Environment International 151 (2021) 106449

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Wood emissions and asthma development: Results from an experimental mouse model and a prospective cohort study

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ARTICLE INFO

Handling Editor: Hanna Boogaard

Keywords:
Wood emission
Volatile organic compounds
Mixture effect
Asthma
Wheezing
FHA
LINA cohort
Murine asthma model
Perinatal exposure

ABSTRACT

Background: Increased use of renewable resources like sustainably produced wood in construction or for all sorts of long-lived products is considered to contribute to reducing society's carbon footprint. However, as a natural, biological material, wood and wood products emit specific volatile organic compounds (VOCs). Therefore, the evaluation of possible health effects due to wood emissions is of major interest.
Objectives: We investigated the effects of an exposure to multiple wood-related VOCs on asthma development.
Methods: A murine asthma model was used to evaluate possible allergic and inflammatory effects on the lung after short- or long-term and perinatal exposure to pinewood or oriented strand board (OSB). In addition, wood-related VOCs were measured within the German prospective mother–child cohort LINA and their joint effect on early wheezing or asthma development in children until the age of 10 was estimated by Bayesian kernel machine regression (BKMR) stratifying also for family history of atopy (FHA).
Results: Our experimental data show that neither pinewood nor OSB emissions even at high total VOC levels and a long-lasting exposure period induce significant inflammatory or asthma-promoting effects in sensitized or non-sensitized mice. Moreover, an exposure during the vulnerable time window around birth was also without effect. Consistently, in our mother–child cohort LINA, an exposure to multiple wood-related VOCs during pregnancy or the first year of life was not associated with early wheezing or asthma development in children independent from their FHA.
Conclusion: Our findings indicate that emissions from wood and wood products at levels commonly occurring in the living environment do not exert adverse effects concerning wheezing or asthma development.

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https://doi.org/10.1016/j.envint.2021.106449
Received 2 October 2020; Received in revised form 22 December 2020; Accepted 3 February 2021
Available online 18 February 2021

1. Introduction

Innovative and sustainably produced wood products, when coupled with sustainable forest management, have been considered to contribute substantially to climate change mitigation (Sathre and Gustavsson 2009; Sathre and O'Connor 2010). Compared with other "non-wood" materials like concrete, steel or plastic, wood products usually have a lower quantity of greenhouse gas (GHG) emissions during product manufacturing (Bergman et al. 2014; Hildebrandt et al. 2017). Furthermore, carbon remains fixed in wood products throughout their service life (Kalt 2018). The GHG saving potential of an increased use of wood in construction but also a growing application of wood for interior works, furniture, doors and countless other long-living products could expand anthropogenic carbon stocks and reduce society's carbon footprint (Hildebrandt et al. 2017; Kalt 2018). However, as a natural, biological material, wood emits specific volatile organic compounds (VOCs). Considering that many people in industrialized nations spend most of their time indoors (Leech et al. 2002), the question arises which effects wood and wood products might have on human health and wellbeing. Widely used wood products in construction but also for flooring and furniture are softwoods like pine and engineered wood like oriented strand board (OSB). Softwoods release the highest concentration of wood VOC because of their emission of terpenes such as α-pinene and 3-carene (Pohleven et al. 2019). Wood materials like OSB emit predominantly terpenes as well as aldehydes (Makowski et al. 2005).

Several epidemiological studies indicate an association between exposure to indoor VOCs after redecoration of dwellings with painting or floor covering and adverse respiratory symptoms as well as an increased risk for allergic manifestations, wheeze or obstructive bronchitis (Diez et al. 2000; Ernstgard et al. 2007; Franck et al. 2014; Wieslander et al. 1997). In contrast, epidemiological studies on health effects of VOCs emitted by wood and wood products are scarce. The few data available are mainly from studies investigating the impact of occupational VOC exposure on respiratory symptoms or irritations on mucous membranes showing no conclusive evidence of an association between terpene or aldehyde exposure and adverse health effects (Cakmak et al. 2014; Glas et al. 2015; Salonen et al. 2009). Studies with healthy adult volunteers who were short-term exposed to different levels of VOCs from pinewood or OSB revealed no sensory irritation of the airways or eyes and no negative effects on pulmonary function either (Gminski et al. 2011a; Gminski et al. 2011b). However, indoor VOC exposure has been shown to impact infant's immune system development (Lehmann et al. 2001; Hörnig et al., 2016; Junge et al., 2014), and respiratory diseases in particular in early childhood even at very low exposure concentrations. Importantly, this harmful impact on children s health might result from prenatal exposure already (Lehmann et al., 2002; Diez et al., 2003; Franck et al. 2014). Unfortunately, there is no information from epidemiological studies so far as to whether exposure to wood-related VOC during pregnancy or in the very first years of life may have an effect on children's asthma risk later in life, in particular if these children were at high risk due to a family history of atopy (FHA). This is important, as pregnancy is not only a period that is particularly susceptible to ambient air pollution (Gruzieva et al. 2019) but at the same time frequently goes along with increased renovation activities and the purchase of new furniture. Moreover, there are no experimental in vivo studies on healthy or allergen-sensitized mice investigating neither the effect of long-term exposure to single VOCs nor to the whole mixture of VOCs emitted by wood and wood products. Therefore, the present study focussed on effects of short- and long-term as well as perinatal exposure to pinewood or OSB on airway inflammation using a murine asthma model. To confirm, that the results on perinatal exposure to wood products and offspring's asthma risk obtained with the murine model are relevant for humans, comparable analyses were performed in the prospective mother–child cohort LINA.

2. Materials and methods

2.1. Mice

Female BALB/cByJ mice were obtained from the Elevage Janvier Laboratory (Le Genest St Isle, France). Mice were purchased with a specified 7-wk age upon delivery followed by a 7-d adaptation period. Mice were bred and maintained in the animal facility at the University of Leipzig (Germany). The exposed mice and the control animals were housed in different ventilated cabinets with 23 °C room temperature, 60% humidity, and 12 h day/night rhythm. Cages were bedded with Vermiculite bedding material. Mice received conventional mouse feed (Altromin, Lage, Germany) and water *ad libitum*. All animal experiments involved groups of 4 mice/cage and were performed at least 3 times according to institutional and state guidelines. The cross-generational experiments were performed two times with 3 dams (each with 2–5 pups). Male Balb/cByJ (8 weeks of age) for mating were also obtained from the Elevage Janvier Laboratory. The Committee on Animal Welfare of Saxony approved animal protocols used in this study (TVV 23/16).

2.2. Exposure of mice to pinewood and OSB

The wooden products were installed at the top of the cages to prevent skin contact with the mice. As the emission rates generally decrease over time, the samples were replaced weekly to maintain a similar range of total VOC (TVOC) levels over the whole exposure period. To minimize other VOC sources different bedding materials had been tested *beforehand*. Silica and vermiculite based bedding emitted least but silica partly adsorbed the unsaturated aldehydes (data not shown). Therefore, vermiculite was consequently used. Solid pine timber boards (*Pinus sylvestris* L., purchased form sawmill) contained mainly heartwood. To provide comparable material, the samples were composed from different boards. Each sample consisted of several pieces of wood (2–3 cm × 12.5–15.0 cm × 2.5 cm). The full size of the samples varied in order to obtain similar VOC level in the cages even with wood samples that have different area specific emission rates. Two different batches of OSB were obtained (industrial mill and hardware store). All were made of Scots pine (*Pinus sylvestris* L.) and bonded with pMDI (poly-methylene diphenyl diisocyanate) resin. High exposure: During the first week of animal exposure, these fresh samples (total surface area: 2.049 cm^2 made of 11 pieces) were used. Therefore, OSB samples were stored in a freezer directly after production until the start of the exposure. For the remaining exposure period from week two on, the OSB samples were stored for one day in a climate chamber for artificial aging in order to change the VOC composition towards a higher aldehyde proportion. For the lower exposure OSB from the hardware store have been used (total surface area: 1.239 cm^2 made of 7 pieces). To provide comparable material, the samples were composed from different boards and panels, respectively. With the emission test chamber method according to DIN EN ISO 16000-9:2008 (Standards-committee 2008) the area specific emission rates (in $\mu g\ m^{-2}\ h^1$) of these samples were determined. Since the climatic conditions (humidity, temperature, and air exchange rate) are fixed in the cages, the defined TVOC levels were obtained by adjusting either the emitting surface sample area, the area specific emission rate, or both. The samples were wrapped in aluminum foil and stored in freezer until start of exposure. Three different exposure protocols were used (A - acute, B - chronic, C - perinatal) as displayed in Supplementary Fig. 1.

2.3. VOC monitoring and analysis in the mouse model

The determination of VOC was performed according to DIN ISO 16000–6:2012 (Standardization. 2012). The air in the cages was monitored several times per week and sampled on stainless steel sampling tubes filled with Tenax TA® sorbent (200 mg, 35/60 mesh). Each tube was spiked with 200 ng toluene-d_8 as an internal standard. The tubes

were thermal desorbed (TD: Ultra Series 2 50:50 and Unity Series 2, Markes International Ltd., USA). Identification and quantification were carried out with an Agilent 7890A gas chromatograph (GC) coupled with an Agilent 5975C mass spectrometer (MS) (Agilent Technologies Inc., USA). For separation a VF1701ms capillary column (CP9151, Agilent Technologies Inc., USA, length: 30 m, inner diameter: 0.25 mm, film thickness: 0.25 μm) with helium as carrier gas was used. The GC temperature program include the following steps: 32 °C hold for 3 min, increase by 6 °C min^{-1} to 90 °C, 90 °C hold for 4 min, increase by 8 °C min^{-1} to 200 °C, increase by 12 °C min^{-1} to 240 °C, 240 °C hold for 2 min. The MS was operated in scan mode with 5 scans s^{-1} in the mass range of 22 – 300 u. The results are presented as concentration of VOC in chamber or cage air (in $\mu g/m^3$). Only a defined number of VOC is considered to characterize the wood-related emission behaviour of the tested materials and the sampled air in the cages. The selection is based on the main representatives of the substantial compound classes (terpenes: α-pinene, β-pinene, 3-carene, limonene, phellandrene, terpinene, terpinolene, tricyclene, camphene, myrcene, cymol; (un)saturated aliphatic and aromatic aldehydes: pentanal, hexanal, heptanal, 2-heptenal, octanal, 2-octenal, nonanal, benzoic aldehyde; organic acids: acetic acid, propionic acid, hexanoic acid and some others: 2-butanone, pentanol, toluene). For most of these VOCs the compound-specific response factors were determined with a multi-point calibration with reference compounds. Substances without reference compounds were quantified using the response factor of compounds with similar chemical structure or the internal standard. In this context the total volatile organic compounds (TVOC) is the sum of the concentrations of the selected VOC. This correspond to at least 95% of all the detected VOC.

2.4. HDM-induced acute and chronic asthma model

To investigate possible adverse effects of pinewood and OSB emissions we induced different asthma phenotypes in mice. For an acute airway inflammation Balb/c mice were sensitized via the airways with 5 μg house dust mite extract (HDM, *D. pteronyssinus 1,* endotoxin: 1.273 EU/ml, Greer Laboratories, USA) in 40 μl saline on day 1 followed by 2.5 μg HDM given intranasally (i.n.) on days 7 to 11 and 14 to 16. Control mice received normal saline i.n. Airway hyperreactivity (AHR) was measured on day 17 and mice were sacrificed on day 18. To induce a chronic asthma-like phenotype, Balb/c mice were immunized with HDM (5 μg) on day 1 and challenged with HDM (2.5 μg) twice per week for 11 weeks (Supplementary Fig. 1). AHR was assessed on day 76 and mice were sacrificed on day 77.

2.5. Measurement of airway responsiveness

Lung resistance was measured by using invasive plethysmography in response to inhaled methacholine, as described previously (Jahreis et al. 2018; Polte et al. 2015). Briefly, to measure lung resistance (RL) mice were anesthetized (100 mg/kg ketamine and 10 mg/kg xylazine, Bayer, Leverkusen, Germany), intubated, and mechanically ventilated at a tidal volume of 0.2 ml and a frequency of 150 breath/min. Baseline RL and responses to aerosolized saline (0.9% NaCl) were measured first, followed by responses to increasing doses (2.5 to 40 mg/ml) of aerosolized methacholine.

2.6. Collection of bronchoalveolar lavage (BAL) fluid

The assessment of cells in the lavage fluid and BAL cell differentials were determined as described previously (Petzold et al. 2014; Polte et al. 2015). Briefly, the trachea was cannulated and the right lung was lavaged three times with 400 μl NaCl 0.9%. Cells in the lavage fluid were counted using a hemocytometer, and BAL cell differentials were determined on slide preparations stained with Diffquick® (Medion Diagnostics AG, Düdingen, CH) on blinded samples by an independent investigator. At least 100 cells were differentiated into eosinophils, macrophages, lymphocytes and neutrophils by light microscopy based on conventional morphologic criteria.

2.7. Lung histology

Left lung was fixed in 10% formalin and stained with Haematoxylin & Eosin (H&E, MERCK, Darmstadt, Germany). For quantification and objective evaluation of the degree of histological inflammation, whole lung sections were scanned with a digital camera (Zeiss, 5 shots per lung) and analyzed with HistoClick-Software based on morphometric image analysis (Petzold et al. 2014; Polte et al. 2015). The degree of inflammation is expressed by the number of pixels, which correlate to the stained cells of interest. Total matrix deposition was assessed on Martius Scarlet Blue (MSB)-stained sections (Polte et al. 2009). Lung sections were also immunostained with anti-α-smooth muscle actin (SMA) primary Ab to distinguish smooth muscle cells. The primary Ab was detected with a HRP-labeled secondary Ab (both Abcam, USA). Digital photographs of four bronchioles per tissue section were taken and analyzed with HistoClick-Software (Polte et al. 2009).

2.8. HDM-specific IgE assay

HDM-specific IgE serum levels were measured by sandwich ELISA according to a standard protocol. Briefly, 96-well microtiter plates (Nunc, Roskilde, Denmark) were coated overnight with 25 μg/ml HDM. After washing and blocking plates, serum was added and incubated at 4 °C overnight. Subsequently, 96-well plates were washed and 100 μl of biotin-anti-mouse IgE (BioLegend, CA, USA) was added and incubated for 1 hr. The wells were washed with PBS followed incubation with avidin-horse radish peroxidase (Biolegend) for 30 min. TMB substrate solution (100 μl) was added and incubated in the dark for 30 min. The OD was determined at 450 nm using a BioTek microplate reader (BioTek Instruments, Bad Friedrichshall, Germany).

2.9. Cytokine production

Splenocytes or mediastinal lymphnode cells (5×10^6 cells/ml per well) were isolated and re-stimulated in vitro with 100 μg/ml HDM in culture medium (RPMI medium supplemented with 10% FCS, 100 U/ml Penicillin, 100 μg/ml Streptomycin) one day after airway function test. After three days cytokines were measured in supernatants from re-stimulated spleen cells or from lung tissues using DuoSet® ELISA kits (R&D Systems, Minneapolis, USA) according to the manufacturer's instructions.

2.10. Collagen analysis

Collagen content was measured in lung tissue homogenates by a biochemical assay according to the manufacturer's instructions (Sircol collagen assay, Biocolor, Ireland) as described previously (Rothemund et al. 2013; Schutze et al. 2010).

2.11. Measurement of 8-isoprostane

Lung tissues were homogenized using lysing matrix A (FastPrep®24 homogenizer, MP Biomedicals, LLC, Eschwege, Germany) and aliquots of the obtained supernatants were hydrolyzed (15% KOH) and deproteinized (ethanol containing 0.01% BHT). 8-isoprostane concentration was determined by specific immunoassay according to manufacturer's instructions (Cayman Chemical Company, Ann Arbor, MI, USA) as described previously (Bönisch et al. 2012; Schutze et al. 2010).

2.12. LINA study design and sample collection

The German prospective mother–child cohort LINA (Lifestyle and environmental factors and their Influence on Newborns Allergy risk)

recruited 622 mothers (629 children) at 34 weeks of gestation between May 2006 and December 2008 in Leipzig, Germany. Mothers with severe immune or infectious diseases during pregnancy were excluded from the study. Standardised self-administered questionnaires were collected annually starting in pregnancy, assessing general information about personal lifestyle, housing and environmental conditions as well as family history of atopy (FHA) and disease state.

Study participation was voluntary and written informed consent was obtained by all participants. The study was approved by the Ethics Committee of the University of Leipzig (file ref # 046-2006, 160-2008, 160b/2008, 144-10-31052010, 113-11-18042011, 206-12-02072012, #169/13-ff, #150/14-ff, 008/17-ek).

2.12.1. Wheezing/Asthma prevalence of children

Respiratory health of children was assessed by questionnaires asking parents annually for physician diagnosed respiratory diseases like asthma, obstructive bronchitis, wheezing etc. From that information, the prevalence for early wheezing (children from whom at least one wheezing episode within the first 2 years of life was reported) as well as the 10-year lifetime prevalence of asthma was used for the present BKMR analyses. As controls, only children who had never experienced any respiratory diseases like asthma, obstructive bronchitis or wheezing within the first 10 years were included. Furthermore, all BKMR analyses were also stratified for family history of atopy (at least one parent positive).

2.12.2. Redecoration activities

Information about redecoration activities of study participants were used from the pregnancy questionnaire at 36th week of pregnancy. Participants were asked if they got new furniture within the last 12 months, and if so, from what material (solid wood, particleboard, others). Further, participants were asked if new flooring was performed in their homes during the last 12 months, and if so, from what material (parquet, laminate, carpet, others).

2.12.3. Assessment of wood-related VOC in LINA

To measure the individual exposure to volatile organic compounds (VOCs) in the homes, passive samplers (3 M monitors, type OVM 3500; 3 M GmbH, Neuss, Germany) were placed in the middle of the room at 1.5–2 m height during pregnancy (sampling from 34th to 38th week) and at the end of children's year one (sampling from 12th to 13th month of life). During pregnancy, the passive samplers were placed in the sleeping room or the living room of the mother. In the first year of life, the measurement was carried out in the child's bedroom or in the living room of the parents depending on the preferred location of the child. Concentrations of VOCs were analysed as described previously (Lehmann et al. 2001).

2.13. Statistical analysis

Experimental data sets from in vivo mouse studies were processed and analysed in GraphPad PRISM 7.02 for windows (GraphPad Software, Inc.). All p-values of less than 0.05 were considered significant using ANOVA and Kruskal-Wallis multiple comparison tests.

With respect to the epidemiological data, analyses were performed using non-parametric tests in general since the majority of parameters were not normally distributed. To address the relationship between wood related VOCs and their indoor source, medians were compared using Mann–Whitney *U* test. To flexibly model the individual and joint effects of exposure to mixtures of wood-related VOCs on early wheeze (n = 483) or asthma prevalence within the first 10 years (n = 282) of life Bayesian kernel machine regression (BKMR) was performed with 50,000 iterations according to Preston et al. (2020) and Bobb et al. (2018). Wood related VOCs were ln-transformed and z-scored. As some VOCs were highly correlated (see Spearman correlation matrix shown in Supplementary Fig. 2A, B) exposures were categorized into non-overlapping groups (group 1: α-pinene, β-pinene, 3-carene, limonene; group 2: pentanal, hexanal, heptanal, octanal, nonanal). Hierarchal variable selection was implemented thus incorporating this information about the structure of the mixture into the model. The following confounders were included in the BKMR model: family history of atopy (except for the analyses stratified for FHA), smoking during pregnancy, maternal age at delivery, gender of the child, parity, parental school education, keeping of pets, delivery mode, breastfeeding duration and overweight development in infancy (being ever overweight from 2 to 10 years of age, classification according to IOTF (Leppert et al. 2020)). The Chi^2-test for cross-relationship was used to compare the analysed BKMR sub-cohort until the age of 10 years with the total cohort according general study characteristics/confounders. Statistical analyses were performed with STATISTICA for Windows, Version 13 (Statsoft Inc.) and R (version 3.6.1; R development Core Team) for the *bkmr* package (Bobb et al. 2018).

3. Results

3.1. Short-term exposure to pinewood/OSB in mice

To investigate the role of VOCs emitted by pinewood or OSB we exposed mice directly to wood samples installed on the top of the cage as described in methods in more detail. The mice were exposed to a TVOC concentration range between 2.1 and 5.6 mg/m^3 (pinewood, Fig. 1A) or between 1.8 and 4.3 mg/m^3 (OSB, Fig. 2A) starting before sensitization until the end of the asthma protocol (Supplementary Fig. 1). VOCs emitted from pinewood were mainly terpenes (>90%, Fig. 1B) and here in particular α-pinene and 3-carene (together > 90%, Supplementary Fig. 3A). Newly purchased OSB emits VOCs with a high portion of terpenes only in the first days, while aldehydes occur later when terpene concentration decrease (Makowski et al. 2005). To mimic this pattern, we therefore started the exposure with fresh OSB samples but used artificial aged samples with lower terpene and higher aldehyde emissions (Fig. 2B) subsequently. Short-term exposure to pinewood for a period of 20 days had no effect on the number of eosinophils or other immune cells in the BAL fluid in HDM-sensitized and non-sensitized mice compared to un-exposed control animals (Fig. 1C, Supplementary Fig. 3B). Furthermore, we did not find significant effects on AHR (Fig. 1D), airway inflammation in the lung as demonstrated by H&E stained lung sections (Fig. 1E) and verified by objective, investigator-independent computer analysis (Fig. 1F). In addition, the HDM-specific IgE levels and the release of Th2 cytokines in cell culture supernatants of HDM-re-stimulated splenocytes (Fig. 1G, H) or lymphnode cells (Supplementary Fig. 3C) were comparable in pinewood exposed and unexposed mice. The same applies for the Th17 cytokine IL-17 and the Th1 cytokine IFN-γ (Fig. 1H).

Unexpectedly, in HDM-sensitized mice short-term exposure to VOCs emitted by OSB even reduced total cell number (Supplementary Fig. 4A) and the number of eosinophils in the BAL fluid (Fig. 2C) and decreased lung inflammation (Fig. 2E and Supplementary Fig. 4B). Moreover, HDM-specific IgE levels and the production of the Th2 cytokines IL-5 and IL-13 but also IL-17 and IFN-γ in re-stimulated splenocytes as well as IL-13 in mediastinal lymphnodes were diminished (Fig. 2F-G and Supplementary Fig. 4C). In contrast, OSB-derived VOCs had no impact on lung resistance (Fig. 2D). Exposure of non-sensitized animals was without any effect on the measured parameters (Fig. 2C-G).

As a positive control, exposure of HDM-sensitized mice to diesel exhaust particles (DEP), which are known to induce adjuvant effects in the lung (Takano et al. 1997) exerted an increased allergic airway inflammation and an impaired lung function (Fig. 2C-G).

3.2. Long-term exposure to pinewood/OSB in mice

To elucidate the effect of long-term exposure to pinewood we used differently stored samples to get a low and a high TVOC concentration

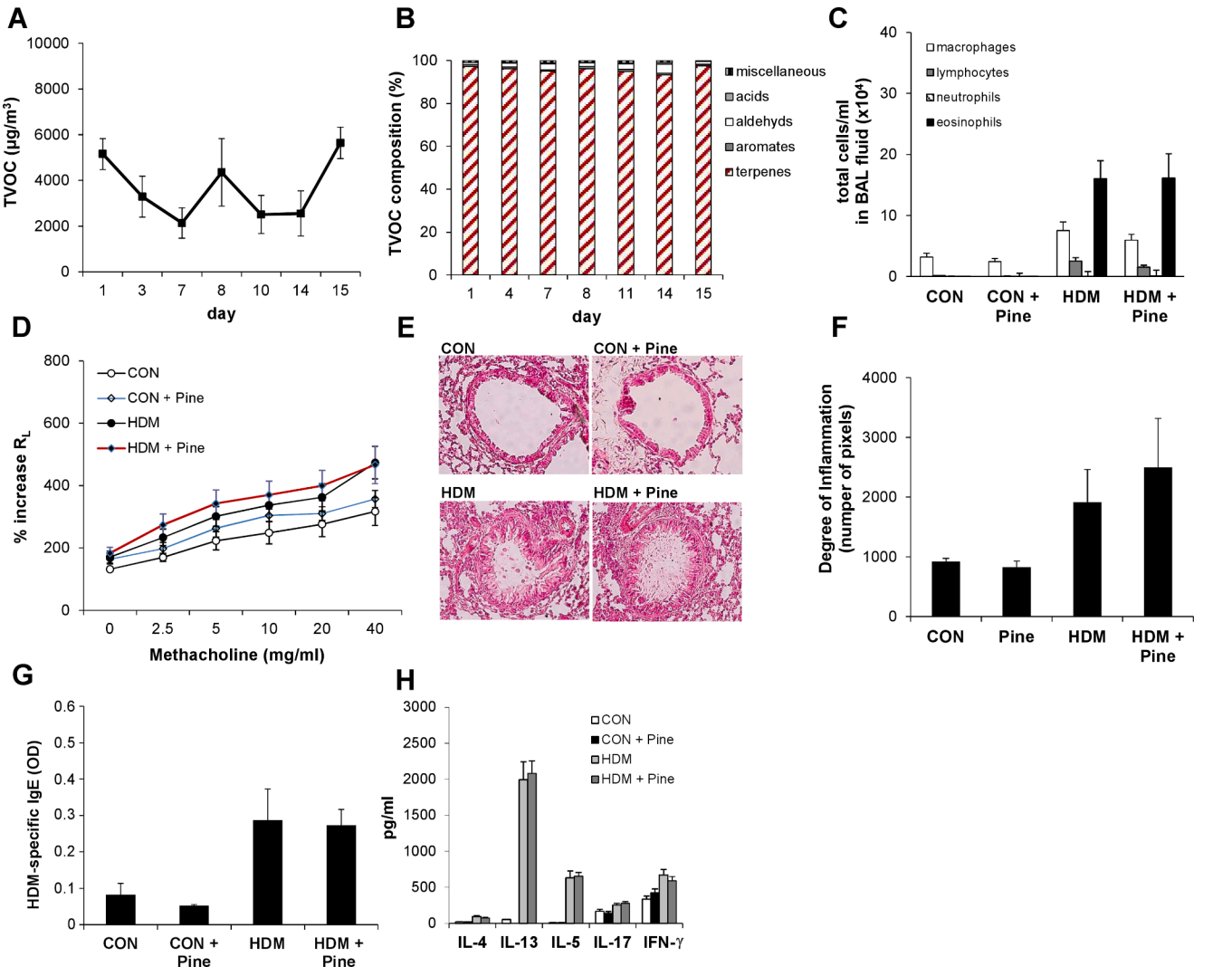

Fig. 1. Effect of short-term exposure to pinewood on asthma development in HDM-sensitized mice. (A) TVOC concentrations and (B) TVOC composition for the whole exposure period are shown. (C) Total cell number in BAL fluid, (D) lung resistance, (E) airway inflammation examined by lung histology (H&E, x100), (F) quantified by an investigator-independent computer-based analysis, (G) HDM-specific IgE serum levels and (H) cytokine production of re-stimulated splenocytes were examined in HDM-sensitized and control mice. Data are expressed as mean ± SEM, n = 3 (A, B), n ≥ 9 (C – H).

range. Pinewood with TVOC emission between 1.5 and 6.3 mg/m^3 over a 12-week period (Fig. 3A, low exposure) was without any effects on eosinophilic inflammation in the BAL fluid, AHR and lung inflammation measured by analysing H&E stained lung sections (Fig. 3B-D, Supplementary Fig. 5A). In parallel, HDM-specific IgE levels (Fig. 4A) and the cytokine release (Supplementary Fig. 5B, C) were unaffected by long-term low exposure to pinewood in HDM-sensitized and non-sensitized animals. Direct exposure of allergen-sensitized or non-sensitized mice to high TVOC concentrations (3 – 18 mg/m^3, Fig. 3A, high exposure) for 12 weeks had also no significant effect on airway inflammation (Fig. 3B, D, Supplementary Fig. 5A), lung function (Fig. 3C), IgE (Fig. 4A) and Th2 cytokine as well as IL-17 and IFN-γ levels (Supplementary Fig. 5B, C).

Furthermore, in this long-lasting asthma model we investigated the effect of continuous exposure to pinewood on airway remodelling. Increased subepithelial deposition of extracellular matrix (ECM) proteins, specifically collagen, and increased smooth muscle mass are prominent features of airway remodelling. We examined matrix deposition (collagen and fibrin) in lung sections stained with Martius scarlet blue and measured the amount of total lung collagen. Long-term exposure to both, low and high TVOC concentrations did not increase matrix deposition and lung collagen in sensitized and non-sensitized mice compared to their respective controls (Fig. 4B, C). Moreover, pinewood exposure at both concentration ranges had no significant effect on smooth muscle cells in the lung (Fig. 4D). To evaluate whether pinewood VOCs may induce oxidative stress we measured 8-isoprostane levels as marker for lipid peroxidation in lung homogenates (Alessandrini et al. 2009). Again, there were no significant differences detectable between pinewood-exposed sensitized or non-sensitized mice compared to the unexposed control animals (Supplementary Fig. 5D).

To simulate long-term exposure to OSB, HDM-sensitized and non-sensitized control mice were exposed over a 12-weeks period to a lower (0.8 – 1.7 mg/m^3) and a higher (1.2 and 4.3 mg/m^3) range of OSB-emitted VOCs (Fig. 5A), whereby the higher concentration range emitted similar TVOC levels as in the acute asthma model. As already reported for short-term exposure, long-term exposure of HDM-sensitized mice to the higher concentration range revealed a significantly decrease in serum IgE (Fig. 6A) and Th2 cytokine levels (Supplementary Fig. 6B). The total cell number (Supplementary Fig. 6A) as well as the number of eosinophils in the BAL fluid (Fig. 5B), IL-17 or IFN-γ levels in HDM-re-stimulated splenocytes and IL-13, IL-5 and IFN-γ production in re-stimulated lymphnode cells were slightly but not significantly reduced (Supplementary Fig. 6B, C). Furthermore, there was again no significant effect on AHR, lung inflammation (Fig. 5C, D), and airway remodelling

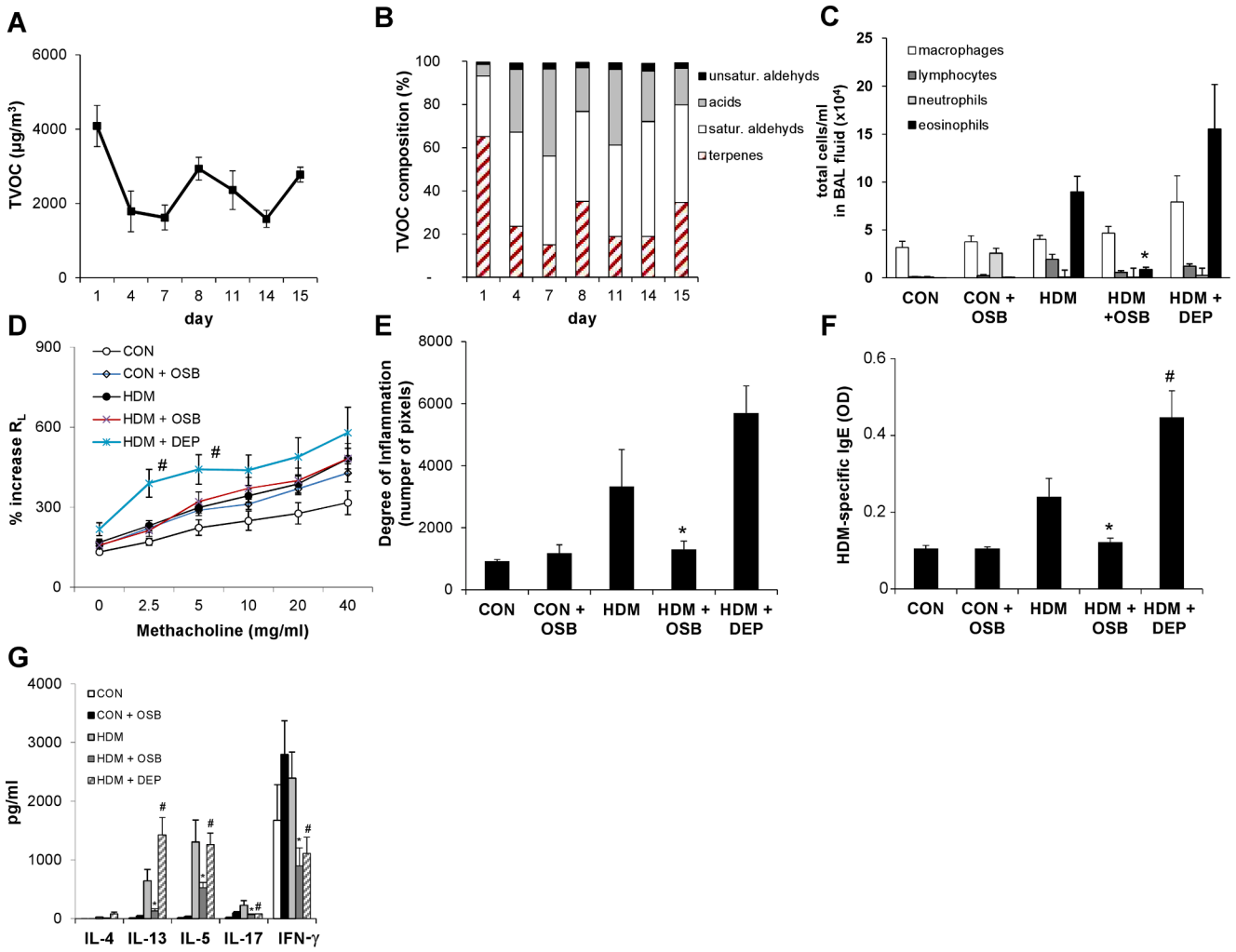

Fig. 2. Effect of short-term exposure to OSB on asthma development in HDM-sensitized mice. (A) TVOC concentrations and (B) TVOC composition for the whole exposure period are shown. (C) Total cell number in BAL fluid, (D) lung resistance, (E) airway inflammation examined by lung histology (H&E, x100), (F) quantified by an investigator-independent computer-based analysis, (G) HDM-specific IgE serum levels and (H) cytokine production of re-stimulated splenocytes were examined in HDM-sensitized and control mice. Mice exposed to diesel exhaust particles (DEP) served as positive control. Data are expressed as mean ± SEM, n = 3 (A, B), n = 6 (DEP, C – G), n ≥ 9 (OSB, C – G). $^{*}P < 0.5$ HDM *vs.* HDM + OSB, $^{\#}P < 0.05$ HDM *vs.* DEP.

(Fig. 6B-D).

Exposure to OSB emitting VOCs at the lower concentration range had no significant effects on the measured parameters in HDM-sensitized mice (Fig. 5B-D, Fig. 6A-D, Supplementary Fig. 6A-C). Both concentration ranges did not affect non-sensitized animals. Furthermore, there were also no signs of oxidative stress detectable (Supplementary Fig. 6D).

3.3. Perinatal exposure to pinewood/OSB in mice

To analyse the effects of an early life exposure on asthma development in the offspring, dams were exposed to wood products during pregnancy and breastfeeding (perinatal). Grown-up offspring were then subjected to antigen sensitization without being further exposed to pinewood or OSB.

Maternal exposure to pinewood (concentration range between 2.2 and 11 mg/m^3, Fig. 7A) had no adverse effect on total cell number or number of eosinophils in the BAL fluid while exposure to OSB (range between 0.9 and 4 mg/m^3, Fig. 7B) significantly reduced the eosinophilic inflammation in the BAL fluid (Fig. 7C, Supplementary Fig. 7A). In contrast, pinewood and OSB both did not affect AHR (Fig. 7D), airway inflammation in the lung as demonstrated by H&E stained lung sections (Supplementary Fig. 7B) and verified by objective, investigator-independent computer analysis (Fig. 7E) in HDM-sensitized offspring compared to HDM-sensitized mice from unexposed controls. In addition, the HDM-specific IgE levels and the release of Th2 cytokines as well as IL-17 in cell culture supernatants of HDM-re-stimulated splenocytes were comparable to those from offspring from pinewood- or OSB-exposed and unexposed dams while IFN-γ production was significantly increased in splenocytes but not in lymphnode cells (Fig. 7F, G, and Supplementary Fig. 7C).

3.4. Sources of VOC emissions in LINA

General study characteristics and factors known to individually influence children's asthma development as well as the early wheezing within the first 2 years and asthma prevalence within the first 10 years of life are shown in Supplementary Table 1. Case numbers are displayed for the total LINA cohort (n = 629), for the sub-cohort used to analyse the VOC sources (information available for new flooring and new furniture of the study participants during pregnancy as well as VOC measurements during pregnancy; n = 598) and for the final sub-cohorts when BKMR analyses were performed (available information about all used confounders, VOC measurements during pregnancy as well as wheezing within the first 2 years; n = 483 or asthma within the first 10 years of life; n = 282). For BKMR analyses at year one, there were 7 (wheezing

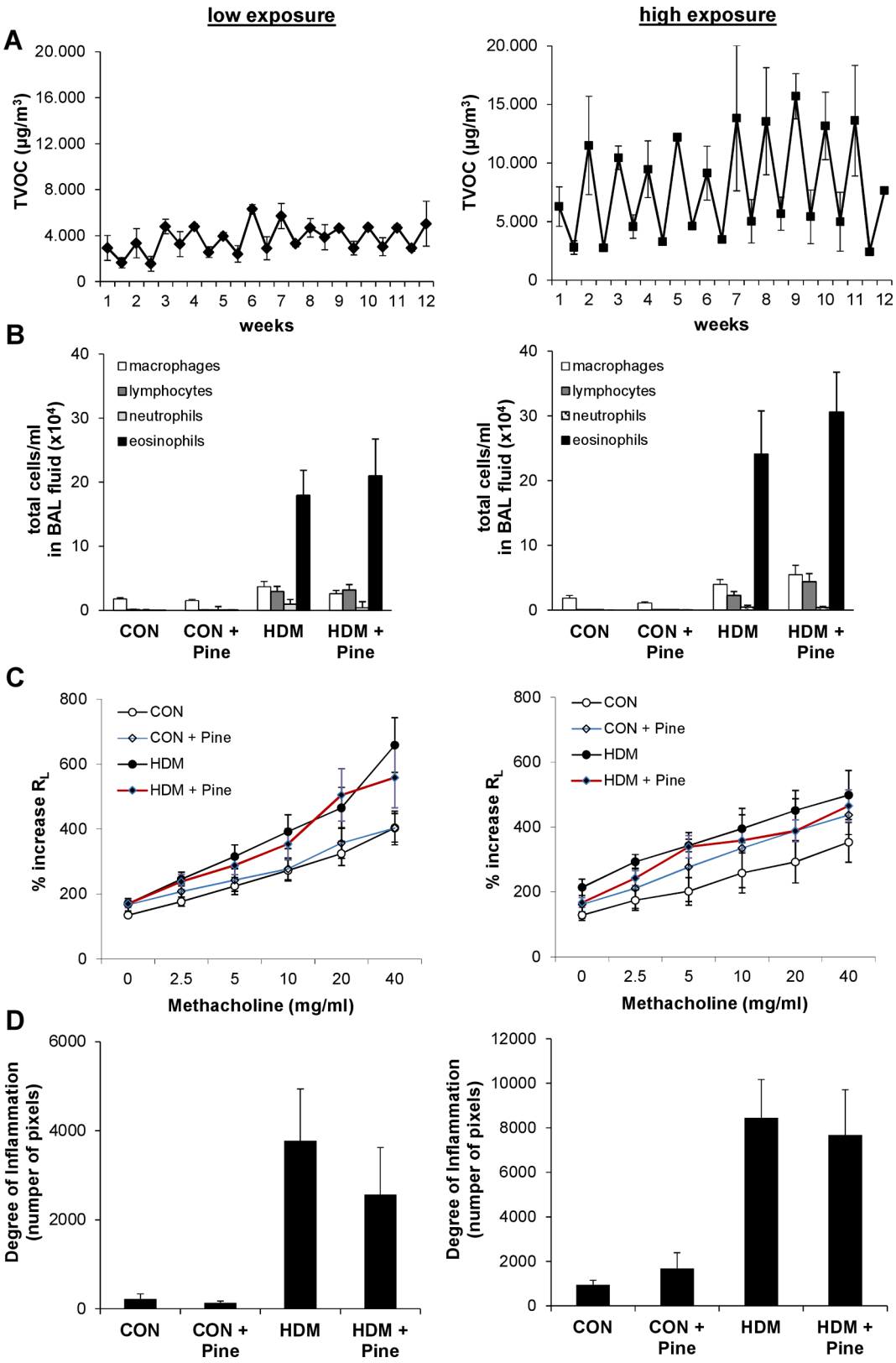

Fig. 3. Effect of long-term exposure to pinewood on airway inflammation and lung function in HDM-sensitized mice. (A) TVOC concentrations for low and high exposure are shown. (B) Total cell number in BAL fluid, (C) lung resistance and (D) airway inflammation were examined in HDM-sensitized and control mice. Data are expressed as mean ± SEM, n = 3 (A), n ≥ 9 (B – D).

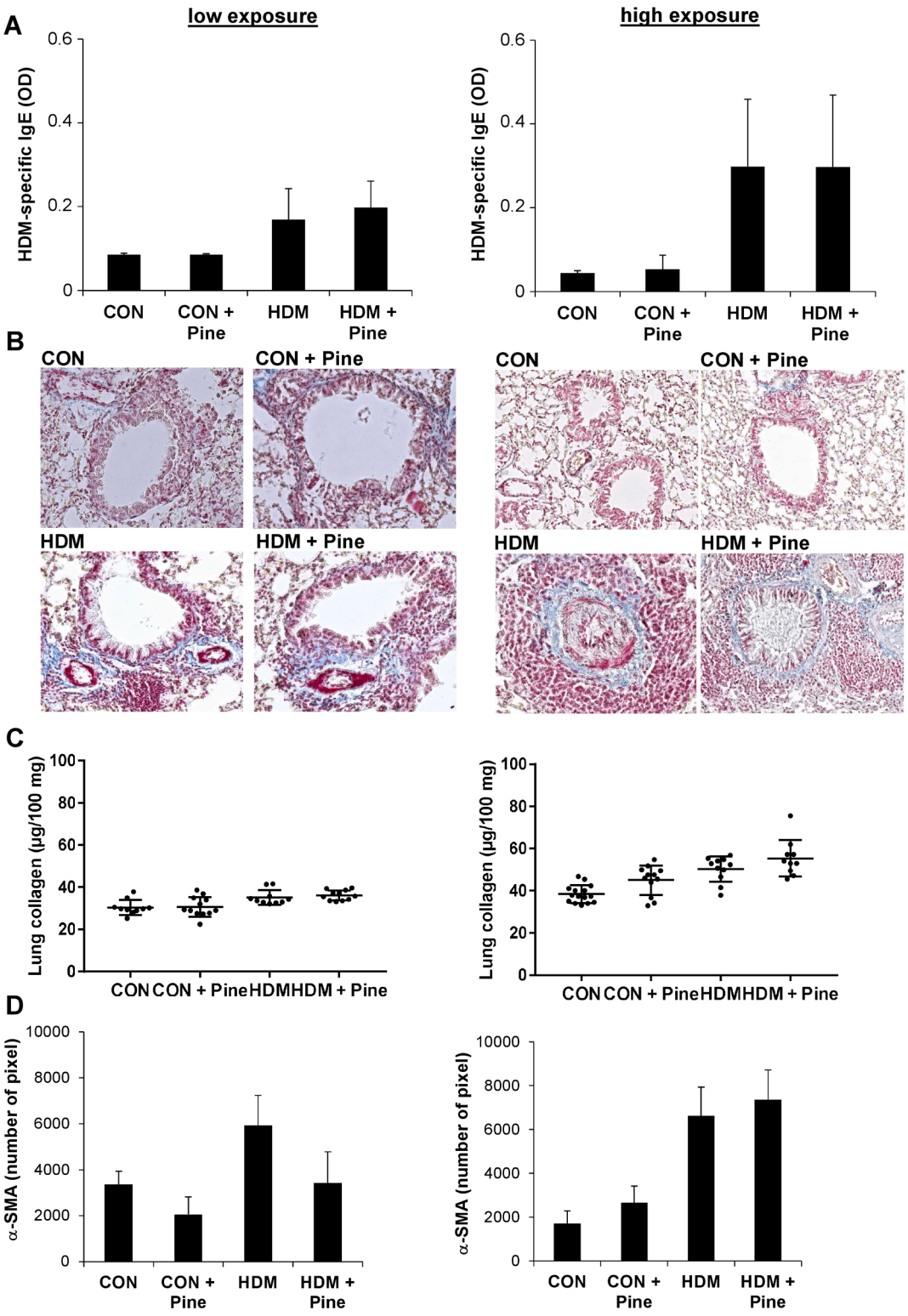

Fig. 4. Effect of long-term exposure to pinewood on IgE level and airway remodeling in HDM-sensitized mice. (A) HDM-specific IgE serum levels, (B) MSB-stained lung tissues (x100), (C) total lung collagen, and (D) proliferation of airway smooth muscle cells as quantified by an investigator-independent computer-based analysis were examined in HDM-sensitized and control mice. Data are expressed as mean ± SEM, n ≥ 9.

model) or 3 (asthma model) missing VOC measurements compared to VOC measurements during pregnancy. There were no differences in the general distribution of study characteristics/confounders in the final BKMR sub-cohorts for wheezing/asthma compared to the entire LINA cohort.

VOCs shown to be emitted by softwood and related products such as terpenes (α-pinene, β-pinene, 3-carene, and limonene) and aldehydes (pentanal, hexanal, heptanal, octanal and nonanal) were present in the homes of the study participants in the highly sensitive perinatal time period. Single wood-related VOC concentrations measured during pregnancy and around children's first birthday are shown in Supplementary Table 2, their total sum being similar for both time points

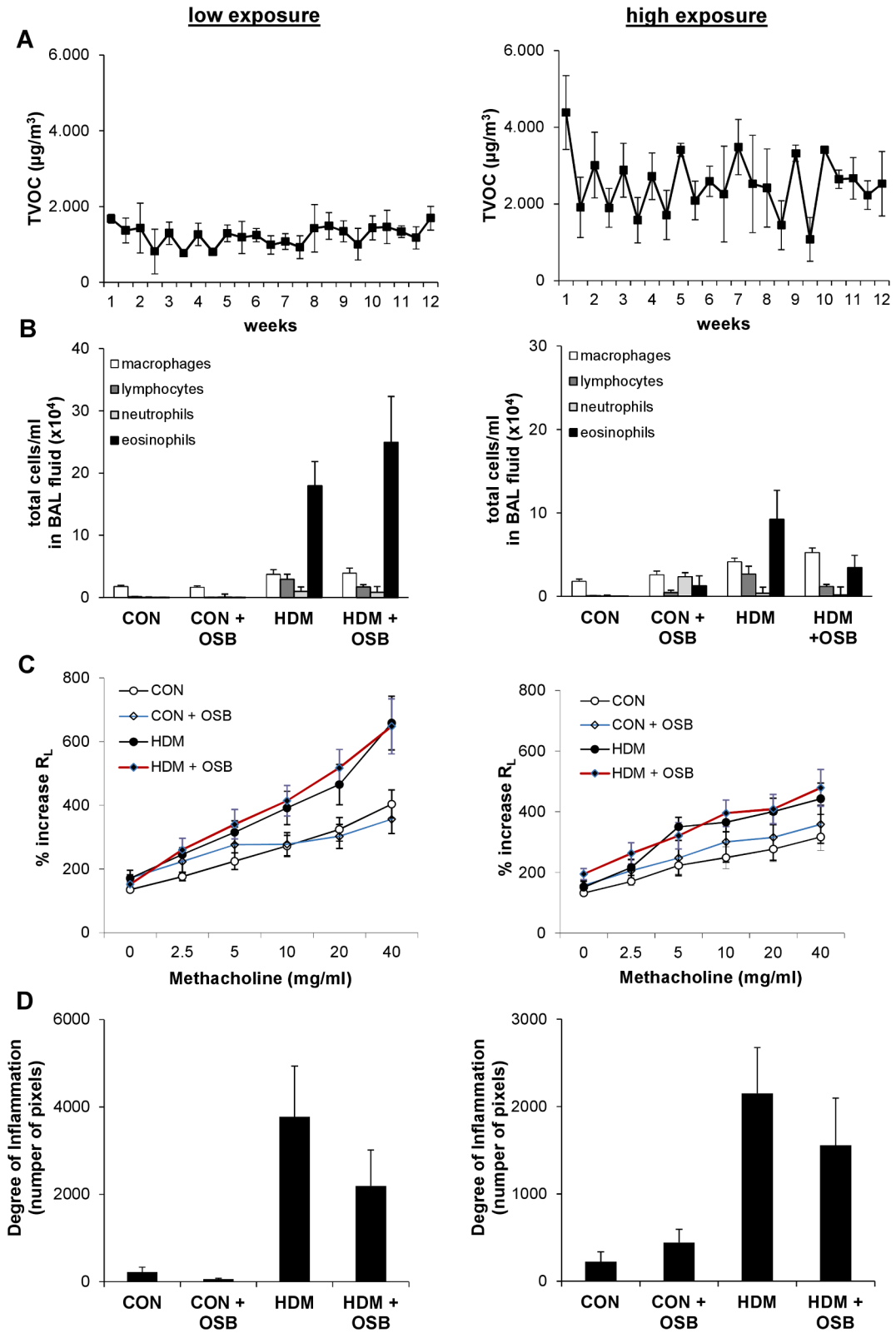

Fig. 5. Effect of long-term exposure to OSB on airway inflammation and lung function in HDM-sensitized mice. (A) TVOC concentrations for low and high exposure are shown. (B) Total cell number in BAL fluid, (C) lung resistance and (D) airway inflammation were examined in HDM-sensitized and control mice. Data are expressed as mean ± SEM, n = 3 (A), n ≥ 9 (B – D).

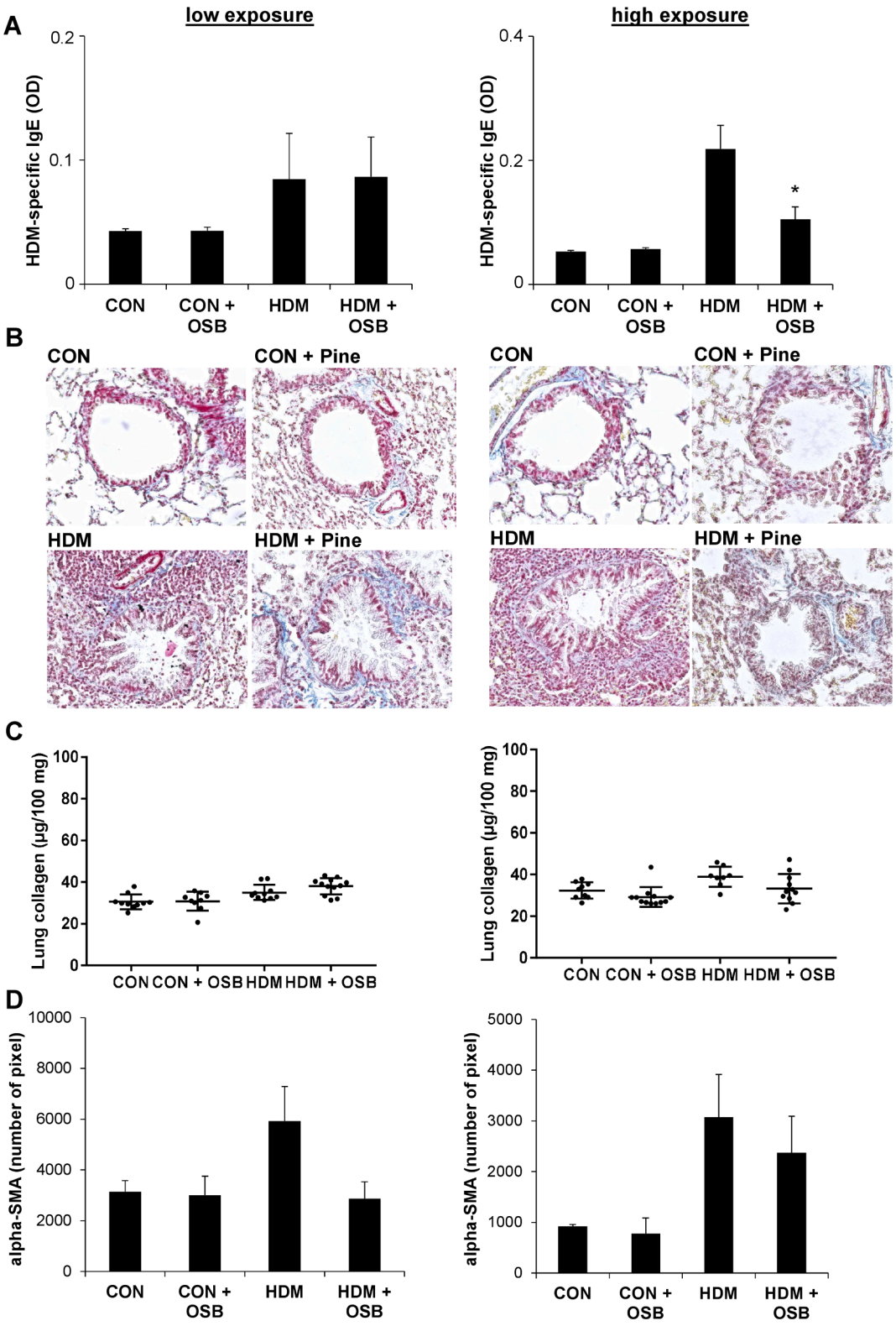

Fig. 6. Effect of long-term exposure to OSB on IgE level and airway remodeling in HDM-sensitized mice. (A) HDM-specific IgE serum levels, (B) MSB-stained lung tissues (x100), (C) total lung collagen and (D) proliferation of airway smooth muscle cells as quantified by an investigator-independent computer-based analysis were examined in HDM-sensitized and control mice. Data are expressed as mean ± SEM, n ≥ 9, *$P < 0.5$ HDM *vs.* HDM + OSB.

(pregnancy: 44.9 µg/m^3; year one: 47.5 µg/m^3).

To further display potential indoor sources of wood-related VOCs, questionnaires were analysed addressing if study participants had purchased new furniture, and if so from what material. Further, information on renovation activities in particular new flooring was considered. Exemplary shown for the time point of pregnancy, participants who documented new furniture from solid wood had a significant higher concentration of wood-related VOCs in their homes compared to participants without new solid wood furniture (Fig. 8A, Supplementary Table 3). In addition, documented parquet flooring significantly

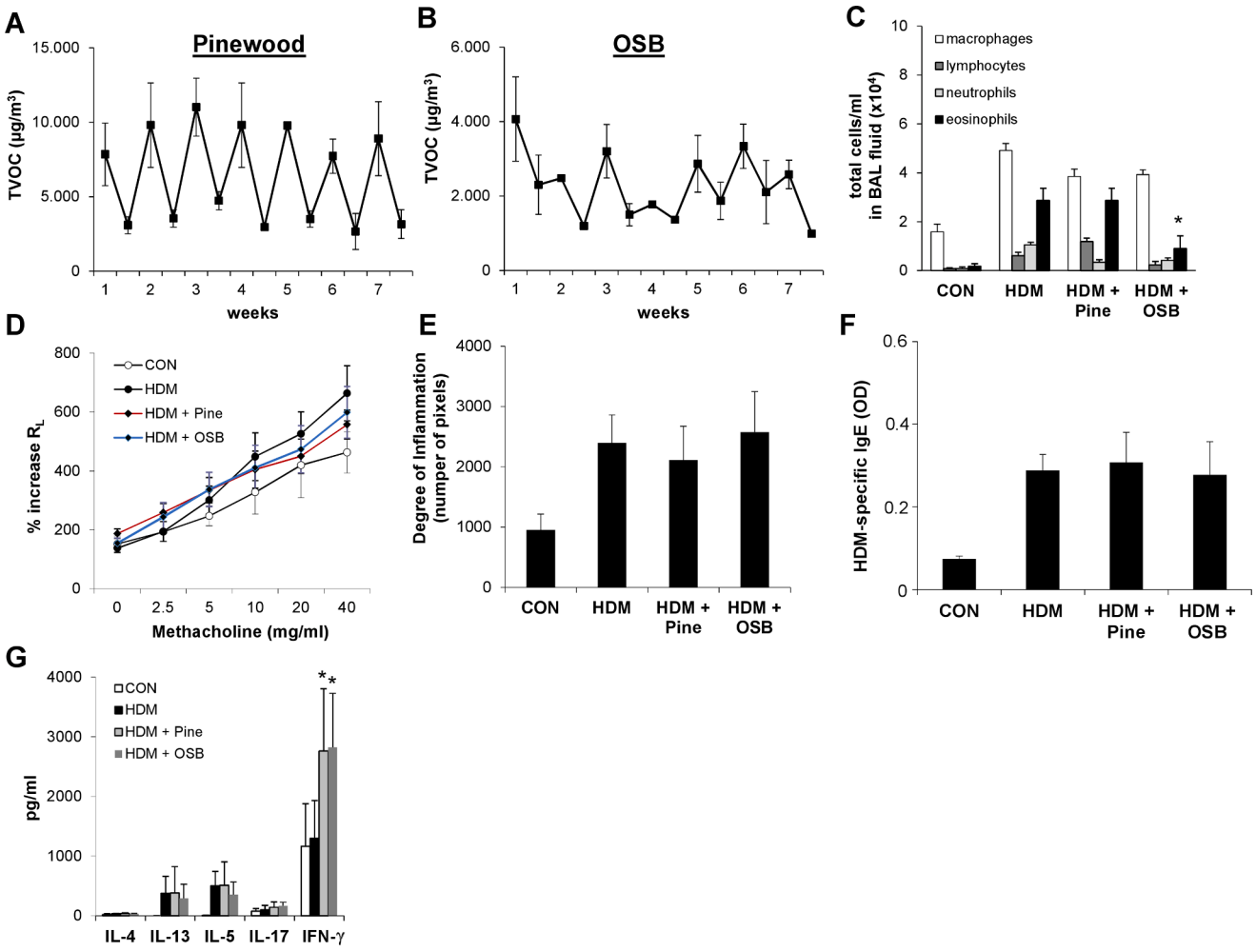

Fig. 7. Effect of perinatal exposure to pinewood or OSB on asthma development in the offspring. TVOC concentrations for the whole exposure period for (A) pinewood and (B) OSB are shown. (C) Total cell number in BAL fluid, (D) lung resistance, (E) airway inflammation examined by lung histology (H&E, x100), (F) quantified by an investigator-independent computer-based analysis, (G) HDM-specific IgE serum levels and (H) cytokine production of re-stimulated splenocytes were examined in HDM-sensitized and control mice. Data are expressed as mean ± SEM, n = 2 (A, B), n ≥ 9 (C – H), *$P < 0.5$ HDM *vs.* HDM + Pine or HDM + OSB.

enhanced the wood-related VOC concentration compared to no parquet flooring. In contrast, particleboard furniture as well as other types of flooring did not influence wood-related VOCs.

3.5. *Wood-related VOC exposure and wheezing/asthma in LINA*

Since our study participants are realistically rather exposed to a complex mixture of wood-related VOCs instead of single VOCs, an epidemiological mixture analyses via BKMR was applied for the LINA data. Within the BKMR subcohort, 141 children (29.2%) developed an early wheeze within the first 2 years of life, 29 children (10.3%) developed asthma within the first 10 years of life, respectively.

Taken together, mixture analyses revealed no effects on early wheeze or asthma risk, neither when exposure to wood-related VOCs was during pregnancy (P) or year one (Y1) nor when only high risk children with a positive FHA were considered. In detail, BKMR offered different calculations to mimic different possible mixture scenarios. The *univariate exposure–response function* pictures the full range of one mixture component when simultaneously all other mixture components are held at their median concentrations (early wheeze: Figure S8A, C (P), Figure S9A, C (Y1); asthma: Fig. 8B, D (P), Fig. 9A, C (Y1)). The *cumulative effect* displays the comparison when all of the mixture components were fixed at their median value, with when all of the mixture components are at a particular (same) percentile (early wheeze: Figure S8B, D (P), Figure S9B, D (Y1); asthma: Fig. 8C, E (P), Fig. 9B, D (Y1)).

Taken together, we were able to show consistent results from experimental mouse and cohort data revealing no harmful effect of wood-related VOCs on respiratory outcomes, independent from an allergic risk/sensitization pattern, and from duration or time point of exposure.

4. Discussion

An increased use of sustainably produced wood in construction or for all sorts of long-lived products might be able to contribute to reducing society's carbon footprint (Hildebrandt et al. 2017; Kalt 2018). In this context, the evaluation of possible health effects by wood emissions is of considerable interest.

In regard to indoor air quality, TVOC levels below 1 mg/m^3 are declared as good air quality by the German Environment Agency while TVOC levels between 3 and 10 mg/m^3 are classified as hygienically critical and TVOC levels higher than 10 mg/m^3 as unacceptable condition (Umweltbundesamt 2007). Therefore, in the present study we exposed mice to wood-generated TVOC concentrations above 3 mg/m^3 up to TVOC levels of more than 10 µg/m^3. In contrast to earlier mouse studies investigating the effect of exposure to single VOCs (Bönisch et al. 2012; Li et al. 2017; Nielsen et al. 2005) we confronted the animals directly to pinewood or OSB and therefore to the whole emission

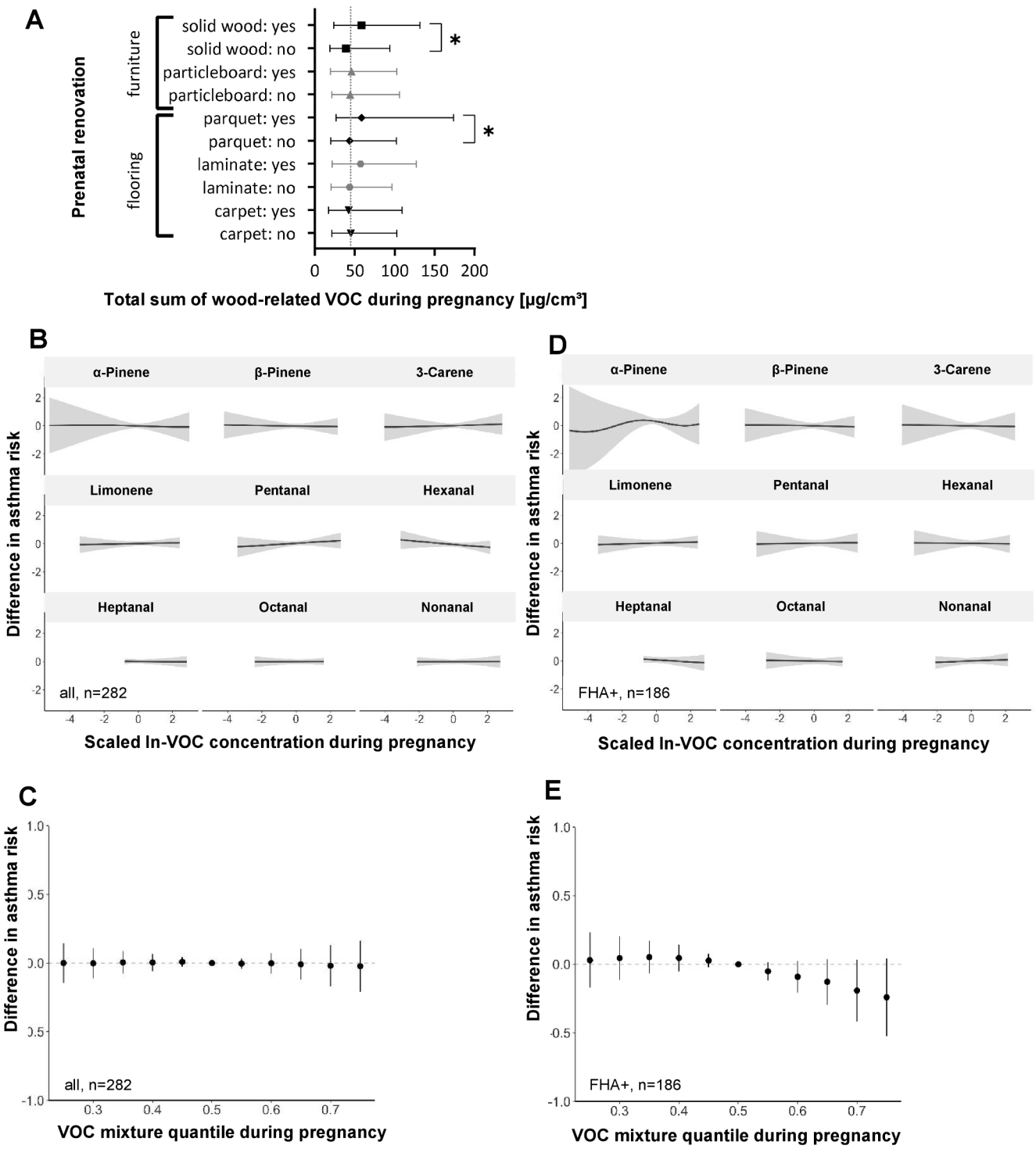

Fig. 8. Wood-related VOCs during pregnancy. (A) Indoor sources of wood-related VOCs: Total sum of wood-related VOCs was calculated from terpenes (α-pinene, β-pinene, 3-carene, limonene) and aldehydes (pentanal, hexanal, heptanal, octanal and nonanal), measured at 36th week of pregnancy. Shown are median with interquartile range; *$p < 0.05$, Mann-Whitney *U* test; vertical line at overall median (44.91 µg/m^3, n = 598); for individual case numbers and concentrations see Supplementary Table 3. (B - C) VOC exposure during pregnancy and asthma risk within the first 10 years of life in all children and (D - E) stratified by their family history of atopy (FHA). Data are estimated by Bayesian Kernel Machine Regression (BKMR) and by considering the following covariates: family history of atopy (except for D, E), smoking during pregnancy, maternal age at delivery, gender of the child, parity, parental school education, keeping of pets, delivery mode, breastfeeding duration and overweight development in infancy (VOCs are ln-transformed, scored and grouped by correlating exposures: α-pinene, β-pinene, 3-carene, limonene and pentanal, hexanal, heptanal, octanal, nonanal). (B/D) Univariate exposure–response function and 95% confidence bands; pictures the full range of one mixture component when simultaneously all other mixture components are held at their median concentrations (C/E) Overall/Cumulative effect; pictures the comparison when all of the mixture components were fixed at their median value, with when all of the mixture components are at a particular (same) percentile, shown are estimated differences in asthma risk and 95% credible intervals.

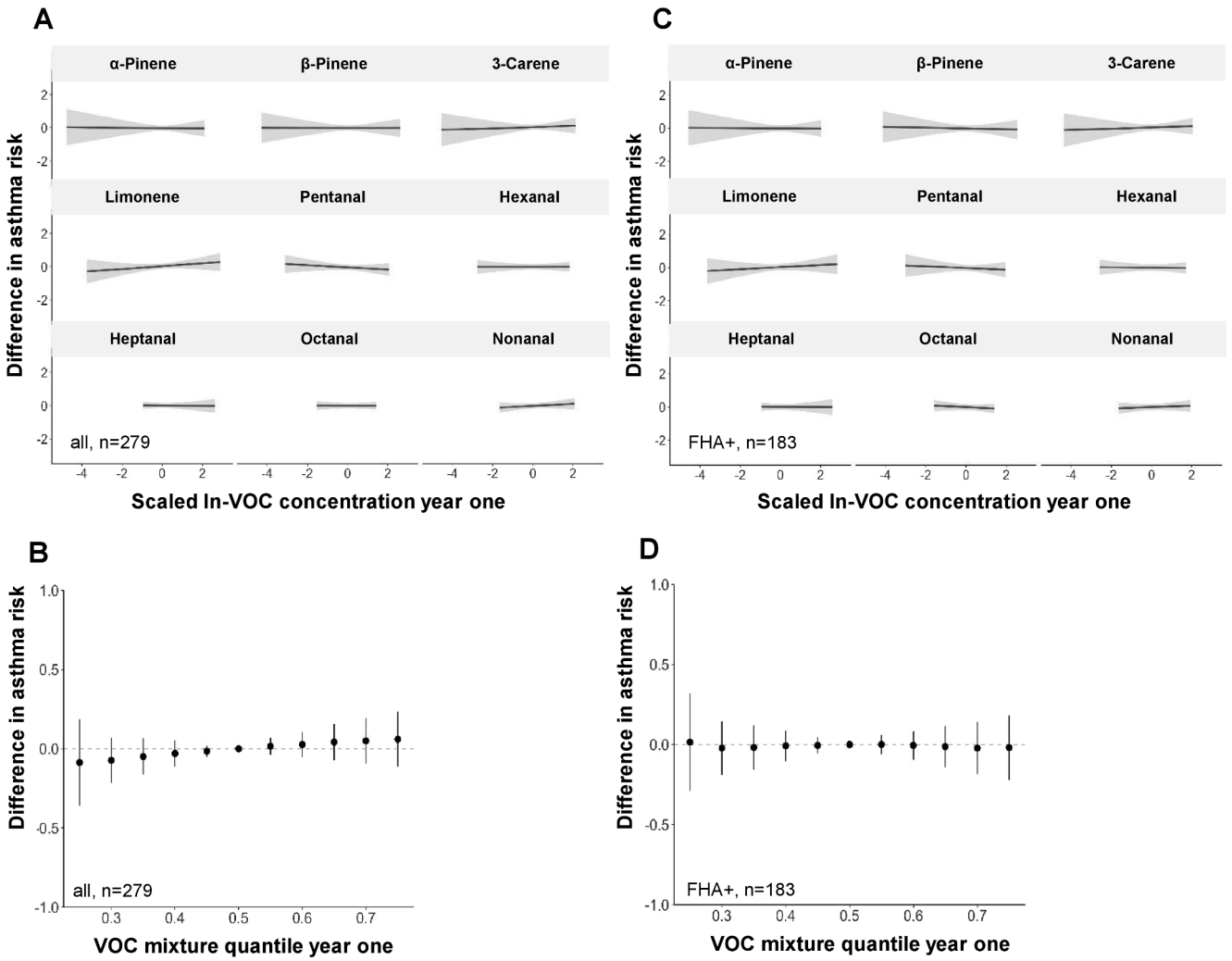

Fig. 9. Wood-related VOCs year one. (A - B) VOC exposure at year one and asthma risk within the first 10 years of life in all children and (C - D) stratified by their family history of atopy (FHA). Data are estimated by Bayesian Kernel Machine Regression (BKMR) and by considering the following covariates: family history of atopy (except for C, D), smoking during pregnancy, maternal age at delivery, gender of the child, parity, parental school education, keeping of pets, delivery mode, breastfeeding duration and overweight development in infancy (VOCs are ln-transformed, scored and grouped by correlating exposures: α-pinene, β-pinene, 3-carene, limonene and pentanal, hexanal, heptanal, octanal, nonanal). (A/C) Univariate exposure–response function and 95% confidence bands; pictures the full range of one mixture component when simultaneously all other mixture components are held at their median concentrations (B/D) Overall/Cumulative effect; pictures the comparison when all of the mixture components were fixed at their median value, with when all of the mixture components are at a particular (same) percentile, shown are estimated differences in asthma risk and 95% credible intervals.

spectrum of the products. This approach also allowed us to mimic long-term exposures about twelve weeks to examine the impact of continuously inhalation of an indoor-relevant VOC mixture on the airways, something that has not been examined so far. Moreover, within the long-lasting asthma model we could also evaluate possible effects on airway remodelling, the structural alterations that occur as result of chronic asthma development (Fehrenbach et al. 2017). Overall, our data demonstrate that neither pinewood nor OSB emissions even at high TVOC levels and a long-lasting exposure period induce significant inflammatory or acute/chronic asthma-promoting effects in sensitized or non-sensitized mice. At most, one could indicate a slight trend of an increased lung resistance and elevated lung collagen and isoprostane levels in non-sensitized mice after long-term exposure to high-emitting pinewood. In that respect, there are a few human studies investigating health effects of occupational VOC exposure in sawmills or joineries with high terpene levels. The data show no association between terpene exposure (9 – 214 mg/m^3) and respiratory symptoms of participants (Eriksson et al. 1997; Eriksson et al. 1996) but also an impaired lung function of workers exposed to an average terpene concentration of 258 mg/m^3 (Hedenstierna et al. 1983). These different findings might be due to the different terpene levels, but it also needs to be considered that other factors occurring in sawmills like dust particles or mould might trigger the observed respiratory symptoms (Hedenstierna et al. 1983). Experimental studies with human participants exposed to wood-related VOCs under controlled conditions using a specific exposure chamber revealed no irritation of the airways or effects on lung function at TVOC levels of pinewood up to 13 mg/m^3 (Gminski et al. 2011b), of OSB up to 9 mg/m^3 (Gminski et al. 2011a) or hexanal concentrations of 42 mg/m^3 (Ernstgard et al. 2006). In contrast, exposure to a VOC mixture (α-pinene, β-pinene, 3-carene) of 450 mg/m^3 induced a mild airway inflammation but had no effect on pulmonary function (Johard et al. 1993). Either way, the few observed respiratory effects only occur at very high VOC levels that do not normally occur in the general living environment.

A more surprising result from our murine asthma model was the significant reduction of allergic airway inflammation after short-term exposure to OSB emitting, beside terpenes, higher levels of aldehydes. In vitro studies indicate that aldehydes might rather have a more

adverse impact than terpenes (Gminski et al. 2010) making it difficult to interpret these findings. It is also interesting, that OSB exposure not only diminished the asthma-relevant Th2 cytokines IL-13 and IL-5 but also the Th17 cytokine IL-17 and the Th1 cytokine IFN-γ suggesting a general immune suppressive function. However, considering that the asthma-reducing effect was observed using a protocol for a mild asthma phenotype the findings should not be overestimated.

Concerning chemical-induced health effects, it became evident that the prenatal and early postnatal period is a critical time window to environmental exposures (Martino and Prescott 2011; Rubin and Soto 2009). In recent studies we could demonstrate that low-dose exposure of adult mice to endocrine disrupting chemicals such as phthalates or parabens had no effect on asthma development or metabolic parameters but led to an increased airway inflammation or weight gain in the offspring after exposure during pregnancy and the lactational period (Jahreis et al. 2018; Leppert et al. 2020). Therefore, we additionally examined the effect of maternal exposure over 7 weeks to pinewood or OSB on asthma development in the offspring. Here as well, both wood products did not decisively affect the severity of the asthma phenotype in the next generation. Next, we evaluated the effect of early-life exposure to wood-related VOC on children's asthma risk in our mother–child cohort LINA. While several epidemiological studies have investigated the impact of terpenes or aldehydes on the disease risk in adults (Cakmak et al. 2014; Glas et al. 2015; Salonen et al. 2009), there are no data so far addressing the effect of prenatal or early-life exposure to wood VOCs on asthma development in children. Within our LINA study, we could confirm wood products as a principal source for wood-specific emission by linking the exposure to new wooden furniture or flooring with increased levels of typical wood VOCs. To investigate the possible impact of prenatal and early postnatal exposure to wood-related VOCs on children's early wheezing until the age of 2 / asthma risk until age 10 we used a mixture model to assess combined effects of the measured VOCs (Bobb et al. 2018; Preston et al., 2020). Individuals are ubiquitously exposed to multiple wood-related VOCs and therefore the understanding of a possible joint VOC effect on wheezing/asthma risk is critically important. Taken together, epidemiological BKMR data did not show any harmful effect of the perinatal exposure to wood-related VOCs measured in the homes of study participants, independent from the time point of exposure (pregnancy/year one) or their individual atopy risk. However, indoor measurements were performed with different time delays after redecoration activities. Thus, the measured concentrations might just be proxies for experienced higher exposure concentrations. Of course, also VOCs from other sources such as tobacco smoke were shown to impact respiratory disease risk, in particular in the highly sensitive perinatal period (Franck et al. 2014; Junge et al., 2014); however this aspect was adjusted for – next to others - by including exposure to environmental tobacco smoke in the BKMR as a confounding factor. The use of BKMR allowed us to examine the joint and individual effects of exposure to multiple wood-related VOCs on children's early wheezing/asthma risk within the first 10 years of life by evaluating potential non-linear exposure–response functions and interactions among wood-related VOCs. With this approach we were able to verify the experimental mouse work showing wood products as non-critical with respect to early wheezing/asthma development in childhood.

A general limitation of the LINA study is the potential bias by high rates of participating atopic parents who may have had special interest in the topic of the study. We have considered this point by always including the parental atopy history as confounding variable in the overall BKMR models. In addition, wheezing and asthma outcome diagnosis is a parental reported doctor's diagnosis that may carry some minor inaccuracies. With respect to the VOC analyses and their potential sources, until now the decay of VOC concentrations after renovation activity is not well described. Moreover, indoor measurements were performed with different time delays after redecoration activities. Thus, the measured concentrations in the homes of the study participants were just proxies for supposedly experienced higher exposure concentrations. However, we were able to overcome this point by a direct exposure scenario within the experimental mouse analyses.

5. Conclusions

We investigated the impact of exposure to VOCs emitted by pinewood and OSB on the airways of allergen-sensitized and non-sensitized mice using an acute, chronic and cross-generational asthma model. We found that neither short-term, long-term nor perinatal exposure to these wood products had pro-inflammatory or asthma-promoting effects in healthy or sensitized animals. In our mother–child cohort LINA, we further examined the outcome of exposure to multiple wood-related VOCs during pregnancy or the first year of life on children's wheezing/asthma risk. Using the BKMR approach, we clearly demonstrated that the mixture of wood-related VOCs has no impact on early wheezing/asthma development in children until age 10. To our knowledge, this is one of the first studies assessing the effects of the whole spectrum of VOC emission from wood products using an in vivo model and BKMR to analyse joint effects of multiple wood-related VOCs on children's wheezing/asthma risk in a mother–child cohort. Our findings indicate that emissions from wood and wood products at levels usually occurring in the living environment do not induce adverse effects in the respiratory system.

Author contribution

T.P. designed and conducted the experimental study; E.E. performed the mouse experiments; K.J. and L.B. analysed the cohort data; K.B. and M.O. measured VOCs in the mouse study; T.K., U.E.R.K and M.v.B. were involved in the VOC analytic in the cohort; I.L., G.H., S.R., M.B. and W.K. developed the LINA study design or performed cohort clinical visits; T. P., K.J., L.B., R.G., J.C.S. and M.O. discussed the data with substantial contributions from I.L.; T.P., K.J., and L.B. wrote the paper with substantial inputs from K.B. and I.L.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Marita Reiprich and Melanie Bänsch for excellent technical assistance and all participants of the LINA study for contributing to the study over all the years.

Funding

This work was supported by the agency for renewable raw materials of the Federal Ministry of Food and Agriculture (FKZ22011015, FKZ22011115, and FKZ22008714).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106449.

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