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Dietary DINCH exposure is associated with altered intestinal homeostasis under high-fat diet-induced metabolic stress in a sex-dependent manner

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ABSTRACT

Metabolic disorders such as obesity are driven by complex interactions between diet and environmental exposures, yet the impact of emerging plasticizers on intestinal homeostasis remains unclear. Di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), introduced as a safer alternative to phthalates, may contribute to metabolic reprogramming, particularly under high-fat diet (HFD) conditions. Building on findings of systemic metabolic and immune alterations, this study investigates whether DINCH exposure affects intestinal macroscopic morphology, mucosal immune homeostasis, and epithelial barrier-associated gene expression under HFD-induced metabolic dysregulation in a sex-dependent manner.

Using male and female mice exposed to HFD with or without DINCH, we performed analysis of intestinal morphology, mucosal and systemic immune cell populations, and barrier-associated gene expression. DINCH exposure modified HFD-induced intestinal remodeling, as evidenced by increased colon length compared to HFD only controls, suggesting altered intestinal adaptation under metabolic stress. Immunological profiling revealed sex-specific effects, with females showing restricted systemic immune modulation characterized by reduced splenic Th2 cells. In contrast, males exhibited broader changes, including increased Th1 and Th17 cell populations in Peyer's patches, indicating enhanced mucosal pro-inflammatory immune activation.

DINCH exposure was associated with altered expression of genes involved in epithelial homeostasis in ileum of male mice. Specifically, the tight junction genes *Cldn8* and *Ocln* were downregulated, while *Tff3*, involved in epithelial repair, and the barrier-associated gene *Muc2* were upregulated, indicating transcriptional alterations related to epithelial homeostasis and stress. Importantly, these changes were transcriptional only and provide no structural or functional evidence of intestinal barrier impairment. In contrast, females showed fewer epithelial transcriptional alterations, supporting a sex-dependent response to DINCH exposure.

Collectively, DINCH exposure was linked to intestinal macroscopic morphology, immune balance, and barrier-related gene expression in a sex-dependent manner within an HFD background. These results extend prior evidence of systemic metabolic effects and identify the intestine as potential target of DINCH under obesogenic conditions.

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1. Background

The global rise in metabolic disorders, including obesity and its associated comorbidities, has been closely linked to both dietary patterns and environmental exposures (Noubiap et al., 2025). High-fat diet (HFD) is a well-established driver of systemic metabolic dysfunction, promoting lipid imbalance, chronic low-grade inflammation, and impaired energy homeostasis (Yang et al., 2012). In parallel, there is growing recognition that environmental chemicals can act as metabolism-disrupting compounds, interfering with endocrine, metabolic, and immune pathways and thereby contributing to disease susceptibility (La Merrill et al., 2025). Given the high percentage of obese people in many countries the question arises if and how the effects of a HFD and xenobiotic exposure are interlinked.

Di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH) has been introduced as an alternative plasticizer to replace conventional phthalates, which are known for their endocrine-disrupting effects (Gore et al., 2015). Although DINCH has been promoted as a safer alternative to conventional phthalates, growing evidence suggests that both DINCH and its primary metabolite, monoisononyl cyclohexane-1,2-dicarboxylate (MINCH), may not be biologically inert (Campioli et al., 2017; Harmon and Otter, 2022; Krupka et al., 2025; Schaffert et al., 2022; Schaffert et al., 2021; Testai et al., 2016). In a recent study using the same experimental cohort as investigated here, it was demonstrated that dietary DINCH exposure induces systemic metabolic reprogramming under HFD conditions (Krupka et al., 2025). Specifically, DINCH was associated with alterations in lipid handling and energy metabolism, accompanied by proteomic changes pointing toward modulation of inflammatory and immune-related pathways (Aldehoff et al., 2025; Krupka et al., 2025). Notably, these effects were sex-dependent, with male mice exhibiting a more pronounced obese phenotype and stronger metabolic perturbations compared to females (Krupka et al., 2025). In addition, circulating markers such as interleukin-17 (IL-17) in blood serum were elevated in males, suggesting a shift toward a pro-inflammatory state (Krupka et al., 2025). However, intestinal morphology, immune responses in Peyer's patches and spleen as well as epithelial barrier-related gene expression were not investigated in that study and are addressed here for the first time.

The primary site of dietary uptake of chemicals such as DINCH is the intestine, which represents a central interface between diet, environmental exposures, and host physiology. Beyond its role in nutrient absorption, it is a key regulator of immune homeostasis and barrier integrity, integrating signals from dietary components, the microbiome, and xenobiotics. Disruption of intestinal function is increasingly recognized as a critical factor in the development and progression of metabolic diseases (Hyun and Cheon, 2025). Both, HFD and environmental contaminants have been shown to affect macroscopic marker of intestinal morphology, epithelial turnover, and mucosal immune responses (Dang et al., 2023; Ma et al., 2026). However, whether DINCH contributes to intestinal dysfunction, particularly in the context of pre-existing metabolic stress, has not yet been systematically addressed.

Importantly, susceptibility to metabolic and immunological disturbances is influenced by sex-specific factors, including differences in hormone signaling, immune regulation, and energy metabolism (Klein and Flanagan, 2016; McClements et al., 2025). Despite this, sex-dependent effects of environmental chemicals on intestinal homeostasis remain insufficiently characterized. The previously observed sex-specific systemic effects of DINCH (Aldehoff et al., 2025; Krupka et al., 2025) highlight the need to further investigate whether similar dimorphisms extend to the intestinal compartment.

2. Objective

Building on prior findings, the present study serves as a follow-up investigation using the samples obtained in the earlier study (Krupka et al., 2025) to specifically address intestinal outcomes. We hypothesized that DINCH exposure, in combination with an HFD, modulates intestinal morphology, immune homeostasis, and epithelial integrity in a sex-dependent manner. To test this, we performed an integrated analysis of intestinal gross morphology, mucosal and systemic immune cell populations, and barrier-associated gene expression in male and female mice. By linking systemic metabolic alterations with local intestinal responses, this study aims to provide a more comprehensive understanding of how exposure to DINCH influences host physiology and to identify potential mechanisms underlying its metabolism-disrupting effects.

3. Methods

3.1. Animal study design and ethics approval

The animal study has been previously described in detail by Krupka et al. (2025). All experiments were conducted in strict accordance with the guidelines of the local authorities of the State of Saxony, Germany, and approved by the responsible animal ethics committee (Landesdirektion Sachsen, Leipzig, TVV38/20, Germany).

In brief, C57BL/6NTac mice (Taconic Biosciences, USA) were bred and maintained under specific pathogen-free conditions at the SIKT, Saxon Incubator for Clinical Translation (University of Leipzig, Leipzig, Germany). Animals were housed in groups of 3-4 per cage under controlled environmental conditions (23 °C, 12-h light/dark cycle) with ad libitum access to water and food.

Mice (n = 3-4) were randomly assigned at 3 weeks of age to ensure comparable baseline body weights across groups. At 4 weeks of age, dietary intervention was initiated and maintained for 16 weeks. Animals received either a standard chow diet (CD; V1534, 9 kJ% fat, Ssniff®, Germany) or a high-fat diet (HFD; 59 kJ% from fat; E15772-34, Ssniff®, Germany). The HFD was supplemented with 1,2-Cyclohexane dicarboxylic acid diisononyl ester (DINCH, IUPAC Bis(7-methyloctyl) cyclohexane-1,2-dicarboxylate, 95 %, CAS 166412–78-8, #AB440048, abcr GmbH, Germany) at two concentrations: 4500 ppm (low dose, LD) and 15,000 ppm (high dose, HD). Diets were prepared by the manufacturer (Ssniff Spezialdiäten GmbH, Soest, Germany). To prevent lipid oxidation, HFD pellets were stored at −20 °C until use. The DINCH doses were chosen to be comparable to those applied in the metabolome study by Langsch et al. (2018), in which Wistar rats were exposed to dietary DINCH over a period of 28 days. They were intended to enable comparison with previous toxicokinetic and metabolomic studies rather than to reproduce typical environmental human exposure. They should therefore be regarded as sustained high exposure conditions.

After the 16-week exposure period, mice were euthanized for endpoint analyses using a lethal dose of isoflurane (Baxter Deutschland GmbH, Germany), followed by cardiac puncture for serum collection. Spleen and Peyer's patches (small intestine) were collected and stored in BSS buffer (9.9 g/L Hank's Salt (#P04-32010P, PAN Biotech),17 mM $NaHCO_3$, 10 mM HEPES, pH 7.2) on ice until further processing. Tissue from ileum was dissected and snap-frozen immediately in liquid nitrogen for subsequent analyses presented in this paper.

The standard chow diet (SD) group served as an unexposed dietary reference. Because no SD + DINCH group was included, DINCH-associated effects were assessed by comparing the HFD + DINCH groups with HFD controls. This design identifies effects of DINCH within an HFD background but cannot determine whether comparable effects occur under standard-diet conditions or whether HFD modifies their magnitude or direction.

3.2. Immune cell isolation and flow cytometry

For isolation of single cells spleen and Peyer's patches were pulped through a 30 μm cell strainer. Erythrocytes were lysed in splenocyte suspension by resuspending the cell pellet in ammonium chloride-based lysis buffer (100 mM NH_4Cl, 20 mM HEPES, pH 7.2–7.4) for 7 min at

room temperature. The reaction was stopped by adding phosphate-buffered saline (PBS)/fetal calf serum (FCS) buffer (1 % [v/v] FCS, 1 x PBS) followed by centrifugation and washing to obtain erythrocyte-depleted splenocytes for downstream applications.

For the staining of surface parameters PBS/FCS buffer containing eBioscience™ Fixable Viability Dye eFluor™ 506 (dilution: 1:200) and appropriate diluted antibodies (Table S1) were added and incubated for 20 min at 4 °C. Afterwards, cells were washed in PBS buffer and fixed for 20 min by using Foxp3 Fixation/Permeabilization Concentrate and Diluent (#00-5523-00, Thermo Fisher Scientific). Following blocking FcR by using FcR Blocking Reagent (#130-092-575, Miltenyi Biotec), cells were stained intracellularly with fluorochrome-labeled antibodies (Table S1) for 20 min, all at 4 °C in saponin buffer (0.3 % [w/v] saponin, 2 % [v/v] FCS, 1 x PBS). Flow cytometric analysis was performed using Attune NxT Flow Cytometer (Thermo Fisher Scientific). FCS Express 7 Research Edition (De Novo Software) was used for data analysis.

After sequential gating on singlets, viable lymphocytes, $CD45^+$ $CD4^+$ T cells, T helper cell subsets were identified based on intracellular expression of the lineage-defining transcription factors T-bet (Th1), GATA3 (Th2), RORγt (Th17), and FoxP3 (Treg), as illustrated in Fig. S1.

3.3. Quantitative PCR for murine transcripts

Ileal tissue was stored at −80 °C. After thawing, 1000 µl Trizol was added prior to homogenization with a Tissue Lyser LT (6 min, 50 1/s, 2 stainless steel beads per vial; Qiagen, Hilden, Germany). The total RNA isolation was performed according to manufacturer's instructions. The RNA concentration was measured using NanoDrop system (Thermo Fisher Scientific). cDNA was synthesized from 1000 ng RNA following the instructions of the cDNA synthesis with the ImProm-II™ Reverse Transcription System (Promega, Mannheim, Germany).

The semi-quantitative PCR was performed on the Biomark HD system (Standard BioTools, San Francisco, CA, USA) using EvaGreen DNA binding Dye with BioMark™ 48.48 Dynamic Array Integrated Fluidic Circuits according to the manufactures recommendations.

All reactions were run in duplicates. Sequences of exon-spanning primers of target genes associated with intestinal homeostasis are listed in Supplementary Table S2. To quantify the relative expression, the expression of the gene of interest was normalized to the reference gene glycerinaldehyd-3-phosphat dehydrogenase (*Gapdh*; dCt).

3.4. Statistical analysis

The data were analyzed with GraphPad Prism 10. Significance was calculated by using the tests indicated in figure legends including ordinary one-way ANOVA followed by Sidak multiple comparison test respectively Kruskal-Wallis test followed by Dunn's multiple comparison test in case of failed Shapiro-Wilk test for normal distribution. To formally assess whether DINCH-associated responses differed between sexes, selected endpoints were additionally analyzed using two-way ANOVA including sex, DINCH exposure, and the sex × DINCH interaction. Values less than 0.05 were considered statistically significant. Data presented as individual mice and mean with standard deviation (SD; parametric statistics) or median with 95 % confidence interval (CI; non-parametric statistics). n = 3-4; p values are indicated as * $p < 0.05$, ** $p < 0.05$, *** $p < 0.001$.

4. Results

4.1. Dietary intake of DINCH affects intestinal macroscopic morphology in C57BL/6N mice

Recently, DINCH and its metabolites were identified as metabolism-disrupting chemicals associated with systemic alterations in lipid and energy metabolism as well as immune-relevant proteomic changes (Krupka et al., 2025). Building on this evidence, we investigated whether these metabolic perturbations are accompanied by functional and morphological effects in the intestine under conditions of dietary stress.

Mice were fed a HFD supplemented with two doses of DINCH (low dose/LD: 4500 ppm; high dose/HD: 15,000 ppm) for 16 weeks (Fig. 1A).

Colon length was assessed as a macroscopic parameter of intestinal morphology. While this parameter provides an overall assessment of intestinal morphology, it does not allow conclusions regarding the underlying histological alterations. HFD was associated with shorter colon lengths in male and female mice, which is a known phenomenon from literature (Fig. 1B and C) (Gulhane et al., 2016; Lindholm et al., 2013; Xie et al., 2020). However, mice exposed to DINCH in combination with a HFD exhibited a significant increase in colon length compared to the respective HFD control group, predominantly in female animals receiving LD (Fig. 1B and C). While not a specific marker of a single underlying process, altered colon length can be interpreted as an indirect indicator of chronic changes in intestinal physiology, such as epithelial turnover or tissue remodeling (Calzadilla et al., 2023; Chassaing et al., 2015; Süßkind-Schwendi et al., 2023). These findings suggest that DINCH exposure under conditions of diet-induced metabolic stress is associated with alterations in intestinal macroscopic morphology.

4.2. DINCH exerts sex-specific effects on systemic and mucosal Th cell polarization

As the previously published study indicated a Th17-mediated inflammatory response, as evidenced by elevated IL-17 serum concentrations in the same cohort (Krupka et al., 2025), we next assessed systemic and mucosal immune alterations focusing on the T helper (Th) cell subpopulations. Hence, Th cell subsets were analyzed in spleen and Peyer's patches based on the expression of lineage-defining transcription factors (T-bet (Th1), RORγt (Th17), GATA3 (Th2), and FOXP3 (T_{reg})).

Distinct sex-specific differences in the immunological response to DINCH exposure were observed. Male animals displayed pronounced alterations in both systemic and mucosal immunity. In the spleen, a decrease in Th2 cells was observed at the LD. Most notably, Peyer's patches showed a dose-independent increase in Th1 and Th17 cells, indicating a shift toward a pro-inflammatory mucosal immune phenotype (Fig. 2A and B). In addition, regulatory T cells (T_{reg}) were increased at the HD compared to the LD, representing a secondary dose-dependent effect within the mucosal compartment.

By contrast, in female animals, effects were restricted to the systemic compartment, where a reduction of Th2 cells in the spleen was detected at both LD and HD compared to HFD controls (Fig. 2A). No significant changes were observed in other Th subsets or in Peyer's patches in females.

4.3. Dietary exposure to DINCH alters intestinal barrier-related gene expression

To further investigate whether the observed morphological and immunological alterations were accompanied by transcriptional changes in intestinal homeostasis pathways, we performed a novel analysis of gene expression for a panel of genes involved in epithelial barrier function, mucosal integrity, and immune-epithelial interaction in ileal tissue.

In males, these changes were particularly evident in the ileum, where trefoil factor-3 (*Tff3*), which is widely regarded as a marker of epithelial restitution and mucosal repair, and mucin-2 (*Muc2*), the major structural component of the intestinal mucus layer, were significantly upregulated, alongside a reduction of the tight junction components claudin-8 (*Cldn8*) and occludin (*Ocln*). This pattern is consistent with epithelial stress (Fig. 3); however, functional barrier integrity was not assessed in the present study, and therefore no conclusions can be drawn regarding changes in intestinal permeability or barrier function. Moreover,

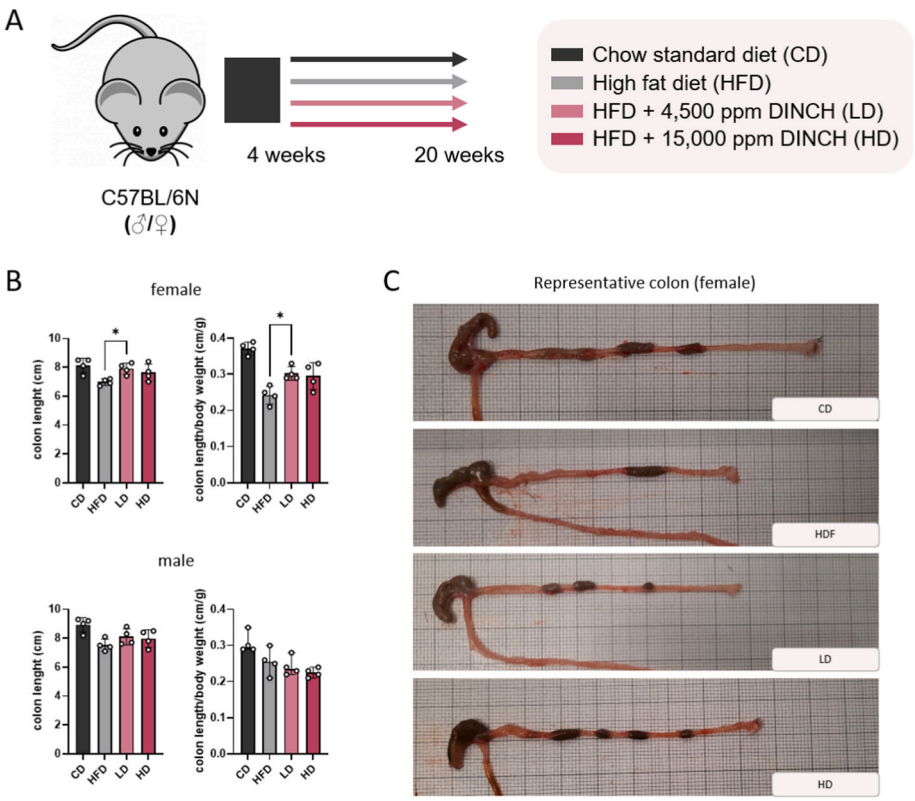


Fig. 1. Experimental setup and gut morphology. Experimental setup of mouse experiments (A). Colon length and colon length/body weight ratio of female and male mice after 16 weeks of feeding with HFD containing DINCH. During treatment mice were fed with a low dose (LD: 4500 ppm) and high dose of DINCH (HD: 15,000 ppm) and compared to mice fed with high-fat diet only (HFD). Data presented as individual mice and mean with SD (parametric statistics) or median with 95 % CI (non-parametric statistics) (A). Representative images of colon of female mice from each dietary group (B). Statistical analysis: Ordinary one-way ANOVA followed by Sidak multiple comparison test respectively Kruskal-Wallis test followed by Dunn's multiple comparison test in case of failed Shapiro-Wilk test for normal distribution. n = 4; p values are indicated as * $p < 0.05$.

expression of the antimicrobial protein regenerating islet-derived protein 3γ (*Reg3γ*) was decreased at HD compared with LD (Fig. 3). In contrast, such pronounced transcriptional alterations were less evident in females, highlighting sex-specific sensitivity to DINCH exposure.

Taken together, these findings suggest that DINCH exposure within an HFD background is associated with alterations of intestinal barrier-related gene expression in a sex-specific manner, with males showing more pronounced transcriptional alterations in genes associated with epithelial homeostasis.

4.4. Sex-dependent DINCH responses across intestinal endpoints

To formally assess whether the intestinal responses to DINCH differed between sexes, sex × DINCH interactions were additionally evaluated using two-way ANOVA. Significant interactions were identified for the colon length-to-body weight ratio (interaction $p = 0.0153$), Th1 cell frequency ($p = 0.001$), Muc2 expression ($p = 0.034$), and Ocln expression ($p = 0.0276$). These findings provide statistical support for sex-dependent effects of DINCH across morphological, immunological, and epithelial barrier-related endpoints. Given the relatively small sample size, however, these interactions should be interpreted with caution.

5. Discussion

The present study expands the previous characterization of systemic metabolic effects of DINCH under conditions of metabolic stress in this animal cohort (Krupka et al., 2025) by providing the first analysis of intestinal macroscopic morphology, mucosal immune responses and epithelial barrier-associated gene expression. Together, these new findings indicate that DINCH-associated metabolic disturbances are accompanied by sex-dependent alterations in intestinal homeostasis within an HFD background.

5.1. DINCH is associated with altered intestinal gross morphology under metabolic stress

A key finding of this study is the increased colon length observed in DINCH-exposed mice on an HFD background, most prominently in females at the LD. Although colon length is a relatively unspecific morphological parameter, it is widely regarded as an indirect readout of chronic changes in intestinal physiology, including epithelial turnover, smooth muscle tone, and tissue remodeling (Cao et al., 2023a; Luck et al., 2015) or inflammation (Fischer et al., 2020; Haange et al., 2019). In our study, colon length was higher under standard diet conditions, but markedly reduced under HFD. The HFD-associated reduction is consistent with previous studies and may reflect inflammatory remodeling (Gulhane et al., 2016), shifts in nutrient-sensing pathways (Lindholm et al., 2013), and altered epithelial renewal (Xie et al., 2020). However, as a macroscopic marker, colon length does not provide information on the underlying histological changes, such as epithelial architecture, crypt morphology, or inflammatory cell infiltration. Therefore, the observed differences should be interpreted as evidence of altered intestinal morphology rather than direct proof of tissue remodeling. Histopathological analyses would be required to determine the cellular basis of these morphological changes.

DINCH exposure partially reversed this effect and increased colon length compared to HFD controls, suggesting that DINCH modifies HFD-induced alterations. Mechanistically, HFD is known to affect intestinal structure through nutrient-sensing pathways, including peroxisome

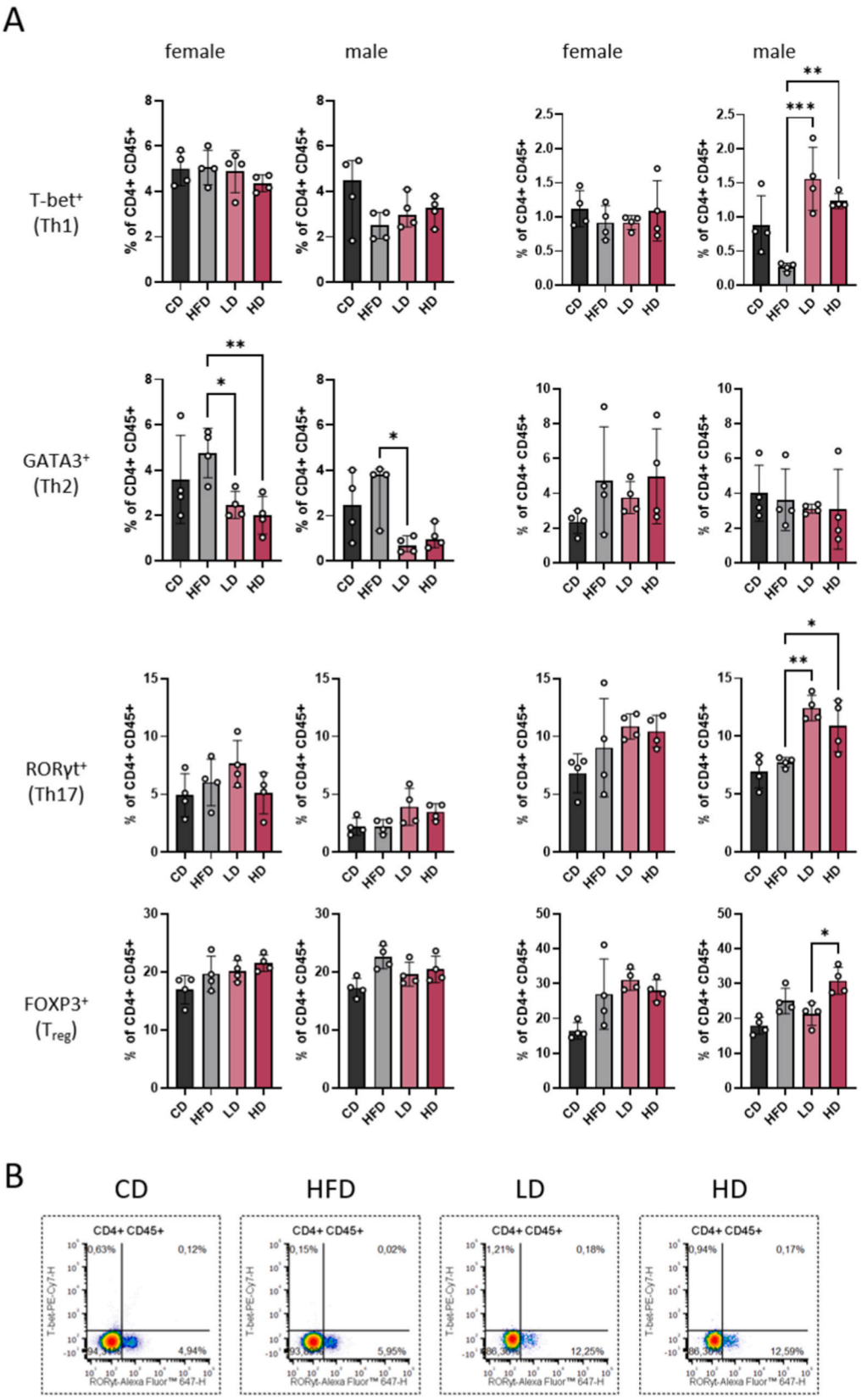


Fig. 2. Effects of dietary DINCH exposure on systemic and mucosal immune cells. Frequency of indicated Th cell subsets was measured by flow cytometry in spleen and Peyer's patches of female and male mice after 16 weeks of feeding with HFD containing DINCH (A). Representative flow cytometry dot plots of male mice from each dietary group showing the expression of T-bet and RORγt in Peyer's patches (B). Statistical analysis: Ordinary one-way ANOVA followed by Sidak multiple comparison test respectively Kruskal-Wallis test followed by Dunn's multiple comparison test in case of failed Shapiro-Wilk test for normal distribution. Data presented as individual mice and mean with SD (parametric statistics) or median with 95 % CI (non-parametric statistics). n = 4; p values are indicated as * $p < 0.05$.

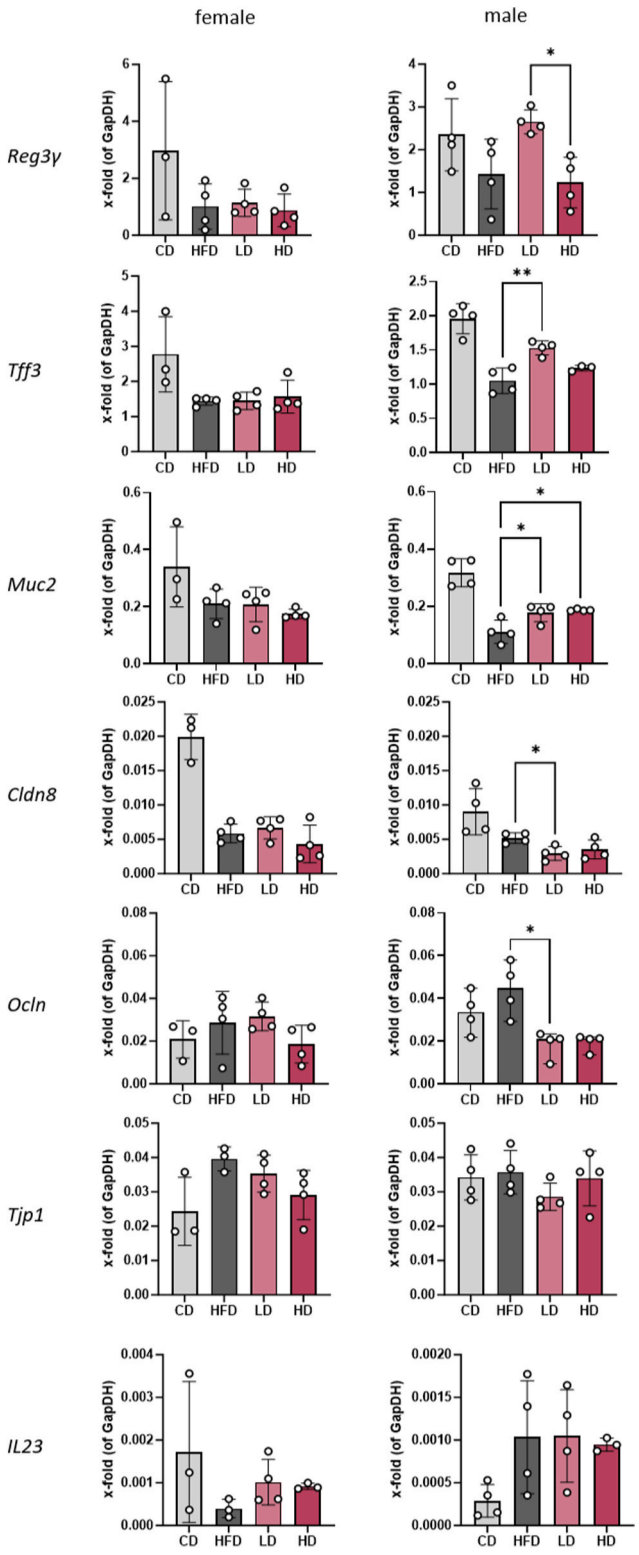


Fig. 3. Effect of dietary DINCH exposure on intestinal gene expression. Expression of indicated genes related to intestinal homeostasis measured by RT-PCR in ileum of female and male mice. Expression of genes of interest were normalized to housekeeping gene *GapDH* (delta Ct). Data presented as individual mice and mean with SD (parametric statistics) or median with 95 % CI (non-parametric statistics). Statistical test: Ordinary one-way ANOVA followed by Sidak multiple comparison test respectively Kruskal-Wallis test followed by Dunn's multiple comparison test in case of failed Shapiro-Wilk test for normal distribution. Outliers identified by Grubbs' test were excluded from the analysis. n = 3-4; p values are indicated as * $p < 0.05$.

proliferator-activated receptors (PPARs) (Stojanović et al., 2021) and AMP-activated protein kinase (AMPK) signaling (Chen et al., 2018; Lindholm et al., 2013; Zhang et al., 2022). In parallel, endocrine-disrupting chemicals (EDCs) such as phthalates can activate PPARα and PPARγ (Hurst and Waxman, 2003) and interfere with AMPK-related pathways (Peng et al., 2024), thereby affecting metabolic and inflammatory regulation in the gut. Although direct mechanistic evidence for DINCH remains limited, it may plausibly act through similar metabolic-immune axes, that regulate intestinal morphology, including colon length (Campioli et al., 2019).

The more pronounced morphological response observed in females may additionally reflect sex-dependent regulation of intestinal physiology. Biological sex influences intestinal homeostasis through sex chromosomes as well as gonadal hormones. In particular, estrogen receptors are expressed throughout the gastrointestinal tract (Liu et al., 2019), and estrogen signaling has been implicated in the regulation of epithelial ion transport, smooth muscle activity, and epithelial proliferation (Hogan et al., 2009; Tuo et al., 2011; Wada-Hiraike et al., 2006; Wan et al., 2023). These sex-dependent regulatory mechanisms could contribute to differences in how the intestine responds to combined dietary and environmental stressors. However, these observations do not establish that estrogen signaling directly mediates the DINCH-associated changes in colon length. Sex hormone concentrations, estrogen- or androgen-receptor activity, and intestinal motility were not assessed in the present study, and the contribution of these pathways therefore remains hypothetical.

Notably, DINCH is rapidly metabolized in vivo into secondary metabolites, including MINCH, which is formed during hepatic biotransformation processes (Krupka et al., 2025; Schütze et al., 2012; Silva et al., 2012). It has increasingly gained attention because some studies suggest that it may exert biological activity itself, including interference with PPAR pathways (Campioli et al., 2019; Schaffert et al., 2022; Useini et al., 2023). Thus, it is conceivable that not only the parent compound DINCH, but also its metabolites such as MINCH, could contribute to the observed intestinal and metabolic effects. More research is necessary to gain a deeper and more accurate understanding of how DINCH and/or MINCH disrupts intestinal integrity.

5.2. Sex-dependent immune modulation in systemic and mucosal compartments

The immunological analyses reveal a sex-specific pattern in DINCH-induced modulation of Th cell subsets. In females, immune alterations were restricted to the systemic compartment, where a consistent reduction in splenic Th2 cells was observed at both exposure doses. This shift suggests a selective sensitivity of type 2 immune responses to DINCH exposure in females, potentially indicating altered systemic immune regulation or impaired anti-inflammatory signaling (Bonder et al., 1999; Scott et al., 2023).

In contrast, male mice exhibited broader immunological changes affecting both systemic and mucosal compartments. While splenic effects were limited to a reduction in Th2 cells at the LD, the most pronounced changes were observed in Peyer's patches, where both Th1 and Th17 cell populations were increased independently of dose. This pattern indicates a shift toward a pro-inflammatory mucosal immune phenotype (Cao et al., 2023b), suggesting that DINCH exposure under HFD conditions may enhance intestinal immune activation specifically in males.

The novel observation of increased Th17 cells in Peyer's patches is consistent with the previously published finding of elevated circulating IL-17 in male mice of the same cohort (Krupka et al., 2025), thereby linking the earlier systemic observations with newly identified local intestinal immune alterations. These changes can contribute to chronic low-grade inflammation and heightened susceptibility to inflammatory tissue damage. The concomitant increase in T_{reg} at the HD may represent a compensatory response to counterbalance heightened inflammatory

signaling within the gut-associated lymphoid tissue (Holzer et al., 2022; Skartsis et al., 2021).

In line with these observations, other EDCs, such as bisphenols, phthalates and dioxins, have also been reported to modulate Th1 and Th17 immune responses (Badr et al., 2007; Li et al., 2016; Luo et al., 2016). The extent and direction of these effects appear to be sex-dependent. For instance, bisphenol A has been shown to induce a more pronounced Th17 response in female mice compared to males (Luo et al., 2016), highlighting that sex-specific immune modulation may vary across different EDCs. One potential, albeit speculative, mechanism involves the aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor that regulates intestinal barrier integrity, immune cell differentiation, and mucosal homeostasis in response to dietary, microbial, and environmental signals (Rothhammer and Quintana, 2019). Several environmental chemicals are known to interfere with AHR signaling (Denison and Nagy, 2003; Li et al., 2016), and DINCH as well as its metabolite MINCH have been reported to activate AHR-associated pathways in human THP-1 macrophages (Schaffert et al., 2021). However, AHR signaling was not investigated in the present study, and it remains unknown whether DINCH or MINCH directly modulate AHR activity in the intestine. Therefore, the involvement of AHR in the observed immune alterations should be regarded as a hypothesis that requires dedicated mechanistic investigation, including analyses of pathway activation and downstream target expression.

Together, these findings point to a sexually dimorphic immune susceptibility, with males showing a more pronounced mucosal immune activation, while females exhibit more limited systemic immune modulation. The biological basis of this sexual dimorphism remains unclear. It may be partly attributable to the interplay between sex chromosomes, which harbor numerous immune-related genes, and the direct and indirect effects of sex hormones on immune function (Dodd and Menon, 2022; Libert et al., 2010). In particular, estrogens promote Th1 or Th2 immunity dependent on the stage of the menstrual cycle, while androgen signaling can exert Th17 and reduce Th1 and Th2 responses (Dodd and Menon, 2022). Such endocrine regulation may contribute to differences of DINCH-associated immune responses between males and females. Importantly, however, the present study did not measure circulating sex hormones, estrogen- or androgen-receptor signaling, or the upstream pathways controlling Th1/Th17 differentiation. Consequently, endocrine regulation provides a biologically plausible explanation for the observed dimorphism but cannot be established as its underlying cause.

Remarkably, male mice from the same animal cohort previously displayed a more pronounced metabolic phenotype following DINCH exposure under HFD conditions (Krupka et al., 2025), suggesting that enhanced metabolic stress may increase susceptibility to intestinal immune activation. Obesity is well recognized to promote Th17-mediated inflammation, and HFD-induced obesity has been shown to increase Th17 cell frequencies and IL-17 production, thereby contributing to chronic low-grade inflammation and metabolic dysfunction (Bertola et al., 2012; Winer et al., 2009). More recent evidence further indicates that obesity-induced Th17 responses are also sex-dependent, with female mice exhibiting an earlier Th17 response than males, although both sexes ultimately develop Th17-mediated inflammation (Schuetz et al., 2024). Thus, the more pronounced metabolic disturbances previously observed in male DINCH-exposed mice may have rendered them more susceptible to the intestinal immune alterations detected in the present study. Taken together, the observed phenotype may therefore reflect an interaction between DINCH-associated metabolic stress, sex-dependent endocrine and immune regulation, and local intestinal environmental signals (Vijayakumar et al., 2026). However, these mechanisms were not directly investigated and therefore remain speculative.

5.3. Changes in epithelial homeostasis-related and barrier-associated gene expression

Consistent with the observed immunological alterations, DINCH exposure was also associated with changes in the expression of genes involved in epithelial barrier integrity and mucosal homeostasis. These effects were particularly evident in the ileum of male animals, where upregulation of *Tff3* and *Muc2* was accompanied by downregulation of the tight junction components *Cldn8* and *Ocln*. This transcriptional pattern is consistent with epithelial stress and altered barrier homeostasis; however, it does not by itself demonstrate impaired barrier function or increased intestinal permeability. Tight junction proteins are essential for maintaining paracellular permeability (Al-Sadi et al., 2011; Günzel and Yu, 2013; Zeissig et al., 2007), while increased *Muc2* expression may reflect a compensatory enhancement of the mucus barrier in response to epithelial stress and impaired barrier function (Renes et al., 2002; Wu et al., 2019). In parallel, *Tff3* is linked to epithelial repair and regeneration (Mashimo et al., 1996). Beyond its barrier-protective role, emerging evidence suggests that *Tff3* may also influence immune responses, including the promotion of Th17-associated pathways (Lin et al., 2024). Thus, elevated *Tff3* expression may reflect both an attempt to restore epithelial integrity and a contributor to ongoing immune skewing. If these transcriptional alterations translate into impaired barrier function, increased permeability could facilitate the translocation of microbial products and thereby promote local Th1/Th17 polarization. However, gene-expression data alone do not demonstrate functional barrier dysfunction. It remains to be determined whether the observed changes in *Tff3*, *Muc2*, *Cldn8*, and *Ocln* are reflected at the protein level and result in functional alterations of the intestinal epithelium. Furthermore, direct assessment of intestinal permeability using assays such as FITC-dextran measurements would be required to determine whether the observed molecular alterations translate into impaired epithelial barrier function.

One potential mechanism underlying these epithelial alterations may involve changes in membrane lipid homeostasis. The previously reported DINCH-associated alterations in lipid metabolism (Krupka et al., 2025), together with evidence that membrane lipid composition influences tight-junction organisation (Gori et al., 2020; Li et al., 2008; Shigetomi et al., 2018), raise the testable hypothesis that epithelial membrane homeostasis may be affected by DINCH exposure. However, membrane partitioning of DINCH or MINCH, epithelial lipid composition, membrane fluidity and raft stability were not assessed here. Direct membrane integration therefore remains speculative and cannot be inferred from the present data. Dedicated mechanistic studies would be required to determine whether alterations in lipid metabolism translate into changes in epithelial membrane properties and tight-junction organisation.

Beyond potential effects on membrane lipid homeostasis, the pronounced response in male mice may involve sex-dependent regulation of barrier homeostasis. Sex steroids can regulate intestinal gene expression, with estrogen signaling can influencing *Muc2* and *Ocln* expression, particularly under inflammatory conditions (Braniste et al., 2010; Braniste et al., 2009; Song et al., 2018), providing a potential endocrine basis for differences in epithelial responses between sexes. However, whether such mechanisms account for the stronger transcriptional response observed in male mice cannot be determined from the present data, because up- and downstream signaling pathways were not assessed. Thus, sex-dependent endocrine regulation should be considered a potential modulator rather than an established mechanism underlying the observed epithelial phenotype.

Another potential contributor is the intestinal microbiota, which may provide an important link between epithelial and immune responses. Although evidence is still limited, emerging studies suggest that DINCH can alter gut microbiome composition (Davias et al., 2024). Since the microbiota and its metabolites are known to regulate epithelial gene expression, including barrier-associated genes such as *Tff3*, *Ocln*,

and *Cldn8* (Braniste et al., 2014; Ghaderi et al., 2025; Heitkemper et al., 2018; Li et al., 2020; Vilchez-Vargas et al., 2022; Wang et al., 2016), microbiome alterations may contribute to the transcriptional changes observed in the present study. Conversely, changes in epithelial integrity and immune-derived inflammatory signals can alter the intestinal microbial environment. The microbiota-epithelium-immune interface could therefore contribute to the concomitant epithelial and immune alterations observed in male mice and may represent one mechanism underlying their apparent coupling. Recent studies have further demonstrated that environmentally induced tight junction alterations can be associated with functional barrier defects and gut microbiota dysbiosis (Wei et al., 2025; Wei et al., 2026). However, because neither intestinal permeability nor microbiome composition was assessed here, a causal link between DINCH exposure, microbial alterations, and impaired epithelial barrier function remains speculative and requires experimental validation.

Notably, similarly pronounced transcriptional alterations were not observed in female animals, despite the DINCH-associated increase in colon length. This suggests that the macroscopic and molecular responses to DINCH may not necessarily occur in parallel and could reflect distinct biological processes. The greater susceptibility of male mice to epithelial and immune alterations may be linked to the more pronounced metabolic disturbances previously reported in this cohort (Krupka et al., 2025), with lipid metabolism, endocrine regulation, and microbiota-dependent signaling representing possible mechanisms linking systemic and local responses. These interconnected pathways may be particularly relevant in the context of the gut-liver axis, which provides a potential interface between systemic metabolic alterations and intestinal homeostasis. The intestine and liver communicate bidirectionally through bile acids, microbial metabolites, dietary components, and inflammatory mediators, thereby contributing to metabolic and gut homeostasis (Jamalinia et al., 2025). Biological sex has a significant influence on the gut-liver axis. For example, differences in the composition and functionality of the gut microbiota between males and females have been described, which are associated with susceptibility to metabolic diseases, including insulin resistance and metabolic dysfunction-associated steatotic liver disease (MASLD) (Jamalinia et al., 2025; Lonardo et al., 2026). Conversely, certain metabolic and hormonal states – such as obesity and menopause – can in turn influence the microbiota (Mayneris-Perxachs et al., 2020). The sex-specific metabolic changes previously observed following DINCH exposure in the same cohort (Krupka et al., 2025) could thus influence intestinal homeostasis. Similarly, changes in intestinal epithelial homeostasis could potentially influence the translocation of microbial products and thereby modulate hepatic or systemic metabolic signaling. Thus, the gut-liver axis may represent a potential interface linking the systemic metabolic and intestinal effects of DINCH exposure. However, gut-liver interactions, including bile acid signaling, microbial metabolites, and microbial composition, were not investigated in the present study. The proposed connection therefore remains hypothetical and requires direct investigation in future studies.

Finally, although consistent sex-dependent effects were observed across multiple independent endpoints, these findings should be interpreted with caution in light of the relatively small sample size. Confirmation in larger, independently powered studies, ideally incorporating functional measurements of epithelial permeability, protein-level assessment of barrier components, microbiome profiling, and characterization of endocrine and metabolic signaling, will be required to determine the mechanisms underlying the observed epithelial phenotype.

5.4. Limitations

This study has several limitations. First, the absence of a DINCH-exposed standard-diet group precludes evaluation of a diet-by-DINCH interaction. The comparison of HFD controls with HFD + DINCH groups supports attribution of the observed group differences to DINCH exposure within the HFD background, but it cannot establish whether similar effects occur under standard-diet conditions or whether HFD modifies their magnitude or direction. Accordingly, the findings should be interpreted within this experimental context and not as evidence that DINCH generally exacerbates HFD-induced intestinal dysfunction. Also, the DINCH concentrations used in this study were relatively high and consequently cannot be directly extrapolated to typical human exposure or used for quantitative human risk assessment.

Second, colon length, while informative as a gross morphological parameter, does not provide mechanistic resolution of underlying histological or cellular changes. Histological analyses, including assessment of epithelial thickness, crypt depth, and inflammatory cell infiltration, would have substantially strengthened the interpretation of the observed morphological differences. However, as the present study represents a follow-up analysis of a previously completed animal experiment, no intestinal tissue suitable for histological analyses remained available. Consequently, these investigations could not be performed and should be addressed in future studies.

Third, functional barrier assessments (e.g., FITC-dextran) were not performed. Consequently, the observed changes in tight junction-associated gene expression cannot be interpreted as evidence of increased intestinal permeability. Future studies should combine transcriptional profiling with permeability measurements to determine whether DINCH-induced molecular alterations translate into functional epithelial barrier defects.

Fourth, the study is primarily descriptive and does not resolve the molecular mechanisms underlying the observed immune and epithelial alterations. Although RORγt was used as a lineage marker for Th17 cells, its functional activity, as well as candidate pathways involved in intestinal immune regulation and barrier homeostasis, including NF-κB, STAT3, and AHR signaling, were not investigated. Likewise, membrane partitioning of DINCH or MINCH, epithelial lipid composition, membrane fluidity, raft stability, and corresponding protein expression of epithelial barrier markers and signaling molecules were not assessed. Consequently, the observed transcriptional alterations cannot be assumed to directly reflect changes at the protein level or pathway activity. These proposed mechanisms therefore remain hypotheses that require validation in future studies integrating transcriptomic, proteomic, and functional analyses.

Fifth, the immunological analyses were restricted to T helper cell subsets in the spleen and Peyer's patches. Other immune cell populations that are critical for intestinal homeostasis, including innate lymphoid cells, macrophages, dendritic cells, and intraepithelial lymphocytes, were not investigated. Consequently, the present study provides only a partial characterization of the intestinal immune response to DINCH exposure. Future studies employing broader immune profiling will be required to obtain a more comprehensive understanding of DINCH-induced immune modulation.

The sixth limitation of this study is the relatively small sample size, particularly for the gene expression analyses, where some groups contained only three biological replicates following outlier exclusion. Because the present work represents a follow-up analysis of a previously completed animal experiment, the number of available samples was predetermined and could not be increased. Consequently, the statistical power to detect subtle biological effects may be limited, and the findings should therefore be interpreted with appropriate caution. Replication in larger, independently powered studies will be necessary to confirm the observed sex-specific alterations and assess their generalizability.

Finally, microbiome composition was not assessed in this dataset, although it represents a potential mediator of both immune and epithelial changes (Davias et al., 2024). This limitation is particularly relevant because microbiota-derived signals could provide a mechanistic link between DINCH exposure, epithelial stress, and mucosal immune modulation, and because such interactions may themselves differ between sexes. However, without microbiome profiling or

measurements of microbial metabolites, no conclusions regarding a microbiome-mediated mechanism can be drawn. Consequently, the mechanistic explanations discussed above should be regarded as hypotheses requiring targeted validation.

6. Conclusion

Building upon the previously published characterization of systemic metabolic alterations induced by dietary DINCH exposure (Krupka et al., 2025), the present study provides the first evidence that the same exposure is associated with sex-specific changes in intestinal macroscopic morphology, mucosal immunity and epithelial barrier-related gene expression within an HFD background (Table S3). Males appear particularly susceptible to pro-inflammatory mucosal immune shifts and transcriptional alterations in barrier-associated genes consistent with epithelial stress, whereas females exhibit more restricted systemic immune changes. Importantly, the alterations in barrier-associated genes observed in this study are transcriptional only and do not constitute evidence of structural damage or functional impairment of the intestinal epithelial barrier. No conclusions regarding barrier permeability, epithelial integrity, or functional barrier competence can therefore be drawn from these gene expression changes alone. These results extend the concept of DINCH as a metabolism-disrupting chemical by highlighting its potential to modulate gut homeostasis under obesogenic conditions in a sex-dependent manner; however, they do not establish whether these effects depend on HFD exposure, nor do they establish pathological tissue remodeling or functional barrier impairment, which require further histological and functional validation.

CRediT authorship contribution statement

Florence Fischer: Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. **Sontje Krupka:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Beate Fink:** Writing – review & editing, Methodology. **Mario Bauer:** Writing – review & editing, Methodology. **Tobias Kretschmer:** Writing – review & editing, Methodology, Conceptualization. **Julia Howanski:** Writing – review & editing, Methodology. **Nora Klöting:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Kristin Schubert:** Writing – review & editing, Supervision, Conceptualization. **Anne Schumacher:** Writing – review & editing, Supervision, Conceptualization. **Martin von Bergen:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Matthias Blüher:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Ana Claudia Zenclussen:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Ethics declaration

This study was conducted in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines as well as the following guidelines for animal welfare and/or reporting: German Animal Welfare Act (Tierschutzgesetz, TierSchG) and the German Ordinance on the Protection of Animals Used for Experimental or Other Scientific Purposes (Tierschutz-Versuchstierverordnung, TierSchVersV). This study was approved by the Landesdirektion Sachsen. (Approval No. TVV38/20).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthias Blüher reports a relationship with Amgen Inc that includes: consulting or advisory. Matthias Blüher reports a relationship with Abbott that includes: speaking and lecture fees. Matthias Blüher reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory and speaking and lecture fees. Matthias Blüher reports a relationship with Boehringer Ingelheim Pharma GmbH & Co KG that includes: consulting or advisory and speaking and lecture fees. Matthias Blüher reports a relationship with Bayer Corporation that includes: consulting or advisory and speaking and lecture fees. Matthias Blüher reports a relationship with Eli Lilly and Company that includes: consulting or advisory and speaking and lecture fees. Matthias Blüher reports a relationship with Novo Nordisk Inc that includes: consulting or advisory and speaking and lecture fees. Matthias Blüher reports a relationship with Daiichi Sankyo Inc that includes: speaking and lecture fees. Matthias Blüher reports a relationship with Merck Sharp & Dohme Corp that includes: speaking and lecture fees. Matthias Blüher reports a relationship with Novartis Pharma AG that includes: speaking and lecture fees. Matthias Blüher reports a relationship with Pfizer that includes: speaking and lecture fees. Matthias Blüher reports a relationship with Sanofi that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2026.129372.

Data availability

Data will be made available on request.

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