Impacts of High Fat Diet on Ocular Outcomes in Rodent Models of Visual Disease

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Abstract

High fat diets (HFD) have been utilized in rodent models of visual disease for over 50 years to model the effects of lipids, metabolic dysfunction, and diet-induced obesity on vision and ocular health. HFD treatment can recapitulate the pathologies of some of the leading causes of blindness, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR) in rodent models of visual disease. However, there are many important factors to consider when using and interpreting these models. To synthesize our current understanding of the importance of lipid signaling, metabolism, and inflammation in HFD-driven visual disease processes, we systematically review the use of HFD in mouse and rat models of visual disease. The resulting literature is grouped into three clusters: models that solely focus on HFD treatment, models of diabetes that utilize both HFD and streptozotocin (STZ), and models of AMD that utilize both HFD and genetic models and/or other exposures. Our findings show that HFD profoundly affects vision, retinal function, many different ocular tissues, and multiple cell types through a variety of mechanisms. We delineate how HFD affects the cornea, lens, uvea, vitreous humor, retina, retinal pigmented epithelium (RPE), and Bruch’s membrane (BM). Furthermore, we highlight how HFD impairs several retinal cell types, including glia (microglia), retinal ganglion cells, bipolar cells, photoreceptors, and vascular support cells (endothelial cells and pericytes). However, there are a number of gaps, limitations, and biases in the current literature. We highlight these gaps and discuss experimental design to help guide future studies. Very little is known about how HFD impacts the lens, ciliary bodies, and specific neuronal populations, such as rods, cones, bipolar cells, amacrine cells, and retinal ganglion cells. Additionally, sex bias is an important limitation in the current literature, with few HFD studies utilizing female rodents. Future studies should use...
ingredient-matched control diets (IMCD), include both sexes in experiments to evaluate sex-specific outcomes, conduct longitudinal metabolic and visual measurements, and capture acute outcomes. In conclusion, HFD is a systemic exposure with profound systemic effects, and rodent models are invaluable in understanding the impacts on visual and ocular disease.

**Keywords**

high fat diet; HFD; diet-induced obesity; vision; retina; age-related macular degeneration; diabetic retinopathy; diabetes

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1. **Introduction**

Diet high in fat, specifically saturated fats, are a common exposure with significant public health implications. High fat diets (HFD) are associated with metabolic disease(Feskens et al., 1995), cancer(Carroll et al., 1986), and neurological disease(Kalmijn et al., 1997). Total fat and saturated fat consumption is associated with the development of Type II diabetes(Risérus et al., 2009), which can lead to serious complications such as DR and blindness. Additionally, dietary fat is considered an important contributing factor in the global obesity epidemic(Hall, 2018; James et al., 2001). The global prevalence of obesity in the adult population is approximately 12%, numbering more than 600 million adults(2017) and expected to continue growing. These trends are promoted by lifestyle factors such as diet and reduced physical activity that cause inflammation and weight gain, leading to obesity and metabolic diseases such as diabetes(2017). Likewise, approximately 9% of the global population, 463 million people, are living with diabetes and this number is expected to rise to 578 million people by 2030(Saeedi et al., 2019).

Dietary fat is a well-known modulator of neurological health and disease. Consuming unhealthy trans and saturated fats is associated with dementia, cognitive disorders(Freeman et al., 2014), and Alzheimer’s Disease(Bayer-Carter et al., 2011). HFD consumption also exacerbates outcomes in animal models of brain injury(Shaito et al., 2020) and neurodegenerative disorders(Kothari et al., 2017; Nam et al., 2017). HFD drives these outcomes via immune activation and inflammation, atherosclerosis and vascular dysfunction, and altered hormonal and cell signaling cascades.

As part of the brain, the eye is also impacted by HFD, particularly in ocular diseases such as diabetic retinopathy (DR) and age-related macular degeneration (AMD). The epidemiological evidence linking fat consumption to DR development is mixed(Alcubierre et al., 2016; Dow et al., 2018), but when stratified by diabetes control, saturated fat intake increased the odds of DR development among people with well-controlled diabetes(Sasaki et al., 2015). Additionally, total and saturated fat consumption worsen DR risk factors, which improve with decreased saturated fat consumption(Cundiff and Nigg, 2005). AMD is also associated with altered lipid signaling and may be exacerbated or ameliorated by dietary fat(Chapman et al., 2019; Dighe et al., 2020; Merle et al., 2015; van Leeuwen et al., 2018). Lipid homeostasis is a significant driver in the development and progression of AMD, and polymorphisms in genes related to cholesterol metabolism and lipoproteins, such as *ABCA1* and *APOE*(Fritsche et al., 2016), as well as the complement system and *CFHR*(Fritsche et al., 2016).
2016; Klein et al., 2005), are implicated in AMD. Likewise, consumption of saturated fatty acids and trans fats may contribute to AMD, but epidemiological studies are mixed (van Leeuwen et al., 2018).

Animal models are invaluable in understanding the impacts of HFD on DR and AMD disease mechanisms. Surprisingly, while the HFD model has been used in visual research for over 50 years, there are no comprehensive reviews summarizing the use of HFD in models of visual disease. Therefore, we systematically review and synthesize the scientific literature on the use of HFD in mouse and rat models of ocular disease. Additionally, we discuss current gaps and limitations in the literature to guide future research directions.

2. Methods for systematic review and results

In conducting this literature review, Pubmed, Web of Science, and ScienceDirect databases were systematically searched for peer-reviewed literature using the following search keywords: (high fat diet OR HFD OR western diet OR high fat) AND (retina OR eye OR ocular OR visual) AND (mouse OR mice OR rat). The search was performed for all years up to the last search date of July 18, 2020 and results de-duplicated prior to sorting.

Results were considered eligible for inclusion if they utilized a high fat diet (approximately 25-60% kcal fat), had an outcome that involved the eye or retina, and utilized a mouse or rat model. Results were excluded if they were published in a language other than English, only used qualitative methodology, were published as a conference abstract or non-peer reviewed journal, did not include relevant visual health outcomes (for example, non-rapid eye movement), did not include HFD or an appropriate description of the HFD model with brand information or diet breakdown, did not include appropriate control groups that allowed for the evaluation of the impact of HFD or the interaction of HFD on ocular outcomes, or were otherwise considered irrelevant to the topic. Additionally, duplicates or studies where the full text was unavailable were also excluded from the review.

The initial search resulted in 806 studies after de-duplication. Of these, 695 studies were considered irrelevant after initial abstract screening, leaving 111 studies considered for eligibility in full-text screening. On further inspection, 45 of these studies were excluded, yielding a total of 66 studies remaining for inclusion in this review (Figure 1, Supplemental Table 1). The references cited in the included studies were combed for additional articles that were not found in the original search but met eligibility requirements, producing 1 of the total 66 studies included in this review.

Characteristics of the reviews, such as diet composition and sex, were extracted and graphs created using R (data and code available on GitHub: https://github.com/dclarktown/HFD_review/tree/v1 DOI: 10.5281/zenodo.4003038).

3. HFD treatment

HFD rodent models have been used in research since at least the 1940’s (Samuels et al., 1942) and have only become more commonly used as the prevalence of obesity and metabolic diseases has increased (Blüher, 2019). Metabolic syndrome and diabetes are
complex, systemic endocrine diseases that are growing public health crises. While societal and infrastructural change is necessary to slow and reverse these trends (Blüher, 2019), prevention and treatment approaches such as diet and lifestyle changes and medicines such as insulin and metformin, an oral hypoglycemic, are often prescribed for patients. Because these diseases are so prevalent, and only expected to keep rising (Saeedi et al., 2019), it is imperative to understand the mechanisms and impacts of these diseases and find new treatment options.

In animal models of diabetes and similar disorders, HFD treatment can induce metabolic disruption and diet-induced obesity. HFD perturbs metabolism and drives disease through multiple mechanisms, leading to chronic inflammation and inflammatory processes. HFD consumption also increases the absorption and signaling of free fatty acids (FFAs), which can directly exert inflammatory effects and promote insulin resistance by binding to Toll-like receptors (Könner and BrCining, 2011; Lee et al., 2015). The gut microbiome may also be an important mediator in the initial and chronic inflammatory response of HFD, as germ-free mice are protected from HFD-induced obesity (Bäckhed et al., 2007) and HFD consumption alters microbiota composition and increases intestinal permeability (Murphy et al., 2015; Sanmiguel et al., 2015). HFD research has been paradigm-shifting in many ways and has helped us gain a broader understanding of the roles of lipids in neurodegeneration, developmental metabolic programming, and the role of the immune system in metabolism.

In addition to the large body of research on HFD and development, metabolism, the microbiome, cardiovascular disease, and neurological disease, HFD is useful in modelling and understanding the influence of metabolic disease on ocular tissues and visual outcomes. The eye is a window to the brain (London et al., 2013), and as such, it is not only an easily-accessible visual organ, but serves as a biomarker of neurologic and systemic health (London et al., 2013). This is very useful in clinical applications, as non-invasive or minimally invasive biomarkers can allow for earlier detection (Safi et al., 2018) and treatment of disease, improving patient outcomes and preserving vision.

3.1 Systemic and metabolic effects of HFD

HFD treatment affects systemic metabolic processes and energy balance. The most commonly reported outcomes of HFD treatment are diet-induced obesity and increased body weight (Table 1). Other common outcomes include impaired glucose tolerance, decreased insulin sensitivity, increased fat mass or percentage, increased serum cholesterol levels, and increased free fatty acid levels. Some outcomes, such as blood glucose and serum triglyceride levels, are very mixed. Differences in outcomes may be due to duration of diet, age of diet induction, strain, measurement error, and/or diet model used. However, approximately half of all the reviewed HFD studies provided information on body weight or systemic metabolic outcomes, which future studies should strive to include.

HFD studies tend to evaluate outcomes after chronic (≥2 months) exposure to HFD. While most studies reported weight and metabolic changes after a few months of HFD treatment, some have reported significant differences in body weight after only 1 (Kim et al., 2017) or 2 (Barakat et al., 2019) weeks of HFD treatment. However, the sparsity of studies with acute measurements leave a gap in the current literature.
Overall, because measurements of systemic outcomes are useful, future studies of HFD in models of visual disease should include longitudinal measures of (non-endpoint) metabolic impacts and/or biomarkers of disease. These longitudinal outcomes could also be utilized to evaluate correlations with ocular outcomes, possibly providing insight for improved early detection methods in human disease. Future studies should also evaluate acute (hours, days, weeks) effects of HFD on ocular outcomes.

### 3.2 HFD models of diet-induced obesity and diabetes

Models of obesity, diabetes, and DR generally employ HFD treatment to cause significant weight gain and metabolic disturbance. These models are utilized in vision research to better understand the visual and ocular impacts of metabolic dysregulation and hyperglycemia. Diabetes is a chronic metabolic disease characterized by problems in glucose homeostasis and can be elicited in animal models with chronic (≥2-5 months) HFD treatment, when fasting blood glucose levels typically rise above 250 mg/dL (Heydemann, 2016). This HFD model is useful in tracking the progression of metabolic dysfunction and in identifying early biomarkers of disease. There are a number of forms of diabetes, but the most common are Type 1 diabetes (approximately 5-10% of cases) and Type 2 diabetes (approximately 90-95% of cases). Type 2 diabetes generally begins with tissues becoming less responsive to insulin over time, driving a feedback loop of hyperglycemia, oxidative stress, damage to pancreatic beta cells, and decreased insulin output (Stumvoll et al., 2005). Unlike Type 1 diabetes, which is generally considered an autoimmune disease, Type 2 diabetes is most associated with metabolic dysfunction driven by obesity and diet (Hu et al., 2001; Taylor, 2013).

Hyperglycemia is modeled in rodents by damaging pancreatic beta cells, HFD feeding, utilizing specific strains or genetic knockouts, or a combination of these approaches. Of the studies that induce metabolic dysfunction solely through HFD feeding, there are a number of HFD models. Generally, HFD treatment consists of feeding a diet 25%-60% kcal from fat. There are some variations, such as the “Western diet” HFD model, which is generally composed of 40-45% kcal from fat and has an enriched amount of saturated fat. Other variants are the high fat-high sucrose (HFHS) and high fat-high fructose models, which incorporate high levels of sucrose or fructose as part of the carbohydrate portion of the HFD. While not included in this review, the ketogenic diet, a diet that is low in carbohydrates and very high in fat (~75%+ kcal from fat), has gained renewed interest among researchers. The specific impacts of HFD on ocular tissues and outcomes are described in detail in the ocular tissue sections.

### 3.3 STZ with HFD models of Type 1 and Type 2 diabetes and DR

In addition to HFD feeding, diabetes is also modelled in rodents using a combination of HFD and high or low-dose streptozotocin (STZ), a beta cell toxin. Type 1 diabetes is characterized by autoimmune loss of the insulin-producing beta cells of the pancreas, causing blood glucose levels to rise because of decreased insulin output (Belle et al., 2011). The streptozotocin (STZ) model is a well-characterized animal model of Type 1 diabetes and it is commonly utilized in models of diabetic retinopathy (DR) and diabetic neuropathy (Furman, 2015). Originally isolated from soil bacteria, STZ has antibiotic
properties and inhibits DNA synthesis. As a toxic analog of glucose, it is preferentially taken up by pancreatic beta cells via glucose 2 transporters, where it causes cell death through methylation, oxidative stress, and other mechanisms (Eleazu et al., 2013); however, it is also taken up by other tissues that express this transporter and have high glucose absorption, such as the liver, kidneys, and brain (Eleazu et al., 2013), an important consideration when utilizing the STZ model.

To induce diabetes, STZ is given intraperitoneally to the mouse or rat, usually parceled out in a few low-dose injections in the mouse model or as a single injection in the rat model (Furman, 2015). The effectiveness of STZ in causing beta-cell loss and hyperglycemia is strain and sex-dependent, with females generally showing less overt hyperglycemia than males (Furman, 2015; Kolb, 1987), possibly due to the protective and antidiabetic effects of estradiol (Le May et al., 2006). In addition to using STZ as a Type 1 model of diabetes, low-dose STZ treatment is also sometimes combined with HFD feeding to model Type 2 diabetes. These models are also utilized in vision research to model DR. While mouse and rat models do not adequately model the later stages of DR (for example, retinal neovascularization), they do recapitulate many characteristics of the disease, such as inflammation, decreased retinal function, visual function, pericyte loss, and vascular leakage (Robinson et al., 2012).

In this review, the studies that modelled Type 1 or Type 2 diabetes and DR using a combination of STZ and HFD treatment equally utilized mouse and rat models (Figure 2A, Supplemental Table 1). However, the majority used males, with only 1 study (Coppey et al., 2018b) reporting the inclusion of female animals (perhaps partly due to the sex differences in responsiveness to STZ). All studies initiated HFD feeding at 1-3 months of age and most (90%) fed a HFD containing 40-60% calories from fat (Figures 2B–C). A majority of these studies focused on corneal outcomes (60%) while the remaining focused on retinal and RPE outcomes. Corneal defects included decreased corneal sensitivity (Coppey et al., 2020; Davidson et al., 2014; Fink et al., 2020), decreased corneal nerve fiber density (Alamri et al., 2019; Coppey et al., 2020; Coppey et al., 2018b; Davidson et al., 2014; Yorek et al., 2015), and decreased corneal nerve fiber length (Coppey et al., 2020; Coppey et al., 2018b; Davidson et al., 2014) (Table 2). HFD in combination with STZ was also found to heighten immune activation and inflammatory processes (Barakat et al., 2019; Jo et al., 2019; Mancini et al., 2013), but not all studies include appropriate control groups to allow assessment of the interactions between HFD and STZ treatment.

### 3.4 HFD and genetic models of AMD

AMD, one of the most common causes of blindness, is caused by retinal degeneration that leads to gradual visual field loss. Pathological features of AMD include deposition of membranous debris containing proteins, lipids, and/or complement proteins (Curcio et al., 2001; Curcio et al., 2005; Mitchell et al., 2018; van Lookeren Campagne et al., 2014) and basal laminar deposits, made up of thickened extracellular matrix material between the retinal pigment epithelium (RPE) and Bruch’s membrane (BM) (Mitchell et al., 2018; Sarks et al., 2007; Sura et al., 2020). HFD alone or with exposures such as cigarette smoke...
promote basal laminar deposit growth and alter BM and RPE morphology (Espinosa-Heidmann et al., 2006; Roddy et al., 2019).

With age the RPE becomes less efficient at clearing waste products, leading to buildup of cellular debris and lipids and causing inflammation and cell death (Ebrahimi and Handa, 2011; van Lookeren Campagne et al., 2014). Risk factors for AMD development include age (>50 years), having a history of smoking, and certain genetic polymorphisms (Chakravarthy et al., 2010). AMD is more prevalent among females, possibly because AMD is highly age-related and women tend to live longer than men (Owen et al., 2012). Because of these risk factors, rodent models of AMD sometimes use aged female rodents (Cousins et al., 2003; Espinosa-Heidmann et al., 2006; Schmidt-Erfurth et al., 2008), as well as genetically modified strains fed a HFD (Figure 2).

The AMD HFD models reliably produce sub-RPE deposits, particularly in aged rodents. As lipid metabolism and complement factor signaling are implicated as the primary genetic (Fritsche et al., 2016) and pathological drivers of AMD, AMD models commonly utilize strains with genetically manipulated complement factor proteins or lipoproteins (Pennesi et al., 2012). Other drivers of AMD include oxidative stress and aging processes (Beatty et al., 2000), which may act in concert with the complement system. Therefore, exposure to cigarette smoke or blue light is also sometimes utilized in animal models to recapitulate the human disease (Table 3).

All reviewed studies modelling AMD or sub-retinal lipid deposition utilized mouse models (Figure 2A, Supplemental Table 1). The majority of these studies fed a HFD with 25-39% fat kcal (78%), initiated HFD feeding at or after 3-6 months of age (61%), utilized a genetically modified strain (78%), and used female animals (56%) (Figures 2B–G). Many of the reviewed studies utilized genetically manipulated strains to better model the known genetic risk factors identified in human population studies (Table 3). Among these, Apolipoprotein E (APOE) (Huang and Mahley, 2014), peroxisome proliferator-activated receptor-γ coactivator 1-α (Pgc1α) (Zhang et al., 2004), scavenger receptor class B type 1 (SR-B1) (Rhainds and Brissette, 2004), low density lipoprotein receptor (LDLr) (Go and Mani, 2012), ATP binding cassette subfamily A member 1 (ABCA1) (Phillips, 2018), and apolipoprotein B-100 (ApoB100) (Olofsson and Borén, 2005) play roles in lipid metabolism while Complement factor H (Cfh) (Ferreira et al., 2010) and Nuclear factor erythroid 2-related factor 2 (Nrf2) (Itoh et al., 2004) mediate immune and inflammatory responses. These genetic models are useful in understanding the contributions and interactions of genetic and environmental impacts on AMD development (Pennesi et al., 2012).

Across some of the reviewed studies, HFD alone increased thickness and lipid deposition of BM (Dithmar et al., 2001; Roddy et al., 2019; Zhang et al., 2018) and impaired retinal pigment epithelium (RPE) integrity (Zhao et al., 2014) (Table 3). HFD in combination with blue light or cigarette smoke, exposures that cause oxidative stress, led to increased lipid deposition (Cousins et al., 2002; Cousins et al., 2003; Espinosa-Heidmann et al., 2006) (Table 3). Results from studies that utilized HFD in combination with a genetically manipulated strain were dependent on the targeted gene, but overall tended to increase sub-RPE deposition and alter RPE morphology and/or signaling (Ding et al., 2011; Lee et al.,

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4. Effects of HFD on ocular tissues and possible mechanisms

As HFD treatment is a systemic exposure, it impacts many different ocular tissues – an important consideration when designing studies and evaluating results. Here, we discuss how HFD treatment impacts different ocular tissues. Tissue sections are organized starting from the front of the eye and moving towards the back of the eye and grouped according to the focus of the reviewed literature.

4.1 Cornea, lens, uvea, and vitreous humor

The impacts of HFD on the cornea have been evaluated primarily in the context of diabetes and diabetic neuropathy. This tissue not only makes up the majority of the eye’s total refractive power, but also acts as a defensive barrier, producing tear film with lubricating and anti-microbial properties (Blackburn et al., 2019; Dartt and Willcox, 2013). Well-organized unidirectional collagen fibers make the cornea transparent and allow light to pass through corneal tissue into the eye chamber, unlike the irregular fibers of the opaque sclera. Because of the cornea’s role in vision, it is important to understand how diabetes and metabolic disturbance may impair corneal integrity and function.

There are reports of HFD altering corneal morphology and structure (Table 4). While no differences were found in thickness of the corneal epithelia, the stromal layer was found to be thicker after HFD (Kneer et al., 2018). HFD exposure also decreased corneal endothelial cell density and hexagonal cell number, possibly due to disrupted tight junctions between corneal epithelial cells, increased oxidative stress (Bu et al., 2020), and increased keratinization and matrix metalloprotease expression (Wu et al., 2020). Additionally, HFD may influence the development of dry eye symptoms and impair the integrity of the corneal surface; HFD treatment increased corneal permeability, decreased tear production, and decreased the number of goblet cells (Wu et al., 2020) responsible for producing mucins for ocular tear film and eye lubrication (Figure 3).

Particular attention has been paid to the impact of HFD on corneal nerve integrity and response, as the cornea is one of the body’s most highly innervated tissues (Bonini et al., 2003). It impairs corneal sensitivity (Coppey et al., 2020; Davidson et al., 2014; Fink et al., 2020) and corneal nerve fiber density and length (Alamri et al., 2019; Coppey et al., 2020; Coppey et al., 2018a; Coppey et al., 2018b; Davidson et al., 2014; Yorek et al., 2015) in the central region of the cornea (Alamri et al., 2019), where nerve length is longest, and in the inferior whorl (Davidson et al., 2014), an innervated area of the cornea located inferior and nasal to the corneal center. The structure of the corneal whorl is also disrupted by HFD (Kneer et al., 2018). Additionally, peripheral and central corneal cold thermoreceptors populations (as labelled by TRPM8), but not corneal nociceptor populations (as labelled by TRPV1), appear to be vulnerable to HFD (Alamri et al., 2019). Because corneal nerves are responsible for sensing stimuli as well as stimulating tear production and the blinking reflex, damage to them can impair tear film production and corneal integrity.
Research on how HFD impacts the lens and vitreous is sparse (Table 4). The lens is a tissue with a layered life history, with the core developing in utero and the outer cortex developing postnatally. While the lens is a continually-growing tissue, embryonic lens cells are preserved in the central core with cells layered postnatally in the outer cortex (Augusteyn, 2010). As a tissue with both embryonic and adult components, the lens can be useful in investigating the impacts of prenatal and postnatal exposures, such as nutrition. A developmental study found that prenatally undernourished rats (males and females) developed significantly more markers of oxidative stress in the lens core and cortex when postnatally fed a HFD (Jayaratne et al., 2017). When the control group (not prenatally undernourished) were fed a HFD, males (but not females) had increased markers of oxidative stress in the lens cortex (Jayaratne et al., 2017). HFD feeding has also been found to decrease levels of the antioxidants glutathione and ascorbic acid in the lens (Nakazawa et al., 2019). Metabolic disturbance such as diabetes can cause cataract formation (Javadi and Zarei-Ghanavati, 2008) and has been reported in a rat model of diabetes, but the HFD only group did not show signs of cataract (Su et al., 2014). These findings support the idea that the lens can serve as a biomarker for exposures across the lifespan, but more research is necessary to understand the relationship between the lens and visual outcomes in HFD models.

The uvea comprises the choroid, ciliary body, and iris. It plays important roles in metabolic support, light regulation, and accommodation. HFD treatment was found to exacerbate outcomes in an experimental model of autoimmune uveitis (Muhammad et al., 2019), suggesting it can worsen immune-related outcomes. The vitreous humor, encapsulated by the vitreous membrane, is a gel-like substance filling the space between the lens and the retina. HFD treatment has been found to increase the expression of inflammatory markers such as IL-1β, IL-6, IL-13, IL-17, and IL-18 in the vitreous humor of rats fed a HFHS diet (Collins et al., 2018). These inflammatory markers were also significantly correlated with body fat, suggesting that diet-induced obesity may increase ocular inflammation and influence the development of ocular disease with inflammatory components, such as DR and uveitis (Collins et al., 2018).

### 4.2 Retina

The majority of HFD research in ocular disease models focuses on retinal outcomes (Table 5). For its size, the retina is one of the most metabolically active tissue in the body (Arden et al., 2005). This thin layer of tissue draws from the retinal and choroidal blood supply and its own rich fatty acid stores to support energy demands. Because it is so metabolically active, it has many mechanisms to scavenge and quench reactive oxygen species; however, it is still vulnerable to oxidative stress (Saccà et al., 2018). Additionally, the rich stores of polyunsaturated fatty acids in the retina are susceptible to oxidation (Stone et al., 1979). As disruption of retinal nutrient supply can lead to pathologies such as abnormal angiogenesis and photoreceptor degeneration (Sun and Smith, 2018), it is reasonable to assume that HFD-induced metabolic disruption would negatively affect retinal health.

The effects of HFD on retinal morphology are mixed, with some authors reporting no differences in retinal layer thickness (Atawia et al., 2020; Chang et al., 2015) and others
reporting axonal (Zhu et al., 2018) and retinal thinning (Marcal et al., 2013), possibly due to increased retinal cell death (Dai et al., 2018a) (Figure 3, Table 5). When comparing these studies for sources of variability, the strains, age at which diet began, and diet duration were similar, but dietary fat ratio was different. Those that reported no differences used a 59-60% fat kcal diet, while those that did report differences used a 39-45% fat kcal diet. Alternatively, the variability may be due to measurement sensitivity and error.

HFD induces vascular changes in the retina, causing retinal vascular endothelial cell injury, increased expression of adhesion markers such as ICAM-1 in retinal vessels (Barakat et al., 2019), and increased acellular capillaries (Mohamed et al., 2014), a hallmark of DR. However, others report no difference in ratio of endothelial cells to pericytes after HFD treatment (Agardh et al., 2000), although this could be due to decreases in both endothelial cells and pericytes. HFD also increases the permeability of retinal vessels (Rajagopal et al., 2016; Zhu et al., 2018) and can even lead to bleeding in retinal vessels (Katsumata, 1970), one of the mechanisms that leads to abnormal angiogenesis and neovascularization in the eye. However, while disorders such as DR are often viewed as vascular in nature, it is now understood that neuronal dysfunction in the retina often precedes vascular symptoms (Lynch and Abràmoff, 2017; Simó et al., 2018), highlighting the need for neuronal assessments.

Feeding a diet high in fat may also alter the lipid composition of the retina (fats comprise approximately 20% of the retina’s dry weight (Fliesler and Anderson, 1983)), influencing the retina’s vulnerability to oxidative stress, energy availability, and altering retinal signaling. Lipids act as ligands and signaling molecules and mediate vesicle secretion and fusion (Wymann and Schneiter, 2008). It has been shown that HFD treatment alters retinal fat composition, decreasing levels of tetracosanoic acid, palmitoleic acid, and vaccenic acid, and increasing ratios of linoleic acid:alpha-linolenic acid (Albouery et al., 2020) and retinal sphingolipids (Dai et al., 2018a), including ceramide, which is implicated in retinal and neurodegenerative disease (Simón et al., 2019). Therefore, these HFD-induced changes in retinal lipid composition could be an important component of retinal disease.

While the retina has robust systems in place to neutralize oxidative stress, it is nevertheless vulnerable to fatty acid oxidation and metabolic disturbance. HFD increases retinal lipid peroxidases (Mohamed et al., 2014) and disrupts retinal glycolytic processes (Katsumata, 1970). This metabolic dysregulation can cause inflammation. HFD has been shown to activate retinal microglia (Atawia et al., 2020; Lee et al., 2015), potentially via TLR4, which may be responsible for the increased inflammatory markers (Chang et al., 2015), cytokines (Kim et al., 2017; Lee et al., 2015), and immune cells (Lee et al., 2015) also found following HFD treatment. Insulin resistance, glucose intolerance, and microglial activation appear to occur simultaneously in the retina (Lee et al., 2015). HFD also increased expression (Tuzcu et al., 2017) and phosphorylation (Lee et al., 2015) of NF-κB and decreased retinal Nrf-2 (Tuzcu et al., 2017), well-known regulators of inflammatory signaling. Interestingly, HFD-fed mice with astrocyte-specific conditional deletion of IKKβ, part of the NF-κB pathway, had improved glucose tolerance (Douglass et al., 2017). All together, these studies suggest that the immune system is an important mediator in the metabolic responses to HFD and modulating it may ameliorate some of the impacts of HFD.
A number of other signaling mechanisms have been implicated in the retinal effects of HFD (Table 5). HFD may influence retinal metabolic dysfunction by increasing protein O-GlcNAcylation (Dai et al., 2018b), altering retinal Akt/JNK signaling (Dai et al., 2018a; Miller et al., 2017), and decreasing AKT1 (Marcal et al., 2013) and GLP-1 expression (Shu et al., 2019), a proglucagon peptide that decreases blood glucose by increasing insulin secretion. Decreased expression of the GLUT4 glucose transporter in the retina (Chang et al., 2015) suggests altered retinal glucose trafficking after HFD treatment. Increased iNOS (Tuzcu et al., 2017) and decreased eNOS and nNOS (Marcal et al., 2013) may also be mediators or symptoms of the noted vascular pathology, as iNOS is produced during inflammation and eNOS and nNOS promote vasodilation (Förstermann and Sessa, 2012). Additionally, the decrease in miR-150 following HFD (Shi et al., 2016) may underlie some of the vascular pathologies, as miR-150 suppresses ocular vascularization (Liu et al., 2015). The axonal changes in the retina may be a cause or effect of decreased synaptophysin expression after HFD exposure (Shu et al., 2019; Zhu et al., 2018). Other perturbations driven by HFD include decreased LXRβ and HIF1α (Asare-Bediako et al., 2020), increased expression of crystallins (Mykkanen et al., 2012), VEGF, ICAM-1 (Tuzcu et al., 2017), and abnormal tau phosphorylation (Zhu et al., 2018) in the retina.

Clearly the retina is negatively impacted by HFD, similar to other HFD studies of neural tissue (Arnold et al., 2014; Dutheil et al., 2016). However, because it is easier to access and measure non-invasively than brain tissue, the retina is ideal for measuring the longitudinal effects of metabolic perturbation on neural function. While much research exists on HFD and the retina, more research is needed on the effects of HFD on specific retinal neuron types (for example, retinal ganglion cells).

### 4.3 Retinal pigment epithelium and Bruch’s membrane

The RPE and BM lie between the metabolically demanding photoreceptors and the energy-providing choriocapillaris. The RPE is a richly pigmented, monolayered tissue in intimate contact with the rod and cone photoreceptors, engulfing and phagocytosing photoreceptor discs during regular disc shedding (Kevany and Palczewski, 2010). The melanin pigments within the RPE prevent light scattering and sharpen image quality by absorbing light and also provide a photoprotective role against excess reactive oxygen species (Seagle et al., 2005). The RPE transports nutrients from the choriocapillaris and is responsible for regenerating 11-cis-retinal from all-trans-retinol, thereby sustaining the visual cycle (Kevany and Palczewski, 2010). Likewise, the collagen-rich BM plays an important role in mediating nutrient and waste exchange between the choriocapillaris and retina, as well as providing structural support for the RPE (Booij et al., 2010).

HFD alters the morphology of the RPE and BM (Table 6), causing RPE lesions (Zhao et al., 2014), RPE cell death (Roddy et al., 2019), increased RPE vacuoles (Barathi et al., 2014), BM thickening (Dithmar et al., 2001; Roddy et al., 2019), and decreased fenestrations (Zhang et al., 2018). One of the most pronounced changes in morphology is pathological lipid deposition in the RPE and BM (Roddy et al., 2019; Zhang et al., 2018). These lipid deposits may act as a barrier for nutrient transfer, impairing the function of the RPE and BM (van Leeuwen et al., 2018). Because they perform vital roles in maintaining the health of
photoreceptors, impairment to the RPE and BM can lead to damage and degeneration of photoreceptors, eventually causing vision loss (Sparrow et al., 2010). Likewise, HFD treatment can cause lipid deposition and altered morphology of the BM/choriocapillaris interface (Barathi et al., 2014; Cousins et al., 2003; Miceli et al., 2000), which could ultimately lead to retinal degeneration (Picard et al., 2010; Schmidt-Erfurth et al., 2008).

The RPE and BM appear to be specifically vulnerable to HFD and dyslipidemia, perhaps because they are responsible for transporting lipids to the retina and maintaining cholesterol homeostasis. Treatments that specifically target the RPE and BM to provide protection against the effects of dyslipidemia are needed.

5. Retinal and Visual Function Outcomes of HFD

HFD affects a variety of retinal function measures including electroretinography (ERG), visual evoked potential (VEP), and pattern electroretinography (P-ERG). ERG is a useful, non-invasive tool to measure retinal function. The foundational work of Ragnar Granit in isolating components of the ERG waveform (Granit, 1933) provided the foundation for the later discoveries that the a-wave is generated by rod and cone photoreceptors while the b-wave is generated by bipolar cells (Brown and Wiesel, 1961; Bush and Sieving, 1996; Hood and Birch, 1996; Penn and Hagins, 1969; Robson and Frishman, 1995, 1996; Sieving et al., 1994; Tomita, 1950). Oscillatory potentials (OPs) are believed to originate from amacrine cells, with each OP possibly representing a different cell type (Wachtmeister and Dowling, 1978). ERGs are useful in assessing ocular diseases such as DR, retinitis pigmentosa, and AMD. For example, declines in cognitive and motor function that can occur in diabetes often correlate with retinal dysfunction, with retinal deficiencies occurring prior to other symptoms (Allen et al., 2019; Aung et al., 2013; Motz et al., 2020; Pardue et al., 2014; Shirao and Kawasaki, 1998). The amplitude and timing of ERG waveforms reflect the response of the retina, neural tissue, to a light stimulus. Therefore, any changes to ERG amplitude or timing suggests altered retinal function. Because of these connections between retinal function, cognition, vascular health, and disease, ERGs and similar measurements can be useful in early identification and intervention of disease processes.

When measured with ERG, HFD exposure has varying impacts on retinal function (Table 7). Decreases in a-wave amplitudes and/or decreases in b-wave amplitudes were found after 2-3 (Chang et al., 2015; Kim et al., 2017) and 6-7 (Asare-Bediako et al., 2020; Barathi et al., 2014; Shi et al., 2015) months of HFD. However, other studies found no differences in a-wave or b-wave amplitudes after 1 (Chrysostomou et al., 2017; Kim et al., 2017), 2 (Qu et al., 2020), 3-4 (Datilo et al., 2018; Rajagopal et al., 2016), 6 (Rajagopal et al., 2016), or 12 (Asare-Bediako et al., 2020; Rajagopal et al., 2016) months of HFD treatment. Conversely, another study found increased b-wave and c-wave amplitudes after 4 months of HFHS diet (Atawia et al., 2020), although this could be due to the ERG protocol and/or the HFHS treatment. In another study, after 6 weeks HFHS there were no baseline differences in intraocular pressure (IOP) or positive scotopic threshold response (pSTR) (Chrysostomou et al., 2017), a measure of ganglion cells (Bui and Fortune, 2004). However, in this same study, pSTR amplitudes were significantly lower in HFHS group compared to the control diet after injury by brief IOP increase; these deficits suggest that HFHS diet hinders recovery of
ganglion cells after injury, possibly through mitochondrial impairment (Chrysostomou et al., 2017). When measured with VEP and P-ERG, retinal ganglion cell response was also impaired after 5 months of HFD exposure (Shu et al., 2019; Zhu et al., 2018).

Timing is also an important component of ERG waves, and delayed implicit times are associated with retinal disease (Aung et al., 2013; Bronson-Castain et al., 2007; Fortune et al., 1999; Parisi, 2003). For example, delays in the timing of oscillatory potentials have been found to be an early indicator of DR (Aung et al., 2013; Fortune et al., 1999). Thus, differences in implicit times may indicate dysfunction. Delays in a-wave and b-wave implicit times have been reported after 1 (Kim et al., 2017) and 3 (Chang et al., 2015) months of HFD (Table 7). Additionally, decreased oscillatory potential amplitudes were reported after 1-2 (Kim et al., 2017), 4 (Datilo et al., 2018) and 7 (Shi et al., 2016) months of HFD, with delays in oscillatory potential implicit times after 1-2 (Kim et al., 2017) and 6-12 (Rajagopal et al., 2016) months of HFD treatment.

While some do not report retinal function changes in wildtype mice after HFD treatment (Landowski et al., 2019; Toomey et al., 2015), AMD models of mutant mice show decreased b-wave amplitudes after HFD treatment with (Ding et al., 2011; Landowski et al., 2019; Toomey et al., 2015; Toomey et al., 2018) and without (Ban et al., 2018) cholesterol enrichment. HFD treatment in genetic APOE-4 (Ding et al., 2011), CFH (Toomey et al., 2015; Toomey et al., 2018), CFH-H/H (Landowski et al., 2019), and ABCA1 (Ban et al., 2018) strains caused ERG deficits (Table 3), suggesting that lipid metabolism, complement signaling, and/or morphological changes seen in these models also impair retinal function. An AMD model with ABCA1/ABCG1 mutant mice also found lipid accumulation in RPE, photoreceptor degeneration, and ERG deficits without HFD feeding (Storti et al., 2019), which both suggests that impaired lipid metabolism can cause retinal function deficits and that the addition of HFD in genetic AMD models may act to speed up the emergence of deficits caused by genetic background.

To evaluate whether differences in experimental design could account for this variability in ERG outcomes, methods were compared across studies. Among the studies that found no difference in amplitudes in wildtype mice, one utilized a HFHS diet that did not cause body weight or blood glucose changes (Chrysostomou et al., 2017), one utilized a HFC diet in aged mice (Toomey et al., 2015), and another utilized male Swiss mice (Datilo et al., 2018), a strain that shows less susceptibility to some of the metabolic effects of HFD (Anderson et al., 2014; Marei et al., 2020). Of the studies that did not find differences, four used the Espion Diagnosys system (Chrysostomou et al., 2017; Landowski et al., 2019; Qu et al., 2020; Toomey et al., 2015) and one appears to have built their own system (Atawia et al., 2020). One study did not find decreased amplitudes at 1 month but did find decreases at 2 months (Kim et al., 2017), while another found decreased amplitudes at 6 months but no difference at 12 months (Asare-Bediako et al., 2020). Other possible reasons for variability include retinal circuit differences, compensation with disease, and altered signaling of neurotransmitters such as dopamine. However, the numerous reports of impaired ERG outcomes suggest that HFD treatment impairs retinal function and retinal cell types such as photoreceptors, bipolar cells, amacrine cells, and retinal ganglion cells.
While 17 of the reviewed studies evaluated retinal function (physiological assessments), only one evaluated visual function (behavioral assessments). A study of HFHS diet did not find any changes in spatial frequency thresholds as measured by optomotor response (OMR) in male C57Bl/6J mice (Atawia et al., 2020). As this study also found no difference in ERG outcomes and used a HFHS diet model, the impact of HFD on visual function is an open question. Additionally, only three of the reviewed studies conducted longitudinal ERG measurements (Asare-Bediako et al., 2020; Kim et al., 2017; Rajagopal et al., 2016); because ERGs and OMRs are non-invasive, nonterminal procedures, future HFD studies should strive to conduct longitudinal assessments of both retinal and visual function.

It is surprising that little research has been done in the area of HFD and retinal and visual function. Future studies should further evaluate outcomes of retinal function, including direct recording to assess single retinal cell electrophysiology. It would be useful to evaluate whether specific cell types, such as rods and retinal ganglion cells, are more vulnerable to HFD. Additionally, HFD studies of visual function, such as optomotor or optokinetic response, are missing and should be a focus of future studies. The visual effects of HFD are difficult to evaluate in epidemiological studies, but animal models of HFD exposure represent a way to close this gap.

6. Important considerations in experimental design

HFD is commonly utilized in animal models to better understand and treat human diseases, but epidemiological studies of dietary fat and ocular outcomes are mixed, muddying the translation between human and animal studies. Epidemiological nutrition research has a number of strengths and limitations. For example, diet studies generally rely on food frequency questionnaire data to derive approximate macronutrient and micronutrient components, but this data can be prone to recall bias and/or capture a small window of time, making it difficult to extrapolate to lifelong dietary patterns and capture dietary complexity (Shim et al., 2014). Other considerations are the variety of fats and the interactions between dietary components within the dietary milieu (Spector and Gardner, 2020), which may not be accurately estimated from questionnaire data. On the other hand, epidemiological studies measure real-world exposures, whereas animal models of HFD exposure utilize refined diets that may not fully reflect the diversity of human exposures. Therefore, both epidemiological and animal studies have strengths and limitations, and animal models of diet-induced visual disease are invaluable in understanding mechanisms of disease.

However, research in animal models has its own biases and limitations. One of the major biases in the current literature is the overwhelming use of male animals in HFD research, leading to a paucity of data on female outcomes. In the clinical population, metabolic syndrome (Bentley-Lewis et al., 2007) and diabetes (Wild et al., 2004) are equally prevalent among men and women; however, the incidence of diabetes by age group and the development of complications, such as diabetic retinopathy, may differ by sex (Ozawa et al., 2015).
Of the 66 studies included in this review (Figure 1, Supplemental Table 1), only 18 (27%) used female rodents (Figure 2G). While sex bias towards utilizing males in scientific research is not new (Beery and Zucker, 2011; Holdcroft, 2007; Lee, 2018), this scarcity of data on female outcomes is a loss of knowledge for the scientific community. While the National Institutes of Health has developed a policy to address sex as a biological variable in research (Clayton, 2018), more work needs to be done to ensure that female animals are included in HFD studies. There are a number of reasons why female rodents may not be included in HFD studies. There are valid reasons to use one sex in a study, such as a female model to understand the role of menopause in a disease outcome, but rationale for doing so should be provided. Female rodents may not be included because of assumptions of hormonal variability in response compared to male rodents (Beery, 2018), although this might not always be the case (Prendergast et al., 2014). HFD outcomes, such as dietary-induced obesity or glucose intolerance, may have different timelines or phenotypes in females compared to males (Hong et al., 2009; Parks et al., 2015; Yang et al., 2014).

Likewise, in STZ models with HFD, the use of males over females may be preferred because of sex differences in STZ response. Additionally, to ensure standardized delivery, STZ is often injected in rats via the penile vein (although it is also possible to deliver via the tail vein) (Deeds et al., 2011). To assess sex-specific results, sex-equitable research may require a larger number of animals to maintain statistical power when treatment effects differ by sex, which can be prohibitively expensive. However, because of these differences in outcomes, the use of female animals is arguably even more important in HFD research because sex-specific effects can lead to a deeper understanding of biological mechanisms and, ultimately, successful treatment options (Tannenbaum et al., 2019).

Another common limitation in HFD research is the lack of detailed diet description and/or the lack of a proper control diet. The majority of studies utilize a high fat diet (~35-60% kcal, Figure 2E) with fat derived from lard, vegetable oil, and/or milk fat, but use standard rodent chow as the control diet. While standard rodent chow is low in fat (~10% kcal), it is made of different ingredients and contains additional phytoneutrients and plant-based fiber, thereby providing phytoestrogens (Thigpen et al., 2004) and/or other components not present in the HFD. Because of these ingredient differences, outcomes that occur during HFD treatments are possibly confounded (Warden and Fisler, 2008). These issues can be minimized by choosing an appropriate ingredient-matched control diet, used by 24% of the reviewed studies (Figure 2H), and allow for better standardization across studies. In studies that do not use ingredient-matched control diets but use HFD to investigate the effects of metabolic disease on visual health, results could be validated with other models of metabolic disease (such as with an STZ model for modeling diabetes) or by treating the metabolic disease after inception (such as with insulin or metformin).

Fat percentage of the HFD is another important consideration in study design. Some models use diets on the lower end of HFD range, with approximately 25-35% fat kcal, but include higher amounts of cholesterol to induce atherosclerosis. The more common models of “western diet” exposure generally contain approximately 40-45% fat kcal, while other high fat diets contain approximately 45-60% fat kcal. Both can cause diet-induced obesity in certain rodent strains, but diets with a higher percentage of energy from fat may lead to more rapid weight gain. Additionally, if the goal is to model human disease, another important
consideration is which diet is most comparable to human diets; a rodent diet with 40-45% fat kcal (Figure 2) may more closely model human exposures (Speakman, 2019). Another practical consideration is that the diet texture may change to a more liquid consistency near the 60% fat kcal range. This should also be considered in experimental design, as a higher fat diet may require special food containers and other accommodations.

Other aspects of experimental design, such as the mouse or rat strain used, age of HFD exposure, and experimental timeline are important to consider. For example, some strains are somewhat resistant to diet-induced obesity and other metabolic outcomes (Funkat et al., 2004). Duration of diet and age at exposure are also important considerations (Figure 2), as short experimental timelines (a few days or weeks) of HFD exposure capture an adaptive or acute response, whereas longer (2+ months) timelines of HFD exposure can be used to model chronic outcomes (Heydemann, 2016; Ji et al., 2012; Khazen et al., 2019; London et al., 2017; Williams et al., 2014). Most of the reviewed studies focused on chronic outcomes, but transient or rapid adaptive responses may occur in the first hours, days, and weeks of HFD challenge. Characterizing these initial responses could help us understand disease mechanisms as well as the cumulative effects of repeated, acute dietary exposures.

7. Summary of findings

Overall, HFD affects a multitude of ocular tissues, altering morphology, signaling, and function. Among the common mechanisms identified, oxidative stress, inflammation, and lipid homeostasis were a common thread across HFD studies of ocular disease. Ocular tissues affected include cornea, lens, uvea, vitreous humor, retina, RPE, and Bruch’s membrane. Retinal cell types affected include glia (microglia), neurons (retinal ganglion cells, bipolar cells, amacrine cells, photoreceptors), and vascular support cells (endothelial cells and pericytes). The combination of so many different tissues, mechanisms, and cell types involved implies that HFD has profound effects on ocular health and vision. A greater understanding of the ocular effects of HFD as well as the development of treatments and interventions that target these effects is urgently needed.

This review also identified common limitations of HFD studies and current gaps in knowledge. Factors such as experimental control groups, age at diet start, and diet composition are also important to consider when attempting to model human disease. Due to the sex bias towards the use of male animals, future studies should aim to address sex-specific and female ocular outcomes in HFD research. Studies should also strive to report systemic metabolic outcomes and longitudinal measures of retinal and visual function. The bulk of the literature focuses on corneal, retinal, and RPE or BM outcomes, but the impacts of HFD on other ocular tissues is not well explored. Likewise, more work needs to be done to tease apart the effects of HFD on specific neuronal populations. Additionally, few studies have tested the acute effects (hours, days, weeks) of HFD on retinal function, visual function, and tissue outcomes, which should be a focus for future studies.

In conclusion, HFD models of visual disease are invaluable. These models are used to recapitulate human disease processes such as AMD and DR, leading causes of blindness. In understanding the mechanisms and pathophysiology of the impacts of HFD on ocular
outcomes, we can develop improved treatment strategies to preserve vision and prevent blindness.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**Abbreviations**

- **AMD**: age-related macular degeneration
- **BM**: Bruch’s membrane
- **ERG**: electroretinography
- **HFD**: high fat diet
- **HFHS**: high fat, high sucrose diet
- **IMCD**: ingredient-matched control diet
- **RPE**: retinal pigment epithelium
- **STZ**: streptozotocin

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Figure 1.
Flow-chart of study identification, screening, eligibility criteria, and final studies included for the review.
Figure 2.
Characteristics of the studies included in the review. A) The number of studies that utilize mice, rat, or mice and rat models in the experiment, separated by HFD model. B) Age (weeks) at which HFD treatment started, separated by HFD model; some studies used mice or rats of varying ages, in which case the youngest age at which diet treatment was started was used. C) Number of weeks rodents were treated with HFD, separated by model. D) Timeline of start age (weeks) to end age (weeks) of HFD treatment, separated by model. E) HFD fat % used, separated by model. F) Number of studies that utilized a genetic knockout.
or knock-in strain, separated by HFD model. G) Number of studies by sex specification of rodents used, separated by model. H) Breakdown of the number of studies that did and did not utilize an ingredient-matched control diet (IMCD).
Figure 3.
Diagram of a mouse/rat eye and how HFD affects different parts of the eye. RPE signifies retinal pigment epithelium and BM signifies Bruch’s membrane.
Table 1.
Summary of systemic and metabolic findings from reviewed studies.

| Outcome                  | Direction(s)     | Reference(s)                                                                                                                                 |
|--------------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Body weight              | Increased        | (Agardh et al., 2000; Alami et al., 2019; Albuery et al., 2020; Asare-Bediako et al., 2020; Barakat et al., 2019; Bu et al., 2020; Chang et al., 2015; Collins et al., 2018; Coppey et al., 2020; Coppey et al., 2018a; Coppey et al., 2018b; Dai et al., 2018a; Datilo et al., 2018; Davidson et al., 2014; Fink et al., 2020; Fujihara et al., 2009; Katsumata, 1970; Kim et al., 2017; Kneer et al., 2018; Lee et al., 2015; Marcal et al., 2013; Mohamed et al., 2020; Muhammad et al., 2019; Mykkanen et al., 2012; Nakazawa et al., 2019; Provost et al., 2009; Rajagopal et al., 2016; Shi et al., 2016; Shu et al., 2019; Wu et al., 2020; Yorek et al., 2015; Zhu et al., 2018) |
|                          | No change        | (Chrysostomou et al., 2017; Dai et al., 2018b; Miceli et al., 2000; Miller et al., 2017)                                                                |
| Fat % or mass            | Increased        | (Albuery et al., 2020; Asare-Bediako et al., 2020; Chang et al., 2015; Collins et al., 2018; Marcal et al., 2013; Rajagopal et al., 2016)                                                          |
| Steatosis                | Increased        | (Coppey et al., 2018b; Yorek et al., 2015)                                                                                                                                                           |
| Liver weight             | Increased        | (Miceli et al., 2000)                                                                                                                                                                               |
| Blood pressure           | Increased        | (Mykkanen et al., 2012)                                                                                                                                                                              |
| Blood glucose            | Hyperglycemia    | (Agardh et al., 2000; Albuery et al., 2020; Chang et al., 2015; Datilo et al., 2018; Kim et al., 2017; Marcal et al., 2013; Mohamed et al., 2020; Muhammad et al., 2019; Mykkanen et al., 2012; Shi et al., 2016; Shu et al., 2019; Tuzcu et al., 2017) |
|                          | No change        | (Alami et al., 2019; Barakat et al., 2019; Chrysostomou et al., 2017; Coppey et al., 2020; Coppey et al., 2018a; Dai et al., 2018a; Dai et al., 2018b; Davidson et al., 2014; Fink et al., 2020; Miller et al., 2017; Yorek et al., 2015) |
| Glucose tolerance (GTT) | Decreased        | (Chang et al., 2015; Coppey et al., 2020; Datilo et al., 2018; Davidson et al., 2014; Katsumata, 1970; Kim et al., 2017; Kneer et al., 2018; Lee et al., 2015; Marcal et al., 2013; Rajagopal et al., 2016; Yorek et al., 2015; Zhu et al., 2018) |
|                          | No change        | (Asare-Bediako et al., 2020)                                                                                                                                                                           |
| Insulin sensitivity (ITT)| Decreased        | (Asare-Bediako et al., 2020; Chang et al., 2015; Datilo et al., 2018; Lee et al., 2015; Rajagopal et al., 2016; Zhu et al., 2018)                                                                  |
| Serum insulin            | Increased        | (Agardh et al., 2000; Marcal et al., 2013; Rajagopal et al., 2016; Shu et al., 2019; Tuzcu et al., 2017; Zhu et al., 2018)                                                                           |
| Serum triglycerides      | Increased        | (Barakat et al., 2019; Marcal et al., 2013; Nakazawa et al., 2019; Provost et al., 2009; Tuzcu et al., 2017; Zhu et al., 2018)                                                                    |
|                          | No change        | (Albuery et al., 2020; Coppey et al., 2018a; Fujihara et al., 2009; Schmidt-Erfurth et al., 2008; Yorek et al., 2015)                                                                            |
| Serum cholesterol        | Increased        | (Asare-Bediako et al., 2020; Barakat et al., 2019; Bu et al., 2020; Coppey et al., 2020; Coppey et al., 2018b; Dithmar et al., 2001; Fujihara et al., 2009; Marcal et al., 2013; Nakazawa et al., 2019; Provost et al., 2009; Schmidt-Erfurth et al., 2008; Stanton et al., 2017; Tuzcu et al., 2017; Yorek et al., 2015) |
|                          | No change        | (Albuery et al., 2020; Coppey et al., 2018a)                                                                                                                                                         |
| Low-density lipoprotein (LDL) | Increased        | (Albuery et al., 2020)                                                                                                                                                                               |
|                          | No change        | (Marcal et al., 2013)                                                                                                                                                                               |
| High-density lipoprotein (HDL) | Increased        | (Marcal et al., 2013)                                                                                                                                                                               |
|                          | No change        | (Albuery et al., 2020; Provost et al., 2009; Schmidt-Erfurth et al., 2008)                                                                                                                       |
| Free Fatty Acids         | Increased        | (Coppey et al., 2018a; Mykkanen et al., 2012; Tuzcu et al., 2017; Zhu et al., 2018)                                                                                                                     |
|                          | No change        | (Barakat et al., 2019; Fujihara et al., 2009; Yorek et al., 2015)                                                                                                                                   |
| Hemoglobin A1C (HbA1c)   | Increased        | (Asare-Bediako et al., 2020; Barakat et al., 2019; Yorek et al., 2015)                                                                                                                               |
|                          | No change        | (Davidson et al., 2014)                                                                                                                                                                              |
### Table 2.
Summary of outcomes from studies that utilized a model of HFD and STZ.

| Treatment Group | Outcomes                                                                                     | Reference(s)                                                                 |
|-----------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| HFD, HFD + STZ  | Decreased corneal nerve fiber density and/or nerve fiber length                              | (Alamri et al., 2019; Coppey et al., 2020; Coppey et al., 2018b; Davidson et al., 2014; Yorek et al., 2015) |
|                 | Decreased corneal sensitivity                                                                | (Coppey et al., 2020; Davidson et al., 2014; Fink et al., 2020)              |
| HFD + STZ       | Increased leukocyte adhesion, increased endothelial cell injury and death                     | (Barakat et al., 2019)                                                      |
|                 | Reduced RGC survival                                                                         | (Shanab et al., 2012)                                                        |
|                 | Increased markers of inflammatory and immune response, reduced number of pericytes, increased number of acellular capillaries, decreased retinal thickness and number of retinal ganglion cells | (Mancini et al., 2013)                                                      |
|                 | Increased microglial recruitment to RPE                                                      | (Jo et al., 2019)                                                            |
## Table 3.
Summary of systemic and metabolic findings from reviewed studies.

| Treatment Group | Outcome(s)                                                                 | Reference(s)                                                                 
|-----------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| HFD             | Thicker BM                                                                | (Dithmar et al., 2001; Roddy et al., 2019)                                   |
|                 | No change BM thickness                                                    | (Schmidt-Erfurth et al., 2008)                                               |
|                 | Increased basal laminar deposits, loss of RPE cells                      | (Roddy et al., 2019)                                                         |
|                 | Increased lipofuscin area, decreased number of fenestrations             | (Zhang et al., 2018)                                                         |
|                 | Increased lesions in RPE                                                 | (Zhao et al., 2014)                                                          |
| HFD + blue light | Basal laminar deposits                                                   | (Cousins et al., 2002; Cousins et al., 2003; Espinosa-Heidmann et al., 2006) |
| HFD + cigarette smoke | Sub-RPE deposits                                      | (Espinosa-Heidmann et al., 2006; Stanton et al., 2017)                        |
|                 | Thicker BM                                                                | (Espinosa-Heidmann et al., 2006)                                              |
| HFD + APOE      | Thicker BM                                                                | (Ding et al., 2011; Picard et al., 2010)                                     |
|                 | Increased complement activation, Aβ deposition                           | (Ding et al., 2011)                                                          |
|                 | Increased lipid accumulation in RPE                                       | (Lee et al., 2007)                                                           |
|                 | Decreased ERG b-wave amplitude                                           | (Ding et al., 2011)                                                          |
| HFD + APOE2/3/4 | RPE vacuolization (E2, E3), mottled RPE (E2), thicker BM (E4), hypo and hyperpigmentation of RPE and atrophy (E4), sub-RPE deposits (E4), neovascularization positive for VEGF and Aβ (E4) | (Malek et al., 2005)                                                         |
| HFD + Cth       | Decreased ERG b-wave amplitude, increased number of multinucleated RPE cells | (Landowski et al., 2019; Toomey et al., 2015; Toomey et al., 2018)           |
|                 | Increased complement activation                                           | (Landowski et al., 2019)                                                     |
|                 | Increased sub-RPE deposit height                                         | (Toomey et al., 2015; Toomey et al., 2018)                                   |
|                 | Increased expression of inflammatory genes, increased leukocytes and monocytes in peripheral blood | (Toomey et al., 2018)                                                       |
| HFD + Pgc1α−/−  | Decreased IS and OS thickness, increased expression of genes related to lipid deposition, increased lipofuscin area, decreased number of fenestrations | (Zhang et al., 2018)                                                        |
| HFD + Nrf2−/−   | Increased sub-retinal deposits, increased lesion progression, increased sub-RPE cells, increased lesions in RPE | (Zhao et al., 2014)                                                          |
| HFD + SR-B1−/−  | Thicker BM, sub-RPE deposits, increased VEGF-staining                    | (Provost et al., 2009)                                                       |
| HFD + Ldlr−/−, Ldlr−/− | Increased VEGF expression                                               | (Rudolf et al., 2005; Schmidt-Erfurth et al., 2008)                         |
|                 | Thicker BM, decreased fenestrations, decreased luminal vessel diameter, decreased RPE height | (Schmidt-Erfurth et al., 2008)                                               |
|                 | Increased BM deposits                                                    | (Rudolf et al., 2005)                                                        |
| HFD + Igf-II/Ldlr−/−, Igf-II/Ldlr−/−-ApoB100                             | No change in retinal vasculature, altered retinal morphology                | (Kinnunen et al., 2013)                                                      |
| HFD + Abca1/g1F/F and Abca1/g1F/F-rod/rod                                 | Lipid accumulation, accelerated degeneration of photoreceptor outer segments, decreased ERG b-wave amplitudes (Abca1/g1F/F-rod/rod) | (Ban et al., 2018)                                                           |
| HFD + ApoB100    | Increased basal deposits                                                 | (Fujihara et al., 2009)                                                      |
|                 | decreased WNT signaling in RPE                                           | (Ebrahimi et al., 2018)                                                      |
| Treatment Group                       | Outcome(s)                                                                 | Reference(s)                      |
|---------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|
| HFD + ApoB100+ cigarette smoke        | Increased RPE atrophy, decreased OS and IS thickness, decreased ONL thickness | (Ebrahimi et al., 2018)            |
| HFD + ApoB100+ blue light             | Increased basal lamina deposits                                              | (Espinosa-Heidmann et al., 2004)  |
Table 4.
Summary table of reviewed corneal, vitreous, and lens outcomes after HFD reatment.

| Tissue       | Outcome(s)                        | Direction(s)     | Reference(s)                        |
|--------------|-----------------------------------|------------------|-------------------------------------|
| Cornea       | Corneal endothelial cell density  | Decreased        | (Bu et al., 2020)                   |
|              | Epithelial thickness              | No change        | (Kneer et al., 2018)                |
|              | Stromal thickness                 | Decreased        | (Kneer et al., 2018)                |
|              | Goblet cell number                | Decreased        | (Wu et al., 2020)                   |
|              | Tear production                   | Decreased        | (Wu et al., 2020)                   |
|              | Palmitate concentration in aqueous humor | Increased | (Bu et al., 2020)                   |
|              | Lipid droplets                    | Increased        | (Bu et al., 2020)                   |
|              | Expression of tight junction proteins | Decreased        | (Bu et al., 2020)                   |
|              | Corneal permeability              | Increased        | (Wu et al., 2020)                   |
|              | Corneal nerve fiber density and/or nerve fiber length | Decreased | (Alamri et al., 2019; Coppey et al., 2020; Coppey et al., 2018a; Coppey et al., 2018b; Davidson et al., 2014; Yorek et al., 2015) |
|              | Corneal sensitivity               | Decreased        | (Coppey et al., 2020; Davidson et al., 2014; Fink et al., 2020) |
|              | Corneal whorl integrity           | Decreased        | (Kneer et al., 2018)                |
| Lens         | Markers of oxidative stress       | Increased        | (Jayaratne et al., 2017)            |
|              | Glutathione concentration, ascorbic acid concentration | Decreased | (Nakazawa et al., 2019)            |
| Uvea          | Uveitis                           | Increased        | (Muhammad et al., 2019)             |
| Vitreous humor | Inflammatory markers             | Increased        | (Collins et al., 2018)              |
Table 5.
Summary table of reviewed retinal outcomes after HFD treatment

| Retinal Tissue                  | Outcome(s)                  | Direction(s) | Reference(s)                          |
|---------------------------------|-----------------------------|--------------|---------------------------------------|
| Retinal neuronal morphology     | Retinal thickness           | No change    | (Atawia et al., 2020; Chang et al., 2015; Rajagopal et al., 2016) |
|                                 |                             | Decreased    | (Marcal et al., 2013)                 |
|                                 | Axonal thickness            | Decreased    | (Zhu et al., 2018)                    |
|                                 | Ganglion cell function      | Decreased    | (Shu et al., 2019; Zhu et al., 2018)  |
|                                 | Synaptophysin expression    | Decreased    | (Shu et al., 2019; Zhu et al., 2018)  |
| Retinal vasculature             | Acellular capillaries       | Increased    | (Mohamed et al., 2014; Mohamed et al., 2020) |
|                                 | Endothelial cell:pericyte ratio | No change    | (Asare-Bediako et al., 2020; Rajagopal et al., 2016) |
|                                 | Vascular density            | Decreased    | (Asare-Bediako et al., 2020)          |
|                                 | Vascular leakage / permeability | Increased    | (Asare-Bediako et al., 2020; Mohamed et al., 2020; Rajagopal et al., 2016) |
|                                 |                             | No change    | (Zhu et al., 2018)                    |
|                                 | Vessel branching            | Decreased    | (Mohamed et al., 2020)                |
|                                 | Vessel bleeding             | Increased    | (Katsumata, 1970)                     |
|                                 | Vascular lesions            | No change    | (Shu et al., 2019)                    |
|                                 | Vascular eNOS and nNOS      | Decreased    | (Marcel et al., 2013)                 |
| Inflammatory signaling          | Microglial activation       | Increased    | (Atawia et al., 2020; Lee et al., 2015) |
|                                 | Adherent leukocytes / signaling | Increased    | (Mohamed et al., 2020; Tuzcu et al., 2017) |
|                                 | Immune cells                | Increased    | (Lee et al., 2015)                    |
|                                 | iNOS expression             | Increased    | (Tuzcu et al., 2017)                  |
|                                 | NF-κB signaling             | Increased    | (Lee et al., 2015; Tuzcu et al., 2017) |
|                                 | Markers of inflammation     | Increased    | (Chang et al., 2015; Marcal et al., 2013) |
|                                 | Cytokines                   | Increased    | (Kim et al., 2017; Lee et al., 2015)  |
|                                 | Glutathione and cysteine levels | No change    | (Agardh et al., 2000)                 |
|                                 | miR150 expression           | Decreased    | (Shi et al., 2016)                    |
| Retinal lipids                  | Spots on fundus imaging     | Increased    | (Asare-Bediako et al., 2020; Barathi et al., 2014) |
|                                 | Lipid levels                | Altered      | (Albouery et al., 2020; Dai et al., 2018a) |
|                                 | Lipid peroxidases           | Increased    | (Mohamed et al., 2014)                |
| Other signaling                 | Glycolytic processes        | Altered      | (Katsumata, 1970)                     |
|                                 | Protein O-GlcNAcylation     | Increased    | (Dai et al., 2018b)                   |
|                                 | Abnormal tau phosphorylation| Increased    | (Zhu et al., 2018)                    |
|                                 | Akt/INK signaling           | Altered      | (Dai et al., 2018a; Miller et al., 2017) |
|                                 | AKT1 expression             | Decreased    | (Marcal et al., 2013)                 |
|                                 | HIF1α expression            | Increased    | (Asare-Bediako et al., 2020)          |
|                                 | LXRβ expression             | Decreased    | (Asare-Bediako et al., 2020)          |
|                                 | Crystallin expression       | Increased    | (Mykkkanen et al., 2012)              |
| Retinal Tissue | Outcome(s)   | Direction(s) | Reference(s) |
|---------------|--------------|--------------|--------------|
| GLP-1 expression | Decreased    | (Shu et al., 2019) |
| GLUT4 expression | Decreased   | (Chang et al., 2015) |
### Table 6.
Summary table of reviewed RPE and BM outcomes after HFD treatment

| Tissue                                      | Outcome                                      | Direction(s) | Reference(s)                                      |
|---------------------------------------------|----------------------------------------------|--------------|--------------------------------------------------|
| Retinal Pigment Epithelium (RPE)            | Number of lesions                            | Increased    | (Zhao et al., 2014)                              |
|                                             | Number of RPE cells                          | Decreased    | (Roddy et al., 2019)                             |
|                                             | Vacuoles                                     | Increased    | (Barathi et al., 2014; Schmidt-Erfurth et al., 2008) |
| Bruch’s Membrane (BM)                       | Thickness                                    | Increased    | (Barathi et al., 2014; Dithmar et al., 2001; Roddy et al., 2019) |
|                                             |                                             | No change    | (Schmidt-Erfurth et al., 2008)                   |
|                                             | Basal lamellar deposits                      | Increased    | (Barathi et al., 2014; Roddy et al., 2019)       |
|                                             |                                             | No change    | (Stanton et al., 2017; Toomey et al., 2015)      |
|                                             | Lipofuscin / autofluorescence of what appears to be lipofuscin | Increased | (Miceli et al., 2000; Zhang et al., 2018) |
|                                             | Number of fenestrations in choriocapillaris endothelium | Decreased | (Zhang et al., 2018) |
|                                             |                                             | No change    | (Schmidt-Erfurth et al., 2008)                   |
Table 7.
Summary table of reviewed retinal function outcomes after HFD treatment

| ERG Outcome                  | Direction(s) | Reference(s)                                                                 |
|------------------------------|--------------|-------------------------------------------------------------------------------|
| a-wave amplitudes            | Decreased    | (Asare-Bediako et al., 2020; Barathi et al., 2014; Chang et al., 2015; Kim et al., 2017; Shi et al., 2016) |
|                              | No change    | (Asare-Bediako et al., 2020; Atawia et al., 2020; Chrysostomou et al., 2017; Datilo et al., 2018; Qu et al., 2020; Rajagopal et al., 2016) |
| a-wave implicit times        | Delayed      | (Chang et al., 2015; Kim et al., 2017)                                        |
|                              | No change    | (Chrysostomou et al., 2017)                                                   |
| b-wave amplitudes            | Increased    | (Atawia et al., 2020)                                                         |
|                              | Decreased    | (Asare-Bediako et al., 2020; Barathi et al., 2014; Chang et al., 2015; Kim et al., 2017; Shi et al., 2016) |
|                              | No change    | (Asare-Bediako et al., 2020; Chrysostomou et al., 2017; Datilo et al., 2018; Qu et al., 2020; Rajagopal et al., 2016) |
| b-wave implicit times        | Delayed      | (Chang et al., 2015; Kim et al., 2017)                                        |
|                              | No change    | (Chrysostomou et al., 2017)                                                   |
| c-wave amplitudes            | Increased    | (Atawia et al., 2020)                                                         |
|                              | No change    | (Datilo et al., 2018)                                                         |
| pSTR amplitude               | No change    | (Chrysostomou et al., 2017)                                                   |
| Oscillatory potential amplitudes | Decreased     | (Datilo et al., 2018; Kim et al., 2017; Shi et al., 2016)                     |
| Oscillatory potential implicit times | Delayed     | (Kim et al., 2017; Rajagopal et al., 2016)                                   |
| VEP and/or P-ERG amplitudes  | Decreased    | (Shu et al., 2019; Zhu et al., 2018)                                          |