day feeding (ADF), some modified weekly fasting (MIF), and some time-restricted feeding (TRF). Intermittent fasting regimen durations ranged from three weeks to twelve weeks. Study characteristics for studies with human subjects were identified and organized in Table 1, while animal subject study characteristics were identified in Table 2.

Table 1. Study Characteristics of Intermittent Fasting Studies with Human Subjects

Author/Year	IF Protocol	Study Duration (weeks)	Number of Participants	Studied variables	Mean age per group (years)	Mean weight per group (kg)
Bhutani et al., 2013	ADF	12	64	LDL, HDL, total cholesterol, HR, SBP, DBP, insulin	45	93
Harvie et al., 2011	MIF (2:5)	26	107	Oxidative stress, leptin, TNF-α, isoprostanes, HR, SBP, DBP, LDL, HDL, insulin sensitivity	40	81.5
Heilbronn et al., 2005	ADF	3	16	BP, LDL, HDL, insulin sensitivity	34, 32	59.7, 80.6
Johnson et al., 2007	ADCR	8	9	TNF-α, LDL, HDL	N/A	105
Sutton et al., 2018	TRF (18:6)	5	22	Oxidative stress, HR, BP, insulin sensitivity	36	Not measured
Varady et al., 2009	ADF	12	30	HR, LDL, HDL, Total Cholesterol	47	77, 77
Wegman et al., 2015	ADF	10	24	Oxidative stress, plasma Insulin	24	Not measured

Notes. IF- intermittent fasting, ADCR- alternate day caloric restriction, TNF-α- Tumor Necrosis Factor α, SBP- systolic blood pressure, DBP- diastolic blood pressure, kg- kilograms, HDL- High-density lipoprotein cholesterol, LDL- low-density lipoprotein cholesterol

Table 2. Study Characteristics of Intermittent Fasting Studies with Animal Subjects

Author/Year	IF Protocol	Study Duration (weeks)	Type/ number of animal subjects	Studied variables	Mean age (months)	Mean weight (grams)
Ahmet et al., 2005	ADF	12	Sprague-Dawley/ n=60	HR, inflammation	2	66
Wan et al., 2010	ADF	12	Male Wistar/ n=30	Inflammation, Insulin, BP	2.5	460

Notes. ADF- alternate day feeding, HR- heart rate, BP- blood pressure

The review articles that were included in the review discussed studies that investigated the effects of intermittent fasting on chronic disease risk factors and the implications behind the results of these studies. Of the four review articles, none of them followed systematic review guidelines, but all four of them were found to withstand the inclusion criteria for this study.

Study Outcomes

Each study was reviewed to clarify and confirm or deny implications of previous research on intermittent fasting affects risk factors for developing chronic disease in adults.

Study Outcomes of Human Trials.

A controlled randomized trial study investigating the effects of an intermittent fasting diet and exercise on plasma lipids in obese humans was conducted by Bhutani, Klempel, Kroeger, Trepanowski, Varady (2013). The study examined 64 obese subjects that were randomly selected to one of four groups: combination of alternate day fasting (ADF) and endurance exercise, ADF only, exercise only, and control. ADF subjects were instructed to eat *ad libitum* every other day, followed by a fasting day of 25% of their normal daily caloric intake on a 3-day rotating menu plan provided. After 12-weeks of following the dieting protocol, total cholesterol and LDL cholesterol was reduced in the ADF and combination

intervention groups (12 ± 5%, $P < 0.05$), while HDL cholesterol increased (18 ± 9%, $P < 0.05$). These findings concluded that the combination of intermittent fasting and endurance exercise produce superior changes in lipid indicators of heart disease risk.

Heilbronn et al. (2005) investigated the effects of a short-term intermittent fasting dieting regimen on body weight and biomarkers of longevity in nonobese subjects. Sixteen healthy subjects were recruited and instructed to fast intermittently for three weeks with one day eating *ad libitum*, followed by a day of a complete fast, following a strict alternate-day feeding protocol (ADFP). A fasting blood sample and blood pressure were taken at baseline, throughout, and after the cessation of the dieting period. Results showed a decrease in fasting insulin of 57 ± 4% ($P < 0.001$) and insulin was reduced after fasting days, suggesting an improved insulin sensitivity; however, fasting insulin did not drastically decrease following a 12-hour fast. In addition, systolic and diastolic blood pressure were not significantly reduced by the intermittent fasting intervention. It was noted that this study's design may have affected results because of a lack of dietary adherence from subjects. It was concluded that the intermittent fasting protocol did slightly increase insulin sensitivity, which could help improve benefits of chronic disease; however, these results were inconclusive.

In addition, Johnson et al. (2006) conducted an eight-week study to investigate the effects of ADCR on markers of oxidative stress and inflammation in overweight adults with moderate asthma. The subjects (n=10) were instructed to eat *ad libitum* (at one's desire) for one day, followed by a day of consuming less than 20% of their normal caloric intake. Blood was collected throughout the study in order to measure markers of oxidative stress and inflammation. Results indicated a reduction of all levels of leptin, serum cholesterol, TNF-α, and markers of oxidative stress (isoprostanes). The improved clinical findings demonstrated

rapid and beneficial effects of an intermittent fasting protocol, suggesting a new approach for therapeutic intervention for those with asthma.

With a discussion about the effects of intermittent fasting on all three of the chronic disease risk factors reviewed, Sutton et al. (2018) presented a study that investigated the effects of time-restricted feeding (TRF) on insulin sensitivity, blood pressure, and oxidative stress in men with Prediabetes. In this study, 22 men were separated into two groups, a time restricted feeding protocol group, eating for six hours and fasting for 18 hours of each day, and a control group, that ate and fasted for 12 hours each day. The subjects remained on this diet regimen for five weeks before they changed diet protocols. Throughout and after cessation of the study, blood samples and blood pressure were taken for each subject. They found that subjects following the TRF protocol had an increased insulin sensitivity as well as decreased blood pressure and oxidative stress levels. It was concluded that, because of the results being independent of weight loss, intermittent fasting could improve aspects of cardiometabolic health.

In addition to the findings on chronic disease risk markers, a study by Harvie et al. (2010) researched the effects of both an intermittent and continuous energy restriction protocol on weight loss and chronic disease risk biomarkers in young overweight women. 107 subjects with an average age of 40 were separated into two different groups: an intermittent energy restriction and continuous energy restriction group. The intermittent fasting group followed two days of eating 75% of their normal daily caloric intake, followed by five days of eating according to a nutrient composition Mediterranean-type diet. The continuous energy restriction group followed the Mediterranean-type diet for seven days of the week. The study lasted 6 months (26 weeks) and blood samples were taken at the end of

the first, third, and sixth month of the diet. Results showed similar weight loss in both groups, a modest decrease in fasting insulin in both groups, however, improvements in insulin sensitivity were greater in the intermittent fasting group. Both groups showed a modest reduction in oxidative stress biomarkers, inflammatory biomarker Leptin, LDL cholesterol, total cholesterol, and systolic blood pressure. Limitations were listed as the short-term length of the study and the lack of inclusion of local changes, like food substitutions or environmental/stress changes, that could have occurred.

Varady et al. (2009) investigated the effects of short-term modified alternate day fasting (ADF) on weight loss and cardioprotection. Sixteen obese subjects (twelve women and four men) completed a 10-week ADF protocol, which followed a two-week control phase, four-week ADF controlled phase, and four-week self-selected ADF phase. Blood samples were taken after a 12-hour fasting at the end of each phase. As a product of the 10-week study, dietary adherence remained relatively high (86%), resulting in a decrease of mean body weight of subjects (5.6 $\pm$ 1.1%), total cholesterol (21 $\pm$ 4%) and LDL cholesterol levels (25 $\pm$ 10%), and systolic blood pressure (from 124 $\pm$ 5 to 116 $\pm$ 3 mm Hg). Findings suggested that an ADF diet could help obese individuals reduce weight and decrease coronary artery disease risk.

A 10-week double crossover study, completed by Wegman et al. (2015), investigated the effects of an intermittent fasting regimen on oxidative stress and gene expressions. This study completed a 10-week long regimen of alternate day caloric restriction (ADCR), in which subjects alternated a day of eating 175% of normal daily caloric intake, followed the next day by 25% of their normal daily caloric intake. The subjects were told to report their level of comfort and adherence to the diet throughout. This study found that when subjects

strictly adhered to the intermittent fasting protocol, there was no change of oxidative stress markers, and there was a decreased level of plasma insulin levels. This study suggests that an intermittent fasting dieting paradigm is acceptable in healthy individuals, but further research would need to be conducted to further assess risks and benefits.

Of these previously stated scholarly articles, the resulting effects of intermittently fasting groups are listed in Table 3 and sectioned between their effects of each chronic disease risk factor.

Table 3. Effects of Intermittent Fasting on Chronic Disease Risk Factors in Human Studies

Study	Cardiovascular Effects	Oxidative Stress Effects	Inflammatory Effects
Bhutani et al., 2013	LDL: ↓ (-12 ± 5%) HDL: ↑ (18 ± 9%) Total Cholesterol: unchanged HR: unchanged SBP: ↓ (-3 ± 1%) DBP: ↓ (-2 ± 2%)	Not measured	Insulin: ↓ (-21 ± 15%)
Harvie et al., 2011	LDL: ↓ (-9.7 %) HDL: unchanged SBP: ↓ (-3.7 mm Hg) DBP: ↓ (-4.3 mm Hg)	Oxidative Stress: ↓	Leptin: ↓ (-40.1%) TNF-α: ↓ (-2.1%) Insulin: ↓ (-2.1 μU/mL)
Heilbronn et al., 2005	BP: unchanged LDL: ↓ HDL: ↑	Not measured	Insulin sensitivity: ↑
Johnson et al., 2007	LDL: ↓ (-10.5 ± 8.9%) HDL: ↑ (4.1 ± 1.3%)	Not measured	TNF-α: ↓
Sutton et al., 2018	HR: ↓ BP: ↓	Oxidative Stress: ↓	Insulin sensitivity: ↑
Varady et al., 2009	LDL: ↓ (26.0 ± 8.2%) HDL: Unchanged Total Cholesterol: ↓ (-18.0 ± 4.3%) SBP:↓ (4.4 ± 1.8%) HR: ↓	Not measured	Not measured
Wegman et al., 2015	Not measured	Oxidative Stress: Unchanged	Plasma Insulin: ↓ (-1.01 μU/mL)

Notes. IF- Intermittent fasting, SBP- systolic blood pressure, HR- heart rate

Study Outcomes of Animal Trials

In a 12-week study, Ahmet, Wan, Mattson, Lakatta, Talan (2005) investigated the effects of an intermittent fasting diet on two-month-old rats. The intermittent fasting protocol included an alternate-day feeding intermittent fasting protocol with a standard rat diet *ad libitum* on eating days. After three months of dieting, an electrocardiogram (EKG) was conducted prior to and post a coronary artery ligation, causing a myocardial infarction. The

study found that 24-hours after the induced MI, rats in the intermittent fasting group had a significantly reduced MI, inflammatory response, and apoptotic myocytes when compared to the control group. An electrocardiography was performed on surviving rats 10 weeks after the induced MI, with a continued intermittent fasting regimen, and found that there was less left ventricular remodeling, better left ventricular function, and no MI expansion in the intermittent fasting group compared to the control group of rats. It concluded that intermittent fasting could protect the heart from ischemic injury and aids in anti-inflammatory mechanisms.

In addition, Wan et al. (2010) conducted another study, which looked at the cardio protective effects of intermittent fasting in rats after an induced MI and stroke. This study utilized 30 two-and-a-half month-old male Wistar rats that were maintained for one month prior to initiation of dietary protocol. The rats were separated into either an *ad libitum* or intermittent fasting diet, following a 12-week protocol. At the beginning, during, and near the end of the study, blood samples were taken. At the end of the 12 weeks, the rats had a myocardial infarction induced by a coronary artery ligation surgery. Following the ligation, permanent ligation of the coronary artery and markers of inflammation were significantly smaller in rats following the intermittent fasting diet protocol. In addition, insulin levels were significantly lower in the rats following the intermittent fasting diet than the ones following the *ad libitum* diet. It concluded that these results suggest an intermittently fasted diet could improve cardiovascular health and cardio protective elements compared to an *ad libitum* diet.

Table 4. Effects of Intermittent Fasting on Chronic Disease Risk Factors in Animal Studies

Study	Cardiovascular Effects	Oxidative Stress Effects	Inflammatory Effects
Ahmet et al., 2005	HR: ↓	Not measured	Inflammation: ↓
Wan et al., 2010	HR: ↓	Not measured	Inflammation: ↓ (-18%) Plasma Insulin: ↓

Notes. IF- intermittent fasting

Study Outcomes of Review Articles

In addition to the clinical findings of animal and human studies, four reviews were analyzed to understand the effects of intermittent fasting on chronic disease risk factors.

A review study by Mattson, Longo, and Harvie (2017) analyzed intermittent fasting studies to determine whether or not previous research verifies the efficacy of intermittent fasting in improving general health, and prevention and management of chronic diseases. Mattson found that with studies in animals, there were profound general health benefits for laboratory rats and mice. The studied articles showed animal subjects improving functional outcomes and counteracting disease processes, such as cardiovascular disease, diabetes, cancer, and some neurological disorders. In human trials, health benefits were just as beneficial. Human subjects completing a short-term intermittent fasting protocol were found to have improvements in many health indicators, including insulin sensitivity and reduction in risk factors for cardiovascular disease.

In a study by Varady and Hellerstein (2007) both human and animal studies were analyzed to determine if chronic disease prevention is possible from following a caloric restricted or alternate-day fasting regimen. This review looked at 15 studies that investigated the health benefits of intermittent fasting. Consistently reduced insulin concentrations, reduced resting heart rate and blood pressure, and lowered LDL and total cholesterol levels

were all reported in rats following an alternate-day feeding protocol. In human trials, short-term alternate-day feeding protocols resulted in inconsistent results for insulin sensitivity, blood pressure, and inflammatory effects; however, limitations to these research studies include a limited intervention period. It concluded that alternate-day fasting may effectively result in decreased risk factors of cardiovascular disease and increases of resistance to oxidative stress, which could result in a decreased risk of chronic disease.

In addition, another review performed by Mattson and Wan (2005) investigated the effects of intermittent fasting on the cardiovascular and cerebrovascular systems. Similarly, this review found evidence of decreased resting heart rate, blood pressure, insulin resistance, LDL and total cholesterol levels in addition to a reduction in circulating levels of TNF-α in laboratory rats and mice. In reviewed human studies, there were similar results with obese or overweight subjects. A reduction in inflammation, oxidative stress, heart rate, blood pressure, and LDL and total cholesterol levels were all reported. However, the study stated that there was little research that investigated the same effects of intermittent fasting in humans with a healthy weight.

Lastly, a study conducted by Ganesan, Habboush, and Sultan (2018) examined the effects of intermittent fasting in four randomized controlled studies using adult, human subjects. This review looked at studies that investigated the effects of an alternate day fasting protocol on weight loss and other biomarkers. It was found that short-term use of alternate-day fasting resulted in weight loss across the board as well as reductions in LDL, total cholesterol, and systolic blood pressure. The review also found a decrease in insulin resistance in two of the four studies. In regards to the review's limitations, it concluded that this review was limited to English-speaking adults and obese individuals. Future research

should include evidence on how intermittent fasting could help improve biomarkers in healthy individuals.

Discussion

After a systematic review of the 13 studies, the synthesis of the collected data determined that various intermittent fasting protocols were effective in reducing caloric intake and body weight. In addition, there was evidence supporting the idea that intermittent fasting could reduce chronic disease risk markers in human and animal subjects; however, there were other plausible reasons for the improvements of chronic disease risk markers.

Main Findings

A systematic review of the 13 studies showed that intermittent fasting can play a role in decreasing chronic disease risk factors biomarkers. Yet, there was noticeable variability in the reviewed studies that needs to be taken into consideration. Of the nine reviewed studies with both animal and human subjects, the hypothesis was borne out by decreases in LDL concentrations, systolic blood pressure, diastolic blood pressure, heart rate, oxidative stress, TNF-α, and insulin, and the hypothesis was borne out by increases in HDL concentrations and insulin sensitivity for majority of the human studies. These findings support the claim that intermittent fasting can help decrease risk factors for chronic disease.

Human subjects who were previously diagnosed with a chronic disease showed more drastic improvements of chronic disease risk factors after completing a short-term intermittent fasting regimen than healthy human subjects. With that information, it can be implied that intermittent fasting regimens can be used to reduce risk factors of those who are already diagnosed. Even though it cannot be inferred that intermittent fasting regimens could

treat chronic diseases, statistical improvements of chronic disease risk factors are a step forward for these individuals.

After review of the general main findings, results and implications of each of the chronic disease risk factors are reviewed and stated below.

Oxidative stress. Among the studies investigating the impact of intermittent fasting on oxidative stress, there was supporting evidence that intermittent fasting could decrease oxidative stress in subjects. In studies run by Sutton et al. (2018) and Harvie et al. (2009), oxidative stress decreased following a five month and 26-month stent of alternate day fasting. The reviewed studies found that following an intermittent fasting diet could improve oxidative stress resistance and decrease oxidative stress because of the oxidative stress hypothesis and stress resistance hypothesis (Mattson and Wan, 2005). The oxidative stress hypothesis states that because intermittent fasting protocols cause a reduction in caloric intake, there is less means for the production of free radicals in the mitochondria of the cells. However, this implies that caloric restriction diets would cause the same effect on oxidative stress. On the other hand, the stress resistance hypothesis explains that because of the extended periods of fasting, which causes stress, the body is able to resist the stress of fasting better. This stress resistance can be associated with an increased cellular resistance to oxidative injury. It implied that because of this improved stress resistance from intermittently fasting and restricting caloric intake, the body becomes more immune to stressors and is therefore better prepared to combat chronic disease risk factors and possibly prolong life.

In addition to these two hypotheses, another theory, called the induction of scarcity program hypothesis, explains the decrease in oxidative stress following an intermittent fasting protocol (Varady and Hellerstein, 2007). This hypothesis explains that when one

utilizes an energy restricting diet, cellular and metabolic programs react with the intermittent scarcity of energy consumption, causing a decrease in metabolic processes that contribute to the degradation of cells.

While all three of these theories could explain the induced deficit of measured oxidative stress, evidence for these theories are minimal and only present in trials using rodents and cellular subjects, like yeast. A more extensive exploration of these effects from an intermittent fasting regimen could create improved insight on its effects.

Inflammation.

In both human and animal subjects, the reviewed articles found that inflammatory effects from following an intermittent fasting diet have the potential to be positive. Of the seven reviewed clinical trials with human subjects, six of the studies tested for inflammatory biomarkers, including plasma insulin, insulin sensitivity, and TNF-α. A decrease in plasma insulin, leptin, TNF-α, with an increase in insulin sensitivity was discovered in Sutton et al. (2018). These decreases in inflammation biomarkers in humans can be inferred to help prevent and combat inflammation found in chronic diseases, like diabetes, cardiovascular disease, chronic neurodegenerative diseases, and autoimmune diseases.

The decrease in plasma insulin and the improvement in insulin sensitivity, prevalent in six of the seven human trials, has been shown to cause a reduction in Type-2 diabetes risk (Varady and Hellerstein, 2007). The reasoning for this correlation is based on the increase of fat oxidation during fasting periods of an intermittent fasting protocol, which causes a reduction of intracellular lipid accumulation. For individuals struggling with Prediabetes or diagnosed Type-2 diabetes, intermittent fasting could be a possible health-improving implementation. To add on, leptin, which has been found to lead to insulin resistance and

even breast cancer risk, was also reduced during the one reporting human study (Harvie et al., 2011). This decrease, as stated by Harvie et al. (2011), could have aided in the decrease of plasma insulin and increase in insulin sensitivity, therefore improving the inflammatory response.

In addition, a decrease in TNF-α found in the reviewed human trials point to a decreased risk of inflammation-based chronic diseases. The two human trials reporting TNF-α concentrations discussed that because of TNF-α's previous correlation to suppression of inflammation, a reduction of TNF-α could improve asthmatic symptoms and inflammatory risk factors found in cardiovascular disease, rheumatoid arthritis, and autoimmune diseases (Johnson et al., 2007). Again, this evidence supports intermittent fasting as a potential health implementation for reducing the risk of inflammation-based chronic diseases.

Furthermore, animal studies showed a reduced inflammatory response to cardiac injury by artificial ligation. Ahmet et al. (2005) and Wan et al. (2010) showed a decrease in inflammatory cells within the hearts of surviving rodents 24-hours after a medically-induced ischemic stroke, following six weeks of an alternate day fasting protocol. This evidence suggests that an intermittent fasting diet could help promote cardioprotective effects even prior to a cardiovascular injury. These results can translate to inflammatory-based chronic diseases, as well.

Examined review articles point to a decrease in inflammation after a short regimen of intermittent fasting, causing a decreased risk of cardiovascular disease, a decreased risk of diabetes, and possibly a decrease in certain cancer risks. These results point to an effective improvement of chronic disease risk factors in animals and humans; however, human studies have been equivocal in their determination of direct causation. Because of a lack of objective,

thorough evidence, results pointing toward a reduction in chronic inflammatory diseases cannot be conclusive in human subjects.

Cardiovascular system.

The main findings affecting the cardiovascular system include a lowered heart rate, systolic and diastolic blood pressure, and LDL cholesterol concentration. HDL cholesterol concentrations were found to be raised after a bout of intermittent fasting, while total cholesterol levels were found to decrease or remain the same in human subjects.

The cardiovascular effects were analyzed in the four reviews investigated. These cardiovascular effects include the increase of HDL cholesterol and the reduction of resting heart rate, blood pressure, LDL cholesterol, and total cholesterol concentrations. The reductions of resting heart rate and blood pressure were found to be significant in animal trials. It was found that within animal studies, cardiovascular systems of rats and mice responded to an intermittent fasting treatment similar to the way it responds to aerobic exercise (Mattson, Longo, Harvie, 2017). The relationship between intermittent fasting and its effects similar to those of aerobic-exercise seems compelling enough to state that because of the induced stress of caloric restriction, there is an improvement of health markers.

Resting heart rate and blood pressure reduced significantly within the first few weeks of intermittent fasting and then remain reduced while following an alternate-day feeding protocol. However, these reductions only remained temporarily after the cessation of an intermittent fasting diet, proving that cardiovascular benefits are not sustained much after the end of an intermittent fasting period. So, it implies that intermittent fasting can be used to improve one’s aerobic baseline prior to the beginning of an aerobic exercise protocol. This

comparison has not been researched or evident in human trials, so it cannot be concluded that intermittent fasting could serve as a substitute for physical exercise early in human subjects.

Furthermore, total and LDL cholesterol concentrations following an intermittent fasting period were reduced in both human and animal trials. These reductions, more prominent in previously overweight or obese subjects, can correlate to the reduction in body mass and may not be direct effects from following an intermittent fasting diet. However, these reductions can be expected to decrease the risk of cardiovascular disease and stroke, whether it was from direct effects of the intermittent fasting diet or from the reduction in body mass. Studies following the effects in healthy individuals showed only modest improvements of cholesterol levels, showing that plasma cholesterol levels may not be a major consequence of intermittent fasting.

With these results in mind, it can be concluded that following an intermittent fasting protocol can lead to a modest reduction in resting heart rate, blood pressure, and cholesterol concentrations in healthy, human subjects. These moderate effects improve the overall cardiovascular function and resilience in combatting ischemic injury, prevalent in stroke and heart attacks. It infers that because of these improved biological markers, intermittent fasting has the potential to be a legitimate procedure to follow in order to improve cardiovascular health in overweight or obese individuals prior to the beginning of an exercise protocol.

In the future, while research on intermittent fasting points to the improvement of overall cardiovascular health, more extensive research needs to be expanded in order to understand the direct and indirect effects of intermittent fasting on cardiovascular health.

Limitations

While this study followed an extensive systematic procedure of review, there are limitations that exist. Because of intermittent fasting's recent popularity, there are few studies that are conclusive on the health benefits of this dieting protocol.

In addition, the lack of longitudinal studies on intermittent fasting leaves one questioning the long term effects of the dieting protocol. While short-term intermittent fasting studies show an improvement in chronic disease risk markers, there could be negative effects of intermittent fasting in the long run, although these are not heavily researched.

Intermittent fasting studies showed improvements in chronic disease risk markers, yet these improvements were much more drastic in previously diagnosed chronic disease patients and obese or overweight subjects. Because of this, it infers that intermittent fasting does not directly cause these improvements in chronic disease risk factors, but is indirectly involved in the decrease of these biomarkers because of a decrease in body weight. Weight loss has been shown to improve overall health, which could cause the decrease in these investigated biomarkers. It is important to consider though that intermittent fasting does, in fact, lead to weight loss.

While this study thoroughly investigated the reviewed articles, there were only ten short-term clinical trials studied, which only used a limited number of participants. The number of human subjects ranged from nine to 107 subjects, with an average of 39 subjects per study. While this amount of participants is beneficial, it is hardly conclusive for the general population.

Implications

After assessment and consideration of the results from the reviewed studies, further testing of intermittent fasting is needed. While animal studies of intermittent fasting protocols show a clear, positive effect of intermittent fasting on cardiovascular biological markers, other chronic disease risk factors are not as clearly defined. Of the seven clinical studies with human subjects, only three of these studies discussed the oxidative stress effects from following a short-term bout of intermittent fasting. Within these studies, biological markers were used but were not thoroughly discussed and implications were minimal. Research discussing more in-depth analyses with broader implications is needed in order to establish the beneficial effects of intermittent fasting on the general population, for combatting chronic illnesses.

In the future, intermittent fasting studies should include longer implementation periods for subjects to partake in a larger, more diverse subject population, and a more controlled environment. Additionally, discovered data should be analyzed more in depth in order to correlate weight loss and secondary effects after following an intermittent fasting protocol. A better understanding of how intermittent fasting effects each of the risk factors of chronic disease needs to be analyzed.

But these health implications are relatively positive and reveal improvement of chronic disease risk factors. None of the 13 reviewed articles discussed an increase of health risk following an intermittent fasting protocol in either human or animal trials.

With all things considered, it can be inferred that following an intermittent fasting protocol can positively improve the overall wellness of overweight or healthy humans and

decrease the risk of contracting a chronic illness and reduce the impact it has on one's quality of life.

Conclusion

In conclusion, all 13 of the reviewed studies point to an improvement in biological markers relating to cardiovascular stress, oxidative stress, and inflammation, all of which can lead to major chronic diseases. These biological markers were found to be improved after a short-term regimen of intermittent fasting; however, the studies were found to be more beneficial for animal subjects than human subjects. Human studies found a relatively positive interpretation of results, but, the effects on the reviewed risk markers were not consistent throughout and therefore were not conclusive on whether intermittent fasting could directly correlate to an improvement in chronic disease. Limitations of this review include the partial amount of studies reviewed, the short-term duration of the clinical studies, the contamination of weight loss and prior chronic disease diagnoses in subjects, and the inability to track subjects' dietary choices during the intermittent fasting protocol. In the future, research should include long-term longitudinal studies of a greater subject population that investigate the ability for life-long intermittent fasting to prevent chronic disease. Clinically, it is concluded that intermittent fasting can be beneficial in the improvement of chronic disease risk markers, but more research needs to be conducted in order to produce conclusive results.

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