INTRODUCTION

Exercise is a powerful form of preventative medicine, offering protection from a wide-range of chronic diseases. For example, Nocon et al. (2008) found increased levels of physical activity can reduce cardiovascular-associated mortality by 35% and all-cause mortality by 33% (Nocon et al., 2008) in both cardiovascular risk-factor adjusted and unadjusted populations (Nocon et al., 2008). Physical activity prevents hypertension, hypercholesteremia, type-II diabetes, metabolic syndrome, and alters inflammatory biomarkers—all of which are associated with the development of cardiovascular disease (Lee et al., 2012; Liu et al., 2018). The physiologic benefits of regular physical activity extend beyond the mitigation of risk factors, as physical fitness levels were found to be associated with lower cardiovascular and all-cause mortality rates, even when independently adjusted for cardiovascular disease risk factors (Sandvik et al., 1993).

Recent emerging data has shown that physical fitness not only benefits parental hosts’ health, but also that of their offspring (Carter, Qi, De Cabo, & Pearson, 2013; Denham, 2018; Leite et al., 2017; McCullough et al., 2015; Yeshurun...
These findings have been observed in a variety of measures ranging from insulin sensitivity (Barres & Zierath, 2011) to anxiety profiles (Short et al., 2017). For example, maternal physical activity during pregnancy or paternal physical activity during the pre-conception period was shown to improve offspring glucose tolerance (Carter et al., 2013; Stanford et al., 2018) with pre-conception paternal exercise eliciting more favorable offspring body weight and C-reactive protein profiles (McPherson, Owens, Fullston, & Lane, 2015).

Several complex and interrelated mechanisms have been proposed for this intergenerational effect of exercise, including alterations in gamete presentation, changes in the in utero and offspring rearing environments, and epigenetic modifications (Figure 1). While it was previously thought an organism’s epigenome was erased during gametogenesis and embryogenesis, it is now accepted that some epigenetic modifications are potentially heritable, able to be transmitted from parent to offspring (Portela & Esteller, 2010). The purpose of this brief systematic review was to expound upon epigenetic modulation of exercise and its intergenerational effects. Specifically, we will focus on the two most common epigenetics modifications, DNA methylation and histone modifications, in both humans and animal models (Portela & Esteller, 2010).

2 | METHODS

2.1 | Question

This review question was formulated using the evidence-based model PICO: Population, Intervention, Comparison, Outcome. The population consisted of subjects engaged in reproduction, the intervention was exercise, the comparison was sedentary behavior, and the outcome was epigenetic modifications in offspring. Using these components, the question is as follows: Does paternal and/or maternal exercise status incur epigenetic modifications inherited by offspring?

2.2 | Search strategy

Key words were identified for components of the PICO question (Table 1). The initial search was completed using Pubmed and yielded seven results. To garner a larger number of results, another search was completed in Pubmed using more broad key words (Table 2) which yielded 79 results. A second search also using these “wide net” key words was completed in Embase (Table 3).

2.3 | Inclusion and exclusion criteria

Articles had to include original research. Reviews, book chapter, or position papers were excluded. Articles not in English were excluded. Articles were limited to the years 2008–2018. Study subjects had to be human or rodent models. Exercise had to be an intervention used in the maternal and/or paternal generation. Epigenetic mechanisms had to be measured in the offspring. A PRISMA diagram outlines these inclusion and exclusion criteria (Figure 2). A total of four articles met inclusion criteria.
3.1 | McCullough et al. (2015)

The first included study examined human female subjects’ physical activity levels with the Pregnancy Physical Activity Questionnaire tool for 24 weeks in the prenatal period. DNA methylation of previously identified differentially methylated regions (DMR) regulating imprinted genes were measured in human cord-blood. Total maternal prenatal non-sedentary time was associated with decreased DNA methylation of \textit{Pleomorphic Adenoma Gene-Like 1 (PLAGL1)} DMR ($P_{\text{trend}} = .0136$) after adjusting for race/ethnicity, gestational age at delivery, folic acid intake, and maternal smoking. They also found an inverse relationship between moderate & intense physical activity and birth weight (BW). Conversely, light physical activity was positively associated with BW, but this relationship was attenuated with increasing amounts of light physical activity performed.

3.2 | Laker et al. (2014)

The second included study used a rodent model (C57BL/6 mice). Female mice were divided into a control diet (CD) group or a high-fat diet (HFD) group. The high-fat diet group was further subdivided into a sedentary group or a voluntary wheel access group. Both diet and exercise interventions were implemented 6 weeks before pregnancy and continued throughout. Offspring were either assessed during the neonatal period or at 12 months of age. DNA methylation of \textit{Peroxisome proliferator-activated-receptor gamma coactivator-alpha (Pgc-1 alpha)} CpG site −260 was measured in skeletal muscle. High-fat diet caused hypermethylation of \textit{Pgc-1 alpha} in neonates ($p < .05$), but this difference was completely abolished at 12 months of age in offspring of exercised-founders. There were no differences in mRNA levels between groups in neonatal offspring, but by 12-months of age both diet and exercise impacted mRNA levels. HFD-exercise offspring had higher mRNA levels of \textit{Pgc-1 alpha} compared to CD-Sedentary and HFD-sedentary offspring ($p < .05$). There was no difference in mRNA levels of \textit{Myh2a} and \textit{Sod1} between groups. Longitudinal glucose tolerance tests (GTT) and insulin tolerance tests (ITT) were also conducted on offspring. Although there were no differences between exercise-offspring and sedentary-offspring at both 6 and 12 months, there was a significant difference at 9 months. HFD-sedentary offspring possessed an impaired GTT, and HFD-exercise offspring showed normal GTT ($p < .05$).

3.3 | Xu et al. (2017)

The third included study used female Kumming mice, divided into two groups (sedentary or treadmill training). The

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**Table 1** Identified key words for each component of the PICO question

| Search Strategy | Search Database | Intervention | Population | Outcome | Search Result |
|-----------------|-----------------|--------------|------------|---------|---------------|
| Search Database | PubMed          | "Exercise" OR "Physical Activity" OR "Activity, Physical" OR "Acute Exercise" OR "Chronic Exercise" OR "Aerobic Exercise" OR "Exercise Training" OR "Isometric Exercise" OR "Animal Physical Conditioning" OR "Running" OR "Swimming" | "Placenta" OR "Sperm" OR "Reproduction" OR "Paternal" OR "Maternal, Pregnancy" OR "Inheritance Patterns" OR "Genetic Phenomena" | “Epigenesis, Genetic” OR “Epigenomics” OR “Process, Epigenetic” OR “DNA Methylations” OR “Methylation, DNA” OR “Acetyltransferases, Histone” OR “Acetylation, Histone” OR “Deacetylases, Histone” OR “Histone Deacetylase” | $N = 7$ |

**Table 2** Key words used in a systematic search of Pubmed literature

| Search strategy | Search Database | Intervention | Population | Outcome | Search Result |
|-----------------|-----------------|--------------|------------|---------|---------------|
| Search Database | PubMed          | "Exercise" OR "Physical Activity" | "Sperm" OR "Placenta" OR "Paternal" OR "Maternal" OR "Pregnancy" | “Epigenetic” | $N = 79$ |

**Table 3** Key words used in a systematic search of Embase literature

| Search strategy | Search Database | Intervention | Population | Outcome | Search Result |
|-----------------|-----------------|--------------|------------|---------|---------------|
| Search Database | Embase          | "Exercise" | "Sperm" “Placenta” “Paternal Exposure” “Paternal Inheritance” “Paternal Behavior” “Maternal” “Offspring” | “Epigenetic” | $N = 26$ |

3 | RESULTS

Four studies met the inclusion criteria of original research available in English completed between 2008 and 2018 examining epigenetic outcomes of an exercise intervention in human or rodent offspring (Table 4).
treadmill training occurred for 60 min/day, 5 days/week, and lasted 4 weeks prior to superovulation and oocyte collection for subsequent in vitro fertilization (IVF). Somatic nuclear cell transfer was also performed in separate experiments that are not discussed here due to lack of an intergenerational component. DNA-methylation of CpG sites in select paternal or maternal-imprinted genes, global DNA methylation, and histone methylation were measured in IVF-derived embryos (blastocyst stage). Exercise-embryos (EE) showed increased methylation of maternally-imprinted Igf2, paternally-imprinted Meg3 & H19, and the histone H3K4m2, compared to sedentary-embryos (SE) ($p < .05$). EE had lower methylation, however, of paternally-imprinted Igf2r, global DNA methylation, and histone H3K9m3 ($p < .05$). EE also exhibited lower levels of maternally imprinted Igf2 mRNA and paternally imprinted Meg3 & H19 mRNA ($p < .05$). Yet EE possessed higher levels of paternally imprinted Igf2r and Ampd3 ($p < .05$). H$_2$O$_2$ level (pixels/embryo), ATP levels (pmol/embryo), and mitochondrial membrane potential ($\Delta\psi_m$) were also assessed in offspring. Exercise-embryos (EE) showed lower H$_2$O$_2$ levels yet higher ATP levels and mitochondrial membrane potentials ($p < .05$).

### 3.4 Mega et al. (2018)

The fourth included study assessed male Wistar rats that were divided into sedentary or treadmill training groups. The treadmill training occurred 20 min/day, 5 consecutive days/week, and was implemented for 8 weeks prior to mating. Exercise-offspring exhibited lower percent global DNA-methylation in hippocampal tissue compared to sedentary offspring ($p = .019$). There were no differences in offspring hippocampal and cortex tissue quantified brain-derived...
| Study                  | Population | Diet            | Exercise Intervention                                                                 | Methylation Levels                                                                 | mRNA or Protein Expression | Functional Measurements                                                                 |
|-----------------------|------------|-----------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------|
| McCullough et al. (2015) | Female Humans | Standard        | Prenatal physical activity levels assessed using the Pregnancy Physical Activity Questionnaire tool for 24 weeks | DNA methylation of differentially methylated regions (DMR) regulating four known imprinted genes with roles in fetal development (*H19, MEG3, SGCE/PEG10, and PLAGL1*) Association with prenatal physical activity (PA) after adjusting for race/ethnicity, gestational age at delivery, folic acid intake, maternal smoking | None measured             | Association of prenatal PA with birth weight after adjusting for race/ethnicity and preterm birth |
| Laker et al. (2014)     | Female C57BL/6 Mice | Two diet groups: high-fat diet (HFD) versus control diet (CD) Length: 6 weeks before and throughout pregnancy | Neonatal and 12-month-old offspring skeletal muscle Methylation of *Peroxisome proliferator-activated-receptor gamma coactivator-alpha* (*Pgc−1 alpha*) at CpG site −260 | Neonatal and 12-month-old offspring skeletal muscle mRNA levels | Glucose tolerance tests in 6, 9, and 12-month-old offspring |
| Xu et al. (2017)        | Female Kunming Mice | Standard        | Two activity groups: sedentary versus treadmill training Treadmill training occurred 5 days/week and 60 min/day Length: 4 weeks prior to superovulation and oocyte collection for in vitro fertilization (IVF) | Embryos (blastocyst stage) produced via IVF Methylation levels of CpG sites on imprinting control regions of maternal and paternalimprinted genes Global DNA methylation Histone methylation | mRNA levels of maternal or paternal imprinted genes | IVF-derived embryos (blastocyst stage) H$_2$O$_2$, ATP, and Δψm measurements |
| Mega et al. (2018)      | Male Wistar Rats | Standard        | Two activity groups: sedentary versus treadmill training Treadmill training occurred for 20 min/day and 5 consecutive days/week Length: 8 weeks prior to mating | 54-day-old male offspring Global DNA-methylation of hippocampal tissue | 54-day-old offspring BDNF protein quantification of hippocampal and cortex tissue | Male offspring at 1, 21, and 54 days old Physical activity participation and performance Spatial memory and learning performance Adrenal gland, gonadal fat, and leg muscle weights |
neurotrophic factor (BDNF) protein. There were also no differences in many of the functional outcomes assessed, including body weight, growth, physical activity participation or performance, spatial memory or learning performance, adrenal gland weight, or leg muscle weight. The exception was that exercise-offspring had lower relative gonadal fat weight compared to sedentary-offspring ($p = .026$).

4 | DISCUSSION

To the best of our knowledge, this is the first review to systematically survey the literature for evidence of intergenerational exercise-derived epigenetic modifications. While the number of studies is few, the literature shows altered methylation patterns, mRNA levels, and functional outcomes in offspring of exercised founders. Both global DNA methylation changes and promoter-region methylation of specific genes differed in exercise-offspring. Exercise was also found to attenuate or reverse some of the high-fat diet associated methylation patterns. Many of the genes found to be differentially methylated are implicated in metabolic functions, such as regulation of oxidative metabolism and glucose transportation, which have obvious significance for offspring. In addition to metabolism, exercise has also been shown to impact cognitive development, as hippocampal DNA methylation was found to be lower in exercise-offspring (Mega et al., 2018). Hence, epigenetic intergenerational outcomes appear to be consistent with epigenetic alterations in hosts undergoing exercise.

Both acute and chronic exercise interventions have been shown to induce a number of epigenetic modifications within the exercise host. In human skeletal muscle, decreased whole genome methylation and decreased methylation of promoter regions of key metabolic genes (i.e., *Pgc-1 alpha, PDK4*, and *PPAR delta*) was observed after completing a single-session of cycling at 80% of VO$_{2peak}$ (Barres et al., 2012). Similarly, three months of regular single-knee extension exercise showed genome-wide DNA methylation alterations that were not observed in the untrained leg (Lindholm et al., 2014). Global-DNA methylation changes were also reported in skeletal muscle following 6-months of moderate intensity cycling and aerobic classes (Nitert et al., 2012). Twelve weeks of moderate-intensity training was also shown to reduce global DNA methylation in peripheral mononuclear cells in elderly human subjects (Dimauro et al., 2016). In a study of 1,016 individuals over the age of 70, self-reported physical activity levels were correlated with global DNA methylation even after adjusting for other contributing factors such as body mass index (BMI) or smoking (Luttropp, Nordfors, Ekstrom, & Lind, 2013).

McCullough et al. examined human subjects measured cord-blood methylation in four previously identified DMRs associated with body weight and only one (*PLAGL1*) was found to have a significant association with prenatal physical activity levels (McCullough et al., 2015). Still, *PLAG1*, an important regulator of the cell cycle & apoptosis (Vega-Benedetti et al., 2017), was found to have downstream effects on *Glut4, PPAR delta, PACAP1-R*, and *Rasgrfl*, all of which transcribe proteins involved in carbohydrate metabolism (Vega-Benedetti et al., 2017), and linked with control of fetal growth and the pathogenesis of transient neonatal diabetes mellitus as well as certain types of cancer (Brøns et al., 2010; Hoffmann & Spengler, 2012; Vega-Benedetti et al., 2017). McCullough et al. (2015) did find an inverse association between moderate and heavy prenatal physical activity and infant birth weight. While there are probably many contributing factors to this relationship, the lower methylation of *PLAGL1* associated with physical activity may have beneficial effects on fetal growth.

Studies in rodent models have also shown host epigenetic changes in response to exercise. An exhaustive rotarod session in mice was shown to shift methylation patterns of histones that contributed to upregulation of an exercise-associated isoform of *PGC-1 alpha*, a protein important for mitochondrial biogenesis (Lochmann, Thomas, Bennett, & Taylor, 2015). Treadmill training in mice was also shown to result in 200 genes with altered DNA methylation that negatively correlated with gene expression, indicating DNA methylation may play a role in skeletal muscle adaptation to exercise (Kanzleiter et al., 2015). *AMPK alpha-2*, an important nutrient-sensing energy regulator, was hypermethylated after short-term treadmill training in mice and this was accompanied by a decrease in AMPK alpha-2 mRNA and protein expression (King-Himmelreich et al., 2016). This hypermethylation was not present after a longer-term intervention, suggesting it might have a transient role in adaptation to stimulus and highlighting the impact exercise duration, intensity, and length might have on epigenetic changes (King-Himmelreich et al., 2016).

Changes in methylation levels might be expected to be accompanied by a shift in mRNA levels, as methylation makes the genome more or less available for transcription. mRNA levels both increased and decreased in exercise-offspring depending on which transcripts were surveyed. While there was a lack of consensus across studies of which mRNAs transcripts were surveyed many have been found to have metabolic roles. Exercise increased levels of mRNA transcripts (even in the context of a high-fat diet challenge) that could enhance offspring oxidative metabolism and regulation of growth. Notably, exercise increased levels mRNA transcript levels of *Pgc-1 alpha* (Laker et al., 2014), a transcriptional coactivator which has been referenced as a “master regulator of mitochondrial function (Barres & Zierath, 2011)” and was more methylated in low-birth weight infants (Brøns et al., 2010). Moreover with respect to phenotype, exercised-offspring exhibited molecular-level increases in ATP...
and mitochondrial membrane potential, both of which could help enhance metabolic function (Xu et al., 2017). While offspring of founders exposed to a high fat diet showed impaired glucose tolerance, exercise was able to rescue this impairment (Laker et al., 2014). When functional outcomes measured included cognitive changes there was no difference found between offspring of exercise-founders versus sedentary-founders (Mega et al., 2018). And while there were no differences found in rodent-model offspring body weight, there was an inverse relationship found between moderate & intense prenatal-PA and birth weight when studying human participants (McCullough et al., 2015).

A number of studies have also reported epigenetic modifications in exercised-founder sperm (Benito et al., 2018; Ingerslev et al., 2018; Murashov et al., 2015; Stanford et al., 2018). A high-fat diet caused changes in founder sperm content including altered methylation levels, microRNA (miRNA) content, and transfer ribonucleic acid fragments (tRFs) (Murashov et al., 2015; Stanford et al., 2018). Exercise interventions ameliorated these changes (Murashov et al., 2015; Stanford et al., 2018). Several of the methylated regions and miRNAs studied have metabolic roles such in glucose and insulin signaling. Even in the absence of diet interventions, exercise modified DMRs and piwi-interacting RNAs (pi-RNA) (Ingerslev et al., 2018; Stanford et al., 2018).

Given that exercise impacts sperm, it is reasonable to hypothesize that also has the potential to induce intergenerational effects. Offspring of high-fat diet founders experienced metabolic dysfunction that was improved when founders were exercised (Stanford et al., 2018). Murashov et al. (2015) challenged their offspring (in addition to founders) with a high-fat diet. When this F1 generation intervention was added, male offspring of male exercise-founders showed more metabolic dysfunction than male offspring of male sedentary-founders, while there was no impact in female offspring. This result highlights the complexity of metabolic function and the large impact of variables such as gender, which warrants further exploration. Benito et al. (2018) found offspring of exercise-founders displayed increased hippocampal long-term potentiation, a marker of synaptic function. Assessing epigenetic modifications in both sperm content and offspring could bolster connecting them to observed phenotypic changes.

Several limitations exist in both analyzing the current literature and in the field of intergenerational-epigenetics in general. There are a clear lack of uniform methods across included studies. The length of exercise intervention ranged from 3 to 24 weeks, a variable that could have a large impact on resulting conclusions. There were also discrepancies between whether exercise was used as a stand-alone intervention or was implemented along with changes to diet and environment. Measured outcomes were inconsistent between studies, making it difficult to compare results and assess studies for reproducibility. All of the studies except two used rodent models. Of the two that did not, one measured outcome in sperm (not offspring) and the other measured outcomes in offspring cord-blood. Obviously, using human subjects makes it difficult to tightly control for the environment and other confounding variables. This is especially relevant in the field of intergenerational epigenetics, as it is extremely difficult to show observed modifications in offspring that are due solely to epigenetic modifications. When using female subjects, fetal developmental programming in utero could be responsible for many intergenerational effects. It would be prudent in future studies to examine offspring to the F3 or later generations (Horstemke, 2018).

Much more research is needed to elucidate the potential for exercise to induce epigenetic modifications that have intergenerational effects. Standardization of exercise interventions employed, including length, mode, intensity, and sex, would help shed light on this important topic. Similarly, more uniformity in outcome measurements such as tissue sampled, global versus gene-specific surveillance, and offspring sex could improve ability to compare results between studies. Most importantly, rigorous methods are needed to ensure the greatest likelihood of observed outcomes being attributable to epigenetic modifications. Suggested methods in translational models include using in-bred strains, strictly controlling the environment, studying multiple generations of offspring, and studying germ cells as well as offspring (Horstemke, 2018). Regardless of whether the intergenerational impacts of exercise are due to epigenetic modifications or fetal developmental programming, it could serve as a non-invasive, low-cost intervention during preconception or prenatal periods to help enhance various functional outcomes in offspring. Previous studies have found physical activity interventions during pregnancy are feasible and well tolerated by participants (Callaway et al., 2010; Hunter, 2017). While further studies are needed, these early data suggest exercise can impact intergenerational health through epigenetic modifications.

CONFLICTS OF INTEREST
None of the authors have any conflicts of interest to declare, financial or otherwise.

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**How to cite this article:** Axsom JE, Libonati JR. Impact of parental exercise on epigenetic modifications inherited by offspring: A systematic review. *Physiol Rep*. 2019;7:e14287. https://doi.org/10.14814/phy2.14287