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Diarrhea induced by insufficient fat absorption in weaned piglets: Causes and nutrition regulation

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ABSTRACT

Fat is one of the three macronutrients and a significant energy source for piglets. It plays a positive role in maintaining intestinal health and improving production performance. During the weaning period, physiological, stress and diet-related factors influence the absorption of fat in piglets, leading to damage to the intestinal barrier, diarrhea and even death. Signaling pathways, such as fatty acid translocase (CD36), pregnane X receptor (PXR), and AMP-dependent protein kinase (AMPK), are responsible for regulating intestinal fat uptake and maintaining intestinal barrier function. Therefore, this review mainly elaborates on the reasons for diarrhea induced by insufficient fat absorption and related signaling pathways in weaned-piglets, with an emphasis on the intestinal fat absorption disorder. Moreover, we focus on introducing nutritional strategies that can promote intestinal fat absorption in piglets with insufficient fat absorption-related diarrhea, such as lipase, amino acids, and probiotics.

1. Introduction

Early weaned strategy has been widely applied in pig production, contributing to the improvement the productivity and efficiency of pig-farms. However, during the weaning period, physiological, stress and diet-related changes affect the absorption of dietary fat in piglets, leading to dysfunction of intestinal barrier function, diarrhea, growth retardation, and even death in piglets. In this regard, the development of the pig farming industry has been severely hampered (Boontiam et al., 2022; Campbell et al., 2013; Liu et al., 2019; Yang et al., 2019). Fat, as an important source of energy, plays a crucial role in maintaining animal intestinal health and promoting growth. In livestock and poultry, lipids are generally fed piglets to provide energy and improve fat absorption. Triglycerides are the main fat component in pig diet, and most of the fatty acids in the feed are bound to triglycerides. However, factors, such as carbon chain length and unsaturated fatty acid to saturated fatty acid ratio, influence the abundance of bacteria in piglets, which may result in inadequate fat absorption, even worsen piglet diarrhea, and diminishing growth (Mehta et al., 2021). To address such issues, feed additives such as lipase, functional amino acids, and probiotics, are widely used to regulate digestion, absorption, and metabolism of fat and other nutrients, which prevent piglet diarrhea and promote growth (Asadi Shahmirzadi et al., 2020; Martinez-Guryn et al., 2018; Xu et al., 2021). In this review, we first describe the absorption process of fat in intestinal epithelial cells and its related disorders. Secondly, we discuss molecular mechanisms that regulate intestinal fat absorption, and nutritional solutions that assist in maintaining the intestinal health of weaned piglets, such as lipase, amino acids, and probiotics.

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2. The absorption process of fat and reasons of fat absorption disorders in piglets

2.1. The absorption process of fat in intestinal epithelial cells

Fat is a concentrated source of energy, providing more than twice the calories per gram compared to carbohydrates and proteins. In terms of its composition, fat is composed of triglycerides, which consist of glycerol and fatty acids. Fat absorption mainly occurs in the small intestine (Shao et al., 2022; Zhang, 2022). Medium- and short-chain triglycerides have a low esterification rate and stronger affinity for water than long-chain triglycerides. Most of them are directly absorbed without undergoing hydrolysis by lipase, and enter into blood circulation through intestinal epithelial cells. However, long-chain triglycerides require emulsification by bile salts in the intestine, transport into the intestinal epithelial cells by fatty acid transporters, and then resynthesize into triglycerides in the cells before entering the circulation system (Abumrad and Davidson, 2012; Hussain, 2014). Fatty acid translocase (CD36) is responsible for transferring long-chain fatty acids to fatty acid transporter 4 (FAFT4), which then conducts transmembrane transport of long-chain fatty acids by FAFT4 (Abumrad and Davidson, 2012).

2.2. The connection between insufficient fat absorption and diarrhea

In pig production, early weaning strategy is typically applied to improve the breeding efficiency of pigs. However, piglets have underdeveloped intestinal systems before and after weaning, with low activity of enzymes such as lipase, which results in poor digestion, absorption, wastage of nutrients and diarrhea (Fig. 1). In addition, weaning stress damages the intestinal barrier function of piglets and affects their physiological functions, especially their digestive and absorptive functions, and thus lowering the absorption of fat. The integrity of intestinal morphology and structure is the basis for the digestion and absorption of nutrients in the intestine. Stress and inadequate energy intake induce intestinal barrier damage in piglets, leading to intestinal inflammation, a reduction in the effective absorption area of nutrients, malabsorption of nutrients and poor growth performance (Kwak et al., 2022; Liu et al., 2019; Yamamoto et al., 2018). Weaning stress can also increase the risk of diseases caused by bacteria such as *Escherichia coli* and *Salmonella*, disrupt the gut microbiota, reduce the digestion and absorption of fat, and cause post-weaning diarrhea (Gresse et al., 2017; Liu et al., 2019; Yang et al., 2019). Furthermore, diarrhea activates the NF-κB signaling pathway, which regulates the inflammatory response and markedly diminishes the absorption of intestinal fatty acids in piglets, particularly medium-chain fatty acids (Zong et al., 2019). Under stress, the activity of lipase is significantly decreased, with pancreatic lipase activity at weaning only 1/300 of that at 8 weeks of age (Corring et al., 1978). After weaning, lipase activity reaches its lowest point on day 5 and then begins to rise from day 7 to 9, but it still does not reach the pre-weaning levels (Hedemann and Jensen, 2004). The abundance of small intestine fatty acid transport protein also significantly decreases on day 3 and 7 after weaning, which weaken the digestion and absorption of lipids in the intestine (He et al., 2022). Moreover, piglet diet changes from liquid milk, which is rich in easily digested and absorbed fat (with an apparent digestibility rate of 96%) to solid feed with less fat content, causing a decrease in feed and energy intake after weaning (Lallès et al., 2007). Fat is one of nutrients that has the greatest change in the weaning period and the damage to intestinal function significantly affected the absorption and metabolism of nutrients such as fat, carbohydrates and proteins after weaning (Shao et al., 2022; Yang et al., 2019). These all seriously affect the digestion, absorption and utilization of lipid substances in piglet feed, leading to insufficient energy intake and intestinal barrier dysfunction, exacerbating the weaning stress of piglets (Capurso et al., 2019; Hedemann and Jensen, 2004). When piglets cannot obtain sufficient energy from feed, they can only mobilize the body fat to meet their energy needs. However, the host fat reserves of weaning piglets cannot provide sufficient energy to meet their survival and growth needs (de Albuquerque Maia et al., 2014; He et al., 2018). Furthermore, during rapid growth and development stage after weaning, the increase in fat absorption of piglet can provide enough energy to improve improving piglets' stress resistance and later-stage fat deposition (Luo et al., 2018; Sarr et al., 2010; Yu et al., 2017).

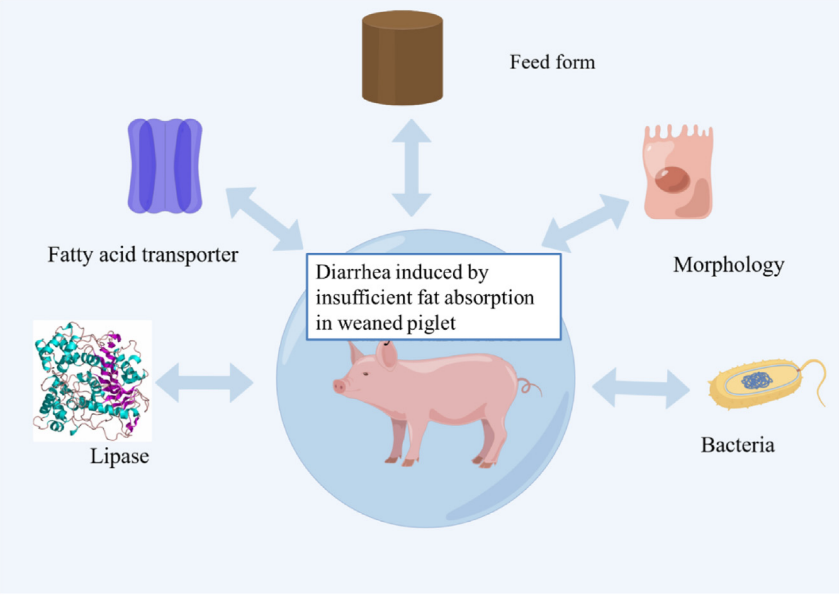

Fig. 1. Reasons of fat absorption disorders in weaned piglets.

3. Signaling pathways promoting intestinal fat absorption

In the gut, fatty acids promote lipid uptake through CD36, pregnane X receptor (PXR), and AMP-dependent protein kinase (AMPK) signaling pathways, delivering energy to cells and promoting gut health. When CD36 and PXR are knocked out, the intestine barrier is impaired and increased susceptibility to inflammation (Fig. 2).

3.1. CD36 signaling pathway

In the small intestine, dietary fat is digested by pancreatic lipase to produce fatty acids, which are then transported to intestinal epithelial cells and extra intestinal tissues by CD36, fatty acid transport proteins (FATPs), and fatty acid binding proteins (FABPs). CD36, which is located on the cell membrane, is a scavenger receptor expressed in multiple cell types (Li et al., 2022b). It primarily transports fatty acids and low-density lipoprotein, and mediates immune recognition, inflammation, molecular adhesion, and cell apoptosis (Son et al., 2018; Wang and Li, 2019). CD36 absorbs fatty acids in an endocytosis manner. Palmitoyl transferases (DHHC4 and DHHC5) palmitoylate CD36 on the Golgi apparatus and cytoplasmic membrane, respectively, to maintain its plasma membrane localization and promote its fatty acid absorption activity (Wang et al., 2019). Furthermore, during the process of fatty acid absorption, CD36 requires to undergo depalmitoylation for endocytosis to transport fatty acids into cells (Hao et al., 2020). Dysfunction of CD36 in intestine leads to abnormalities in fat absorption, which increases susceptibility to inflammation (Drover et al., 2005). CD36 knockout mice exhibits chronic neutrophil infiltration, inflammation, barrier dysfunction, reduced fat uptake, impaired lipid secretion, and chylomicron clearance in the intestine (Cifarelli et al., 2017; Drover et al., 2005). When the expression of CD36 in the intestine increases, it can promote the absorption of fatty acids and intestinal development, especially arachidonic acid and linoleic acid, increase intramuscular fat content in lean pigs, and improve meat quality (Guo et al., 2013; Ma et al., 2022). In addition, CD36 binds fatty acids and enters cells to transport them to mitochondria, converting anaerobic metabolism into aerobic metabolism, providing energy to cells and promoting immunity in *Salmonella*-infected mice (Mistry et al., 2021). Inhibition of CD36 expression reduces the uptake of fatty acids, resulting in insufficient energy supply and increased mouse mortality (Mistry et al., 2021).

3.2. PXR signaling pathway

The PXR is a xenobiotic sensor that acts as a transcription factor in the nucleus to protect cells from toxic damage. PXR is highly expressed in the liver and intestine, where it activates transcription factors such as CD36, increases lipid uptake and reduces fatty acid oxidation. Moreover, PXR inhibits inflammatory signaling pathways, such as NF-κB, regulates immune responses, and improves intestinal mucosal damage (Bautista-Olivier and Elizondo, 2022; He et al., 2017; Zhou et al., 2008). Studies have demonstrated that PXR is a regulator of intestinal homeostasis, and its deficiency is a preliminary driving factor for inflammation-induced intestinal barrier damage and increased permeability (Sun et al., 2022). When PXR is knocked out systemically or specifically in the intestine in mice, hyperlipidemia does not occur, and lipid uptake is absent (Sui et al., 2021). PXR activation regulates the gene expression of CD36 and cholesterol biosynthesis enzyme squalene epoxidase, leading to an increase in lipid uptake and cholesterol biosynthesis in cells (Gwag et al., 2019). In addition, the down-regulation of PXR reduces the expression of fatty acid binding protein 4 (FABP4) and the accumulation of cellular lipids, while overexpression of PXR promotes lipid accumulation and FABP4 expression. FABP4, also known as adipocyte fatty acid binding protein, belongs to a family of intracellular lipid transport proteins that reversibly bind to lipids and transport them to specific areas within cells, such as lipid droplets, endoplasmic reticulum, mitochondria or peroxisomes, as well as the cytoplasm or other enzymes (Yan et al., 2021).

3.3. AMPK signaling pathway

AMPK is a critical energy sensor, involving in multiple physiological processes (O'Neill, 2013). The demand for energy in the host activates AMPK, which induces the recruitment of CD36, leading to an increase in fatty acid absorption and β-oxidation (Balamurugan et al., 2022). Therefore, AMPK promotes the uptake of long-chain fatty acids by intestinal epithelial cells, and its absence impairs

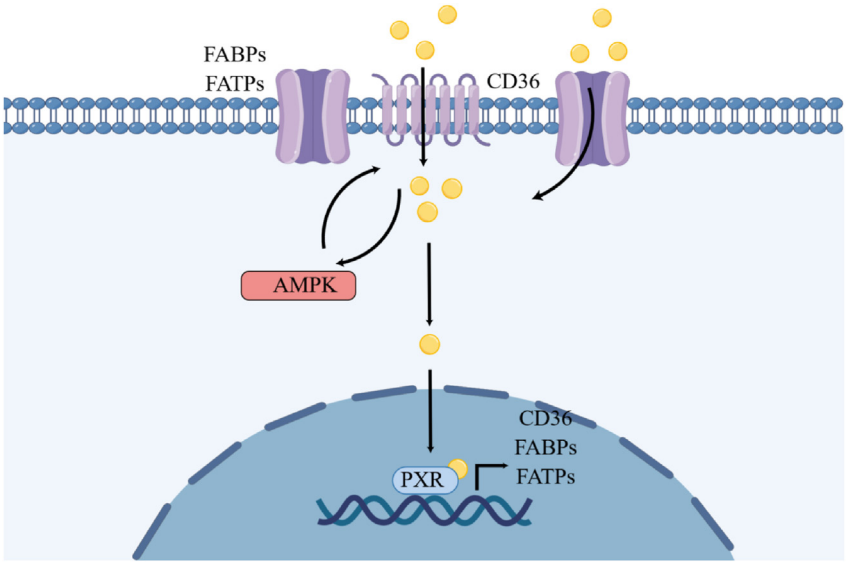

Fig. 2. Fatty acids uptake through CD36, PXR, and AMPK signaling pathways. CD36 = fatty acid translocase; PXR = pregnane X receptor; AMPK = AMP-dependent protein kinase; FATPs = fatty acid transport proteins; FABPs = fatty acid binding proteins.

the uptake of fatty acids in the intestine. The mechanism involves up-regulation of CD36 expression and promotion of CD36 translocation to the plasma membrane to facilitate the uptake of intestinal fatty acids (Wu et al., 2020). On the other hand, CD36 inhibits the expression of AMPK, and releases this inhibition by binding with fatty acids, thereby maintaining the cellular fatty acid homeostasis (Samovski et al., 2015).

4. Nutritional regulation

4.1. Fat

As one of three macronutrients, fat is an important energy source in pig diets due to its high energy content. Fatty acids are also important components of physiological activities such as inflammatory response, hormone synthesis, and cell membrane structure, which have a positive effect on maintaining intestinal health and improving production performance (Jolazadeh et al., 2019; Xu et al., 2021). Dietary supplementation of an appropriate amount of fat promotes feed intake and improves energy digestibility in weaned piglets. However, with increasing amounts of fat, feed intake and fat digestibility decreases (Adeola et al., 2013). This is because different sources of fat result in differences in carbon chain length, saturation, unsaturated fatty acid to saturated fatty acid ratio, and free fatty acid content, leading to significant differences in fat absorption and digestion by piglets. Medium-chain triglycerides have a low esterification rate and are directly absorbed without enzymatic hydrolysis, thus are easily oxidized to provide energy and pass through the mitochondrial membrane (van de Heijning et al., 2017). Lipase has a slower hydrolysis rate for long-chain triglycerides than that for medium-chain triglycerides (Hedemann et al., 2001). Therefore, the absorption rate of fatty acids is negatively correlated with carbon chain length, and shorter chains are more easily absorbed (Straarup et al., 2006). In addition, both short-chain and medium-chain fatty acids have antibacterial properties, which prevent pathogenic bacteria from overgrowing in the gastrointestinal tract (Jiao et al., 2023; Lauridsen, 2020). Generally, unsaturated fatty acids are more easily digestible than saturated fatty acids, which can be attributed to unsaturated fatty acid bonds have higher energy than saturated fatty acids, promoting the metabolism of saturated fatty acids (Lauridsen, 2020). Weng (2017) revealed that a mixture of lard, soybean oil, and coconut oil was preferred by weaned piglets soon after weaning, and feed conversion efficiency was better than that of a single oil. The mechanism is because the proportion of unsaturated fatty acids to saturated fatty acids is higher in this blend, and the proportion of medium- and short-chain fatty acids is more easily absorbed, similar to the composition of breast milk fatty acids (Ren et al., 2020). Therefore, during the weaning piglet stage, it is generally necessary to mix several types of lipids to approximate the composition of breast milk fatty acids as much as possible, in order to improve fat absorption in piglets and be better adapt to weaning.

4.2. Lipase

Lipase, also known as lipid degrading enzyme, can gradually hydrolyze triglycerides into glycerol and fatty acids for absorption and utilization by the body (Liu et al., 2020). Weaned piglets have a low fat digestion and absorption rate due to weaning stress and physiological factors that lead to insufficient secretion of endogenous lipases, such as pancreatic lipase and gastric lipase. Theoretically, dietary supplementation of exogenous lipase can supply the deficiency of endogenous lipase, alleviate weaning stress in piglets, and improve their fat absorption disorders (Liu et al., 2018; Portillo et al., 2021). At the same time, exogenous lipase can lower the incidence of intestinal diseases, especially nutrition-related diarrhea caused by poor fat digestion. Some studies found that lipase enhanced growth performance, digestive enzyme activity, nutrient digestibility and intestinal morphology in weaned piglets (Chen et al., 2014; Yang et al., 2017). However, compared with studies on phytase and other enzymes, the application research of lipase in weaned piglets is relatively rare.

4.3. Emulsifier

There is a significant difference in the apparent digestibility of fat between breast milk and feed for piglets, with one important reason being that breast milk fat is extensively emulsified. However, weaned piglets may not fully emulsify the fat in their feed due to insufficient bile secretion caused by weaning stress (Bach Korsholm Knudsen et al., 2021). Bile salts are excellent emulsifiers that can emulsify fat and form lipid particles, which increases the contact area between pancreatic lipase and fat, facilitates the action of lipases, and promotes fat digestion and absorption (Higuchi et al., 2020; Liu et al., 2022a). Exogenous addition of bile salts improves the growth performance, liver glucose and lipid metabolism, intestinal epithelial integrity and regulates the redox status of weaned piglets (Liu et al. 2022b, 2023).

4.4. Amino acids and their metabolites

Weaned piglets have reduced feed intake and weakened ability to digest and absorb fat, leading to inadequate energy supply in the intestine. Amino acids are important nutrients, which are preferentially used by the small intestine and are the main source of energy for intestinal mucosa (Zhou et al., 2018). For instance, ornithine enters the urea cycle in the body and is a precursor of arginine, citrulline, and proline, as well as a direct precursor of polyamines (spermidine, spermine, and putrescine), which can promote growth hormone secretion and young animal growth. Polyamines are momentary sources of cellular energy that reduce intestinal damage and lower inflammation, thereby alleviating weaning stress (Pruss et al., 2022; Wang et al., 2021). In addition, ornithine significantly increases the gene expression of CD36 in the liver, which alleviates chronic inflammation induced by obesity (Park et al., 2020). Supplementation of arginine in the diet improves pregnancy-induced insulin resistance, increases maternal concentrations of arginine and ornithine, placental glucose and fatty acid transport-related gene expression (including CD36), and promotes offspring growth and health (Robles et al., 2019). Alpha-ketoglutarate is a central molecule in the tricarboxylic acid cycle and a precursor of glutamate and glutamine, which is an important source of energy for intestinal cells. It plays an important role in regulating lipid metabolism and protecting the intestinal mucosal barrier. Studies have revealed that alpha-ketoglutarate activates the PXR signaling pathway, inhibits the NF-κB signaling pathway, repairs damaged intestinal mucosa, and exerts immune functions in the intestine (Bautista-Olivier and Elizondo, 2022; He et al., 2015, 2017). Alpha-ketoglutarate also increases intracellular levels of alpha-ketoglutarate, restores the function of aging stem cells, promotes the generation of brown and beige adipocytes in elderly mice, maintains the health of adipose tissue, suppresses chronic inflammation, and extends lifespan (Asadi Shahmirzadi et al., 2020; Tian et al., 2020). In our previous studies, we confirmed that ornithine-alpha-ketoglutarate, a complex salt of amino acids formed by the ionic bonding of ornithine and α-ketoglutarate, promoted the expression of CD36 and fat deposition in intestinal organoids, alleviated diarrhea and chronic oxidative stress (some of the data has not been published yet) (Li et al., 2020, 2022a). Based on the above, amino acids can maintain intestinal barrier function,

thereby promoting intestinal fat absorption and growth in weaned piglets.

4.5. Probiotics

Microbes play a vital role in the absorption of dietary fat in the gut, especially in the small intestine where they regulate host fat digestion and transportation (Chang and Martinez-Guryn, 2019; Coelho et al., 2019; Sato et al., 2016; Tang et al., 2020). Germ-free mice fed a high-fat diet exhibits higher fecal lipid levels compared to normal mice (Rabot et al., 2010). Martinez-Guryn et al. (2018) found that providing a high-fat diet resulted in fat malabsorption, particularly impairing lipid digestion and absorption in the small intestine of germ-free mice. High-fat diet in mice promotes the growth of specific microbial families such as Clostridiaceae and Streptococcaceae, which enhances fat absorption. Introducing microbes that aid in fat digestion to germ-free mice results in increased fat absorption even when fed a low-fat diet again (Martinez-Guryn et al., 2018). Mechanistically, gut bacteria promote fat absorption by activating adipocytes, producing chylomicrons, and emulsifying lipids (Sato et al., 2016). *Lactobacilli* and their metabolites also promote intestinal lipid absorption, decrease fat oxidation, and increase host fat (Zhong et al., 2022). However, some probiotics like *Lactobacillus rhamnosus GG* compete with host fatty acids for intestinal absorption, and inhibit the metabolism and absorption of fatty acids in the intestine of mice, thereby preventing fatty acid uptake and obesity (Jang et al., 2019). *Propionibacterium freudenreichii* subsp. *shermanii* enhances intestinal cell fat uptake and storage, while *E. coli* aids in lipid breakdown and reduces chylomicron circulation (Tazi et al., 2018).

Native pig breeds exhibit better fat absorption and diarrhea resistance abilities. For instance, Shaziling pigs have high levels of *Lactobacillus reuteri*, *Bifidobacterium adolescentis*, and *Butyrivibrio fibrisolvens*, especially *L. reuteri*, which increases CD36 and peroxisome proliferator activated receptor γ expression and promotes lean pig fat deposition while improving meat quality (Ma et al., 2022). Tibetan pigs possess high levels of Lactic acid bacteria, *Bifidobacteria*, and *Solobacterium*, promoting fat deposition, disease resistance, and stress tolerance (Shang et al., 2022). Fecal transplantation of Laiwu pigs into Duroc × Landrace × Yorkshire pigs increase *Bacteroides uniformis*, *Treponema_pectinovorum*, *Sphaerochaeta globosa*, *Hydrogenoanaerobacterium saccharovorans*, and *Pyramidobacter piscolens* in the gut, and consequently promoting fat deposition in the gut and liver (Xie et al., 2022).

5. Concluding remarks

Fat absorption alleviates intestinal barrier dysfunction and diarrhea in weaned piglets. In this review, we summarize the reasons for intestinal fat absorption disorders in weaned piglets and discuss the regulatory mechanisms of CD36, PXR, and AMPK signaling pathways. In addition, dietary fats, lipases, amino acids, and probiotics can regulate intestinal fat absorption and intestinal barrier function, reducing the occurrence of diarrhea. The review mainly describes a theoretical basis for regulating intestinal fat absorption in weaned piglets and elaborates nutritional regulation methods to prevent diarrhea induced by insufficient fat absorption disorders.

Author contributions

Yuying Li and **Pengjun Shi:** Investigation, Writing—original draft preparation. **Kang Yao**, **Qian Lin**, **Mansheng Wang** and **Hui Diao:** Writing—reviewing and editing. **Zhenping Hou** and **Wenjie Tang:** Conceptualization, Writing—reviewing and editing.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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