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Epigenome-Wide Association of Dietary Fish Oil Intake with Adipose Tissue Inflammatory Gene Expression

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ABSTRACT

Background: Chronic low-grade inflammation in adipose tissue, driven by NF-kB pathway activation, macrophage infiltration, and cytokines such as TNF-alpha and IL-6, is a central mechanism linking obesity to insulin resistance, and dietary fish oil-derived omega-3 fatty acids are widely studied as modulators of this inflammatory tone. Objective: This narrative review synthesizes published literature on the relationship between dietary or supplemental fish oil/omega-3 fatty acid intake, epigenome-wide and targeted DNA methylation changes, and inflammatory gene expression in adipose tissue and related immune cell compartments. Methods: We reviewed epigenome-wide association studies of habitual and experimentally manipulated fatty acid intake in blood and cord blood, controlled feeding and supplementation studies measuring DNA methylation directly in human adipose tissue, and human, cellular, and animal studies of fish oil effects on inflammatory gene expression and macrophage infiltration in adipose tissue. Findings: Omega-3 fatty acid exposure is reproducibly associated with DNA methylation differences at loci enriched for immune and inflammatory gene networks in blood, cord blood, and, in a smaller number of controlled trials, adipose tissue itself, while a considerably larger and more consistent body of evidence shows that fish oil supplementation reduces inflammatory gene expression, macrophage infiltration, and NF-kB and NLRP3 inflammasome pathway activity in adipose tissue and peripheral immune cells; mechanistic cellular work indicates that DNA methylation is not a universal mediator of these transcriptional effects. Conclusions: Dietary fish oil intake is linked to both DNA methylation changes and suppressed inflammatory gene expression in adipose-relevant tissues, but well-powered adipose tissue-specific epigenome-wide association studies remain comparatively rare, and larger standardized trials integrating methylation, gene expression, and macrophage phenotyping are needed to clarify whether methylation causally contributes to fish oil's anti-inflammatory effects in adipose tissue.

Keywords: *epigenome-wide association study; DNA methylation; omega-3 fatty acids; adipose tissue inflammation; NF-kB signaling*

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Introduction

Adipose tissue is now recognized as a metabolically active endocrine organ whose capacity to become chronically inflamed is a central driver of insulin resistance and cardiometabolic disease. The seminal observation that obese adipose tissue accumulates macrophages, and that this infiltration scales with adiposity, reframed white fat from a passive energy depot into a site of active innate-immune signaling involving tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway [1]. NF-kB itself sits at the intersection of inflammation and metabolic disease, integrating cytokine, nutrient, and stress signals in adipocytes and adipose-resident macrophages, and its chronic activation is now considered a unifying mechanism linking obesity to insulin resistance, type 2 diabetes, and atherosclerosis [2]. Long-chain omega-3 polyunsaturated fatty acids derived from fish oil, principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have long been studied as dietary modulators of this inflammatory tone, acting through membrane incorporation, eicosanoid and specialized pro-resolving mediator synthesis, and direct interference with NF-kB and other transcription factor signaling in immune and adipose cells [3].

Over the past fifteen years, the tools available to study these effects have expanded from single-gene expression assays to genome-scale surveys of DNA methylation, the most extensively

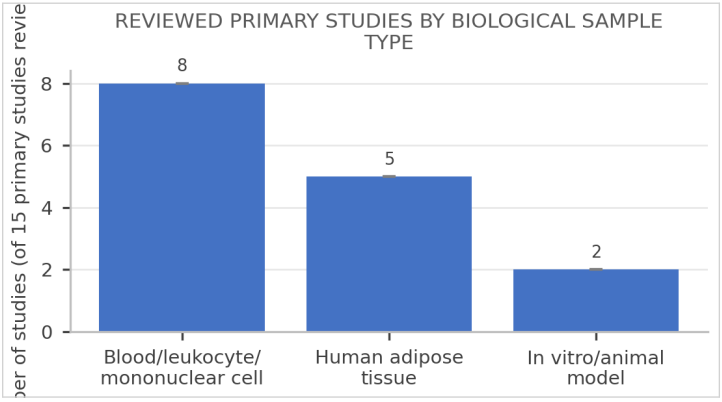
characterized epigenetic mark linking environmental and dietary exposures to sustained changes in gene transcription. Epigenome-wide association studies (EWAS), typically performed with bisulfite-converted DNA hybridized to the Illumina HumanMethylation450 or MethylationEPIC bead arrays, allow investigators to ask whether habitual or experimentally manipulated fatty acid intake leaves a systematic, reproducible signature across hundreds of thousands of CpG sites, and whether that signature maps onto genes with known roles in inflammation. Rigorous conduct of such studies requires careful attention to cell-type heterogeneity, multiple-testing correction, and replication, considerations that have been formalized in methodological guidance for the field and that bear directly on how the fish oil and adipose tissue literature should be interpreted [4].

This narrative review synthesizes the published literature at the intersection of these two developments: dietary or supplemental fish oil and omega-3 fatty acid intake on one hand, and epigenome-wide or targeted DNA methylation changes together with inflammatory gene expression outcomes in adipose tissue and closely related immune cell compartments on the other. We first consider genome-wide and blood-based association studies linking habitual fatty acid intake to DNA methylation patterns, before turning to controlled feeding and supplementation studies that have measured methylation directly in human adipose tissue. We then review the parallel and more extensive literature documenting that fish oil supplementation reduces inflammatory gene expression and macrophage infiltration in adipose tissue, and close by considering methodological and mechanistic questions that the field has yet to resolve, including the extent to which observed transcriptional effects of omega-3 fatty acids are actually mediated by DNA methylation at all.

Epigenome-Wide Association Studies of Dietary Fatty Acid Intake and Blood DNA Methylation

The first generation of epigenome-wide evidence linking omega-3 fatty acid exposure to DNA methylation came largely from population studies of habitual dietary intake rather than controlled adipose tissue sampling. In the Yup'ik population of Alaska, whose traditional diet provides an unusually wide range of marine-derived n-3 fatty acid intake, Aslibekyan and colleagues related red blood cell n-3 fatty acid biomarkers to genome-wide leukocyte DNA methylation and identified methylation at specific CpG sites, including loci near genes involved in lipid and inflammatory signaling, that varied significantly with n-3 fatty acid status, providing early population-level evidence that habitual omega-3 exposure leaves a detectable epigenetic signature [5]. A subsequent genome-wide analysis of whole peripheral blood in an independent human cohort similarly found that circulating fatty acid profiles, including omega-3 and omega-6 species, were associated with methylation at numerous CpG sites, with pathway analysis of the associated genes implicating lipid metabolism and immune and inflammatory signaling networks, reinforcing the idea that fatty acid-methylation associations are not confined to a single population or dietary pattern [6]. Because whole blood integrates methylation signals across multiple leukocyte subtypes, these associational designs cannot on their own establish adipose tissue relevance, but they nonetheless motivated more tissue-specific and intervention-based designs, and they established the analytic template, careful control for cell composition, principal-component correction, and array-wide false discovery correction, that later adipose tissue studies would adopt.

Distribution of primary studies synthesized in this review by biological sample type (blood/leukocyte/mononuclear cell, human adipose tissue, or in vitro/animal model), counted from the 15 primary empirical studies of dietary fatty acid intake, DNA methylation, and/or inflammatory gene expression cited in this review.



A more recent epigenome-wide association study of circulating IL-6, the key downstream cytokine of adipose tissue NF-kB signaling, in a large twin and family-based cohort found that dozens of CpG sites, several with established roles in immunometabolic regulation and cardiometabolic disease risk, were robustly associated with circulating IL-6 concentrations independent of body mass index, and that a subset of these methylation-IL-6 associations showed evidence consistent with a causal, upstream role of methylation rather than a purely reactive one [7]. Although this study did not directly manipulate dietary fat, it provides an important epigenome-wide reference map of the methylation architecture surrounding a cytokine that fish oil supplementation studies consistently report suppressing, and it illustrates a broader point relevant to the entire field: EWAS designs are well suited to nominate candidate loci that mechanistic and interventional fish oil studies can subsequently test directly in adipose tissue.

Complementary pediatric evidence has extended EWAS designs to prenatal and early-life fish oil exposure. In neonates born to mothers randomized to fish oil supplementation during pregnancy, Amarasekera and colleagues performed epigenome-wide profiling of cord blood CD4-positive T cells and identified numerous differentially methylated CpG sites associated with maternal fish oil exposure, several annotated to genes involved in immune cell differentiation and inflammatory signaling, suggesting that the epigenetic imprint of omega-3 exposure on immune-relevant loci can be established in utero [8]. A parallel pilot study applying genome-wide methylation arrays to mononuclear cells from young infants randomized to postnatal fish oil supplementation similarly identified candidate differentially methylated sites, several near genes implicated in inflammatory and immune pathways, although the authors emphasized that the modest sample size of a pilot design limited statistical power and required replication in larger cohorts [9]. Taken together, these EWAS-style investigations across the life course converge on a consistent conclusion: omega-3 fatty acid exposure, whether assessed through habitual diet, biomarker status, or controlled supplementation, is reproducibly associated with DNA methylation differences that disproportionately annotate to immune and inflammatory gene networks, even though the specific CpG sites identified vary considerably across studies, tissues, and developmental stages.

DNA Methylation Changes in Adipose Tissue Following Omega-3/Fish Oil Intervention

Selected studies of DNA methylation in relation to dietary fatty acid or fish oil exposure, by tissue/cell type and design.

Study	Tissue/cell type	Design	Key methylation-related finding
do Amaral et al. 2014	Blood	Overweight women, energy-restricted diet with or without fish oil	Distinct global DNA methylation trajectory in the fish oil-supplemented group
Perfilyev et al. 2017	Subcutaneous adipose tissue	Randomized controlled overfeeding trial, 7 weeks, PUFA vs SFA	Genome-wide differentially methylated CpG sites distinguished by overfed fat type
Orozco et al. 2018 (METSIM)	Subcutaneous adipose tissue	Cross-sectional epigenome-wide association study, adult men	Thousands of CpGs associated with obesity, insulin resistance, and lipid traits
Karimi et al. 2017 (OmegAD)	Blood leukocytes	Randomized controlled trial, 6-month DHA-rich fish oil supplementation	Net decrease in global and site-specific DNA methylation after supplementation
Samblas et al. 2019	Preadipocyte/macrophage-like cell models	In vitro palmitic acid vs DHA treatment	Inflammatory gene expression changed without corresponding promoter methylation change

Direct adipose tissue evidence is sparser than the blood-based literature but has grown steadily through controlled feeding studies. In one of the earliest human intervention studies to combine an energy-restricted diet with fish oil supplementation, Amaral and colleagues followed overweight women through a hypocaloric intervention with or without added fish oil and reported that global DNA methylation changed over the course of the intervention, with the fish oil-supplemented group showing a distinct methylation trajectory relative to the diet-only comparison group, an early signal that omega-3 fatty acids can modify the epigenetic response to caloric restriction itself rather than acting independently of it [10]. A methodologically more rigorous randomized controlled trial by Perfilyev and colleagues overfed healthy volunteers with muffins enriched in polyunsaturated fat (predominantly linoleic acid rather than marine omega-3s) or saturated fat for seven weeks and performed genome-wide DNA methylation profiling of subcutaneous adipose tissue biopsies before and after the intervention, finding several hundred differentially methylated sites that differed by the type of dietary fat overfed, including loci annotated to lipid metabolism and inflammatory gene networks, and establishing that dietary fat quality, not merely caloric surplus, can rapidly reshape the human adipose tissue methylome within weeks [11]. Although the specific overfed fatty acid in that trial was of the omega-6 rather than omega-3 class, its design remains the clearest randomized controlled demonstration to date that adipose tissue DNA methylation is dynamically responsive to dietary polyunsaturated fatty acid composition, and it provides the closest available benchmark against which fish oil-specific adipose methylation effects can be interpreted.

Population-scale mapping of the adipose tissue methylome has further clarified which genomic regions are most likely to be nutritionally responsive. In the METSIM cohort, Orozco and colleagues generated an epigenome-wide map of subcutaneous adipose tissue DNA methylation in several hundred Finnish men and identified thousands of CpG sites associated with obesity, insulin resistance, and circulating lipid traits, several of which mapped to genes with recognized roles in adipose inflammation and immune cell infiltration, providing a population-level reference architecture of adipose tissue methylation against which more targeted dietary fatty acid studies can be benchmarked [12]. At the cellular mechanistic level, Samblas and colleagues directly tested whether the anti-inflammatory transcriptional effects of DHA in preadipocyte and macrophage-like cell models were mediated by promoter methylation of a panel of inflammation-related genes and found that, despite clear differential expression of these genes following palmitic acid versus DHA treatment, the corresponding promoter CpG methylation states were largely unchanged, leading the authors to conclude that DHA's acute anti-inflammatory transcriptional effects in these cell models operate largely independently of DNA methylation, at least on the time scale and at the specific CpGs examined [13]. This finding introduces an important caveat that recurs throughout the field: robust omega-3-induced changes in inflammatory gene expression do not necessarily imply, and in some well-controlled cellular experiments explicitly do not require, a concomitant change in promoter DNA methylation, so that methylation and expression should be treated as related but mechanistically separable readouts rather than as interchangeable proxies for one another.

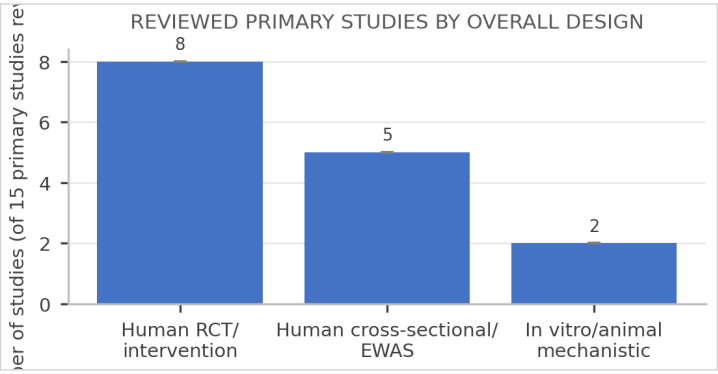
Animal model work has continued to probe this relationship using genome-scale profiling in whole adipose depots rather than cell lines. In diet-induced obese mice, Simão and colleagues supplemented a high-fat diet with fish oil and reported that the fish oil-supplemented animals showed attenuated weight gain and adiposity alongside altered expression of genes governing adipocyte differentiation, lipid handling, and inflammation in visceral adipose tissue, with the authors specifically implicating epigenetic modulation, including altered expression of genes encoding chromatin-modifying enzymes, as a plausible mechanistic contributor to the metabolic phenotype [14]. While methylation was not measured directly at single-CpG resolution genome-wide in that study, its integration of dietary fish oil, adipose transcriptional profiling, and epigenetic gene expression readouts exemplifies the kind of multi-layered design that will be needed to resolve whether adipose tissue DNA methylation is a cause, a correlate, or a largely epiphenomenal companion of the well-established anti-inflammatory transcriptional effects of fish oil in this tissue.

Fish Oil, DNA Methylation, and Inflammatory Gene Expression in Adipose Tissue and Immune Cells

The evidence that fish oil suppresses inflammatory gene expression in adipose tissue and closely related immune compartments is considerably more extensive, and more consistent, than the methylation literature specifically. In a landmark randomized controlled trial in severely obese, nondiabetic patients awaiting bariatric surgery, Itariu and colleagues administered long-chain n-3 PUFAs for eight weeks preoperatively and found reduced expression of pro-inflammatory genes and diminished macrophage marker

expression in surgically obtained adipose tissue, together with lowered circulating inflammatory markers, providing direct human adipose tissue evidence that fish oil intervention measurably dampens the tissue's inflammatory transcriptional program [15]. Complementing this tissue-level evidence, Spencer and colleagues used adipose tissue biopsies from insulin-resistant human subjects before and after omega-3 fatty acid supplementation and demonstrated a reduction in the number and altered activation phenotype of adipose tissue macrophages, the principal cellular source of TNF-alpha and other pro-inflammatory cytokines within obese fat, indicating that fish oil's anti-inflammatory transcriptional effects in adipose tissue are mediated at least in part through changes in resident immune cell populations rather than through adipocyte-intrinsic signaling alone [16]. More recently, Lee and colleagues examined the NLRP3 inflammasome pathway, an upstream activator of interleukin-1beta processing that operates in concert with NF-kB signaling in obese adipose tissue, and reported that omega-3 fatty acid exposure suppressed NLRP3 inflammasome gene and protein expression in adipose tissue and isolated stromal vascular cells from individuals with obesity, extending the anti-inflammatory footprint of fish oil beyond the classical TNF-alpha and IL-6 axis to innate immune sensing pathways more broadly [17].

Distribution of the same 15 primary studies by overall design (randomized or controlled human intervention, human cross-sectional/observational or epigenome-wide association design, or in vitro/animal mechanistic model), illustrating that human intervention studies dominate the fish oil and inflammatory gene expression literature relative to methylation-specific designs.



Peripheral blood mononuclear cells, though not adipose tissue proper, have provided some of the most detailed genome-wide characterizations of fish oil's transcriptional anti-inflammatory program and are frequently used as an accessible proxy for systemic and adipose-adjacent inflammatory tone. Bouwens and colleagues administered high-dose fish oil to healthy men for weeks and performed whole-genome expression profiling of blood mononuclear cells, finding that more than a thousand genes shifted their expression toward a less atherogenic and less inflammatory transcriptional profile, with marked downregulation of pathways converging on NF-kB-dependent inflammatory signaling [18]. The OmegAD study of elderly participants randomized to DHA-rich fish oil supplementation subsequently applied genome-wide methylation profiling specifically to blood leukocytes and reported a net decrease in global and site-specific DNA methylation following six months of supplementation, with several of the affected loci mapping to genes involved in immune and inflammatory regulation, offering some of the most direct human evidence to date that sustained fish oil supplementation can measurably alter leukocyte DNA methylation in parallel with its well-documented anti-inflammatory transcriptional effects [19]. Synthesizing this cellular and tissue-level literature, a review by Pahlavani and colleagues catalogued the principal molecular mechanisms proposed to mediate omega-3 polyunsaturated fatty acids' anti-inflammatory actions in adipose tissue, including direct and indirect inhibition of NF-kB activation, activation of the nuclear receptors PPAR-gamma and PPAR-alpha, engagement of the G-protein-coupled receptor GPR120, and generation of specialized pro-resolving lipid mediators, situating epigenetic modification as one plausible but not yet definitively established mechanism among several converging pathways [20].

Mechanistic and Methodological Considerations

Several methodological themes recur across this literature and merit explicit discussion. First, tissue specificity matters considerably: the majority of genome-wide methylation evidence for fish oil and omega-3 fatty acid exposure derives from peripheral blood leukocytes or mononuclear cells rather than adipose tissue itself, reflecting the relative ease of blood sampling in large human cohorts and repeated-measures intervention designs [5,6,19,7]. Because leukocyte and adipose tissue methylomes are only partially correlated, and because adipose tissue itself is a heterogeneous mixture of adipocytes, preadipocytes, endothelial cells, and infiltrating macrophages and lymphocytes whose relative proportions shift with adiposity and inflammatory state, findings from blood cannot be assumed to generalize directly to fat, a limitation acknowledged in the methodological literature on EWAS design more broadly [4] and one that the adipose-specific intervention studies reviewed here [10,11,12,14] were explicitly designed to address, albeit typically in smaller samples than blood-based cohorts allow.

Second, the relationship between DNA methylation change and inflammatory gene transcription change is not automatic, and the cellular work of Samblas and colleagues stands as a useful corrective to any assumption that methylation is the default or necessary mechanism underlying fish oil's transcriptional effects [13]. Given that the gene-expression literature on fish oil's anti-inflammatory action in adipose tissue and immune cells is considerably larger and more consistent than the methylation-specific literature [18,15,16,17,20], a plausible synthesis is that omega-3 fatty acids exert much of their acute anti-inflammatory transcriptional effect through non-methylation mechanisms, such as direct fatty acid receptor signaling, altered eicosanoid balance, and interference with NF-kB nuclear translocation, while a smaller, more gene- and locus-specific set of methylation changes accumulates with more prolonged exposure and may contribute to longer-term or heritable aspects of the phenotype, as suggested by the OmegAD leukocyte findings after six months of supplementation [19] and by prenatal exposure effects detectable in neonatal immune cells [8].

Third, dose, duration, fatty acid composition, and population characteristics vary substantially across the reviewed studies, from single-digit-week overfeeding challenges with omega-6-predominant polyunsaturated fat [11] to multi-month DHA-rich supplementation in elderly adults [19] to habitual dietary exposure in an Indigenous population with naturally high marine fatty acid intake [5], and this heterogeneity likely explains why no single CpG site or gene has yet emerged as a universally replicated biomarker of fish oil exposure in the way that, for example, smoking-associated methylation at AHRR has become a benchmark locus in the broader EWAS literature. Larger, standardized, adipose tissue-focused randomized trials using

contemporary EPIC array or whole-genome bisulfite sequencing platforms, ideally paired with matched inflammatory gene expression and adipose tissue macrophage phenotyping as in the Itariu and Spencer designs [15,16], will be needed to determine whether specific, reproducible adipose tissue methylation signatures of dietary fish oil intake exist and whether they carry independent prognostic value for cardiometabolic risk beyond what gene expression and circulating inflammatory markers already provide.

Selected studies of fish oil or omega-3 fatty acid effects on inflammatory gene expression in adipose tissue and immune cells.

Study	Population/model	Intervention	Principal inflammatory outcome
Itariu et al. 2012	Severely obese, nondiabetic, presurgical	Long-chain n-3 PUFA, 8 weeks preoperative	Reduced adipose pro-inflammatory gene expression and macrophage marker expression
Spencer et al. 2013	Insulin-resistant adults	Omega-3-acid ethyl esters, 4 g/day, 12 weeks	Decreased adipose tissue macrophage number and MCP-1 expression
Lee et al. 2019	Adults with obesity	Human adipose tissue and stromal vascular cells	Suppressed NLRP3 inflammasome gene and protein expression
Bouwens et al. 2009	Healthy men	High-dose EPA/DHA fish oil supplementation, weeks	Over 1,000 blood mononuclear cell genes shifted toward an anti-inflammatory profile
Pahlavani et al. 2017	Narrative review	Synthesis across human and preclinical studies	Catalogued NF-kB, PPAR, GPR120, and pro-resolving mediator mechanisms of omega-3 action

Conclusion

The literature reviewed here supports a coherent, if still incomplete, picture. Dietary and supplemental fish oil and omega-3 fatty acid intake are associated with DNA methylation differences detectable by epigenome-wide approaches in blood, cord blood immune cells, and, in a smaller number of controlled feeding studies, adipose tissue itself, with the affected loci disproportionately annotating to immune and inflammatory gene networks [5,6,8,9,19,7]. In parallel, and on a considerably firmer evidentiary base, fish oil supplementation reduces inflammatory gene expression, macrophage infiltration, and NF-kB pathway and NLRP3 inflammasome activity in human adipose tissue and peripheral immune cells [15,16,17,18,20]. Direct, well-powered adipose tissue epigenome-wide association studies of fish oil intake remain comparatively rare, and mechanistic cell-based work indicates that DNA methylation is neither a universal nor a necessary mediator of omega-3 fatty acids' anti-inflammatory transcriptional effects [13], underscoring that methylation and gene expression should be interpreted as related but distinct layers of regulation. As methylation array and sequencing technologies become more accessible and as population biobanks increasingly pair dietary biomarker data with adipose tissue multi-omic profiling, the field is well positioned to determine whether specific, reproducible adipose tissue methylation signatures of fish oil intake exist, whether they causally contribute to the well-documented suppression of inflammatory gene expression in this tissue, and whether such signatures could eventually serve as objective biomarkers of dietary omega-3 adequacy or long-term cardiometabolic benefit.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Nielsen S conceived the review, conducted the literature search, and drafted the manuscript. Kralj J contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Gruber S contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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