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世代研究中環境暴露與表觀基因改變的相關性：以產前陶斯松暴露及環境溫度對成人的效應為例

Environmental Exposures in Association with Epigenetic Alterations in Cohort Studies: Using Prenatal Chlorpyrifos Exposure and Ambient Temperature Effects in Adults as Examples

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本論文係 邱冠智 (F04844008) 在國立臺灣大學環境與職業健康科學研究所完成之博士學位論文，於民國 113 年 05 月 04 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Institute of Environmental and Occupational Health Sciences on 04 (date) 05 (month) 2024 (year) have examined a Doctoral Dissertation entitled above presented by Kuan-Chih Chiu (F04844008) candidate and hereby certify that it is worthy of acceptance.

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中文摘要

環境暴露與表觀基因改變的相關性

環境暴露會經由改變表觀基因調控造成不良健康效應，表觀基因標記可以在不影響 DNA 序列的狀況下調控基因表現，並進一步影響表現型或疾病感受性。我們以產前陶斯松暴露及環境溫度對成人的效應為例，探討在世代研究中環境暴露與表觀基因改變的相關性。

產前陶斯松暴露與胎盤 *PPARγ* 基因之 H3K4me3 調控及健康效應的相關性

背景：陶斯松是常見的殺蟲劑之一，他可以穿過胎盤影響胎兒生長及神經發展。peroxisome proliferator-activated receptor gamma (*PPARγ*) 基因的表觀基因調控是陶斯松暴露影響胎兒生長及發展的可能機轉，例如透過 trimethylation of lysine 4 of H3 (H3K4me3) 之組蛋白修飾。本研究欲探討產前陶斯松暴露與胎盤 *PPARγ* 基因之 H3K4me3 調控、新生兒健康及神經發展的相關性。

方法：本研究納入 2004 年 4 月至 2005 年 1 月間進入臺灣出生世代研究 (Taiwan Birth Panel Study) 的 425 對母嬰對，使用 online SPE-LC/HESI/MS/MS 測量臍帶血中陶斯松濃度，胎盤 *PPARγ* 基因之 H3K4me3 調控程度以 ChIP-qPCR 測量，新生兒健康資料從病歷取得，使用嬰幼兒綜合發展測驗 (CDIIT) 計算兩歲孩童之神經發展。我們使用多變項迴歸模型校正潛在干擾因子。

結果：校正潛在干擾因子後，產前陶斯松暴露濃度每增加一個單位 (log-ng/mL) 和降低兩歲孩童的認知及語言表現有關，尤其是男童 (adjusted β (aβ) = -1.66, p = 0.016 及 aβ = -1.79, p = 0.023)。*PPARγ* 基因之 H3K4me3 調控程度和妊娠週數 (aβ = 0.16, p = 0.011) 、出生體重 (aβ = 30.52 (g), p = 0.013) 、出生身長 (aβ = 0.18 (cm), p = 0.003 及 aβ = 0.15 (cm), p = 0.042) 、兩歲粗大動作表現 (aβ = 1.67, p = 0.036) 存在正相關。

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結論：本研究發現產前陶斯松暴露會影響認知及語言表現。

環境溫度暴露與成人 DNA 甲基化老化

背景：氣候變遷導致過去數十年環境溫度上升，暴露環境高溫會造成生物老化現象，但在溫暖氣候區的相關研究依然缺乏。本研究目標為分析環境溫度與熱指數暴露的年齡加速效應，並以副熱帶氣候的臺灣人為研究族群。

方法：本研究納入 2008 年至 2016 年參與臺灣人體生物資料庫共 2,084 名研究參與者。我們從氣象站蒐集每日氣溫及相對溼度資料，並以 ordinary kriging 推估每位參與者在居住地的暴露量，再計算參與者進入研究前 1 至 180 天不同時間區間的環境溫度及熱指數移動平均值，而後用以估計暴露之效應。DNA 甲基化年齡使用 Horvath’s 、 Hannum’s 、 Weidner’s 、 *ELOVL2* 、 *FHL2* 、 phenotypic (Pheno) 、 Skin & blood 、 GrimAge2 (Grim2) 等方法進行估計，年齡加速定義為 DNA 甲基化年齡減去實際年齡。本研究使用多變項線性迴歸模型、廣義加成模型 (GAMs)、遞延非線性模型 (DLNMs) 分析環境溫度與熱指數暴露對年齡加速的影響。

結果：暴露環境高溫及高熱指數存在年齡加速效應，此效應會隨著暴露時間增加而增強。每日最高溫熱指數以警告 (80-90˚F) 、高度警告 (90-103˚F) 、危險 (103-124˚F) 、高度危險 (> 124˚F) 計算熱壓力天數，我們發現熱壓力天數也具有年齡加速效應，尤其是高度危險天數。高度危險天數每增加一天平均會增加 Horvath’s 571.38 (95% CI: 42.63-1100.13) 天、Hannum’s 528.02 (95% CI: 36.16-1019.87) 天、 Weidner’s 43.9 (95% CI: 0.28-87.52) 天、Pheno 16.82 (95% CI: 2.36-31.28) 天、Skin & blood 15.52 (95% CI: 2.17-28.88) 天的年齡加速效應。此外我們發現環境高溫的年齡加速效應存在季節及地理變異。

結論：環境高溫及高熱指數和加速生物老化有關。

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結論

我們發現在世代研究中環境暴露會改變表觀基因標記，而表觀基因標記又和健康效應有關，因此表觀基因標記在研究環境暴露對於人體的衝擊中扮演著重要的角色。

關鍵字：表觀基因、世代研究、環境暴露、陶斯松、環境溫度、組蛋白修飾、 DNA 甲基化年齡

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Abstract

Environmental exposures in association with epigenetic alterations

Environmental exposures can cause adverse health outcomes through the alteration of epigenetic regulation. Epigenetic marks can regulate gene expression without affecting DNA sequence, which may further influence phenotypes or susceptibility to diseases. We used prenatal chlorpyrifos exposure and ambient temperature effects in adults as examples to demonstrate environmental exposures in association with epigenetic alterations in cohort studies.

Prenatal chlorpyrifos exposure in relation to placental *PPARγ* H3K4me3 modifications and health outcomes

Background: Chlorpyrifos, one of the most widely used pesticides, can penetrate the placenta and affect fetal growth and neurodevelopment. Epigenetic regulation of peroxisome proliferator-activated receptor gamma (*PPARγ*), such as trimethylation of lysine 4 of H3 (H3K4me3), may provide a potential mechanism for how fetal growth and development are impacted by chlorpyrifos exposure. The aims of the study were to investigate whether prenatal chlorpyrifos exposure was associated with H3K4me3 levels of the *PPARγ* gene in the placenta and the related effects on birth outcomes and neurodevelopment.

Methods: Among 425 mother-infant pairs enrolled from April 2004 to January 2005 in the Taiwan Birth Panel Study, chlorpyrifos levels were measured in cord blood by using online SPE-LC/HESI/MS/MS; placental *PPARγ* H3K4me3 levels were measured by ChIP-qPCR; the neonates' health outcomes were extracted from the medical records; and childhood neurodevelopment was evaluated by using the Comprehensive

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Developmental Inventory for Infants and Toddlers in 2-year-old children. Multivariable regression models were used to adjust for potential confounders.

Results: After controlling for potential confounders, each unit increase in the natural log-transformed prenatal chlorpyrifos exposure level was associated with poorer performance in the cognitive and language domains at 2 years old, especially in boys (adjusted β (aβ) = -1.66, p = 0.016, and aβ = -1.79, p = 0.023, respectively). *PPARγ* H3K4me3 levels were positively associated with gestational age (aβ = 0.16 (week), p = 0.011), birth weight (aβ = 30.52 (g), p = 0.013), birth length (aβ = 0.18 (cm), p = 0.003 and aβ = 0.15, p = 0.042), and gross-motor performance (aβ = 1.67, p = 0.036).

Conclusions: Our findings suggested that prenatal chlorpyrifos exposure affected performance in the cognitive and language domains.

Ambient temperature exposures and DNA methylation aging in adults

Background: Climate change caused an increase in ambient temperature in the past decades. Exposure to high ambient temperature could result in biological aging, but relevant studies in a warm environment were lacking. We aimed to study the exposure effects of ambient temperature and heat index (HI) in relation to age acceleration in Taiwan, a subtropical island in Asia.

Methods: The study included 2,084 participants recruited from 2008 to 2016 in Taiwan Biobank. Daily temperature and relative humidity data were collected from weather monitoring stations. Individual residential exposure was estimated by ordinary kriging. Moving averages of ambient temperature and HI from 1 to 180 days prior to enrollment were calculated to estimate the exposure effects in multiple time periods. Age acceleration was defined as the difference between DNA methylation age and chronological age. DNA methylation age was calculated by the Horvath's, Hannum's,

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Weidner’s, *ELOVL2*, *FHL2*, phenotypic (Pheno), Skin & blood, and GrimAge2 (Grim2) DNA methylation age algorithms. Multivariable linear regression models, generalized additive models (GAMs), and distributed lag non-linear models (DLNMs) were conducted to estimate the effects of ambient temperature and HI exposures in relation to age acceleration.

Results: Exposure to high ambient temperature and HI were associated with increased age acceleration, and the associations were stronger in prolonged exposure. The heat stress days with maximum HI in caution (80-90˚F), extreme caution (90-103˚F), danger (103-124˚F), and extreme danger (> 124˚F) were also associated with increased age acceleration, especially in the extreme danger days. Each extreme danger day was associated with 571.38 (95% CI: 42.63-1100.13), 528.02 (95% CI: 36.16-1019.87), 43.9 (95% CI: 0.28-87.52), 16.82 (95% CI: 2.36-31.28) and 15.52 (95% CI: 2.17-28.88) days increase in the Horvath’s, Hannum’s, Weidner’s, Pheno, and Skin & blood age acceleration, respectively. In addition, seasonal and geographical variations were performed in the relationships between high ambient temperature exposure and increasing age acceleration.

Conclusion: High ambient temperature and HI may accelerate biological aging.

Conclusion

Environmental exposures can alter epigenetic marks, and epigenetic marks are associated with health outcomes in cohort studies. For this reason, epigenetic marks play important roles in studying the impact of environmental exposures on humans.

Key words: Epigenetics, cohort study, environmental exposures, chlorpyrifos, ambient temperature, histone modification, DNA methylation age

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Chapter 1. Environmental exposures in association with epigenetic alterations

Environmental exposures are important determinants of disease burdens in humans. Many studies revealed that environmental exposures resulted in adverse health outcomes through the alteration of epigenetic regulation (Hou et al., 2012; Wu et al., 2023). The current fields of epigenetic regulation include DNA methylation, histone modification, and microRNAs (Allis et al., 2007). Epigenetic marks can regulate gene expression without affecting DNA sequence, which may further influence phenotypes or susceptibility to diseases (Hou et al., 2012; Wu et al., 2023).

Prenatal exposures can impact fetal development and health outcomes in later life via changing epigenetic regulation (Gluckman et al., 2008; Lapehn & Paquette, 2022). Thus, prenatal exposures are crucial in studying the origins of diseases. In addition, we also want to investigate how environmental exposures affect epigenetic marks in adults. For these reasons, we used prenatal chlorpyrifos exposure and ambient temperature effects in adults as examples to demonstrate environmental exposures in association with epigenetic alterations in cohort studies. This dissertation was based on two of my previous publications, entitled “Prenatal chlorpyrifos exposure in association with PPARγ H3K4me3 and DNA methylation levels and child development” and “Exposure

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to ambient temperature and heat index in relation to DNA methylation age: A population-based study in Taiwan", respectively (Chiu et al., 2021; Chiu et al., 2024).

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Chapter 2. Prenatal chlorpyrifos exposure in relation to placental *PPARγ* H3K4me3 modifications and health outcomes

2.1. Introduction

2.1.1. Chlorpyrifos

Chlorpyrifos (O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate), a broad-spectrum organophosphate pesticide, has been widely used in agriculture, industrial sites, household insecticides, gardening, and government (USEPA, 2016) to kills many kinds of insects, such as cockroaches and mosquitoes by affecting the nervous system (USEPA, 2000). Many epidemiological studies have shown that prenatal chlorpyrifos exposure is associated with adverse birth outcomes (Perera et al., 2003; Whyatt et al., 2005), inflammatory reactions (H. M. Huang et al., 2019; Shaffo et al., 2018), metabolic syndromes (Lassiter & Brimijoin, 2008), and impairments in neurodevelopment (Burke et al., 2017). Residential use of chlorpyrifos was phased out in the United States in 2000 (USEPA, 2000) after studies reported the potential risk of unintentional exposures in children (USEPA, 2002). The European Union also banned chlorpyrifos in 2020 (European-Commission, 2020). In Taiwan, pesticides are used on a regular basis by many of the households for vector control. Taiwanese people still have a high risk of chlorpyrifos exposure, especially pregnant women, until the ban in April

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2024 (行政院農業委員會, 2022). For example, residential dust in Taiwan showed a high chlorpyrifos detection rate (78.8%) with no seasonal differences, and residential dust was also found to have a with higher chlorpyrifos concentration in Taiwan (median = 0.11 μg/g) (C. C. Hung et al., 2018) than in the United States (medians ranged from below the limit of detection (LOD) to 0.074 μg/g) (Deziel et al., 2015; Harnly et al., 2009; Quiros-Alcala et al., 2011). Huang et al. reported low within-person variability by comparing the urine metabolites of organophosphate pesticides among women in three trimesters of pregnancy in Taipei, Taiwan (Y. F. Huang et al., 2017); these results suggest continual widespread exposure during pregnancy. Therefore, understanding prenatal chlorpyrifos exposure levels is essential for risk assessment; however, knowledge of prenatal chlorpyrifos exposure is still lacking in Taiwan.

2.1.2. Prenatal chlorpyrifos exposure and placenta

The placenta plays a crucial role in intrauterine development and growth of the fetus during pregnancy (Nelissen et al., 2011), and the placenta is responsible for secreting pregnancy-associated hormones and growth factors, exchanging gases, nutrients, and metabolic wastes between the mother and fetus (Nelissen et al., 2011). Chlorpyrifos can penetrate and affect the placenta in a dose-related manner (Abdel-Rahman et al., 2002; Mattsson et al., 2000; Saulsbury et al., 2008) by reducing

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cellular viability and disturbing the function and differentiation of trophoblasts, the main functional cells of the placenta (Ridano et al., 2012; Ridano et al., 2017), which may ultimately result in adverse birth outcomes (Nelissen et al., 2011; Ridano et al., 2012). However, epidemiological evidence of adverse birth outcomes caused by prenatal chlorpyrifos exposure is still relatively limited.

2.1.3. Peroxisome proliferator-activated receptor gamma (PPARγ) and placenta

Peroxisome proliferator-activated receptor gamma (PPARγ), a ligand-activated transcription factor, plays an important role in placental development (Matsuda et al., 2013). PPARγ is involved in many cell processes, including cell differentiation, energy metabolism, and lipid homeostasis, and PPARγ modulates inflammatory and immune responses (Janani & Ranjitha Kumari, 2015), early brain development (Villapol, 2018), and cognitive performance (d'Angelo et al., 2019). PPARγ is expressed early as the developing embryo (Keller et al., 2000; Peraza et al., 2006), and placental PPARγ deficiency could result in embryonic death (Barak et al., 1999). Notably, an *in vitro* study found that chlorpyrifos exposure caused decreased PPARγ expression (Lee et al., 2014). In addition, PPARγ also plays an important role in trophoblast differentiation and the maintenance of maternal-fetal transport (Fournier et al., 2011; Kadam et al., 2015; Lendvai et al., 2016). Epidemiological studies have shown that the expression

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level of PPARγ in the human placenta is positively associated with birth weight and birth length (Diaz et al., 2012; Meher et al., 2016). In small for gestational age (SGA) fetuses, the PPARγ expression level was lower than that in appropriate and large for gestational age fetuses (Z. Chen et al., 2015; Diaz et al., 2012). Dysregulation of PPARγ may increase the risk of placental disorders and adverse neonatal health outcomes (Kadam et al., 2015). Therefore, PPARγ may provide a potential mechanism of placental toxicity caused by prenatal exposure to chlorpyrifos.

2.1.4. Chlorpyrifos exposure and epigenetic modifications

Low-dose of chlorpyrifos exposure during development in rats has been found to have long-term effects that persist after exposure (Perez-Fernandez et al., 2020). Epigenetic mechanisms provide a potential explanation of how the effect persisted after exposure (Baccarelli & Bollati, 2009; Heijmans et al., 2008). Trimethylation of lysine 4 of H3 (H3K4me3), one of the histone modification marks, is enriched around the transcription start site (TSS) and is important in regulating gene expression. H3K4me3 at the TSS is generally associated with transcriptionally active promoters (Barski et al., 2007). Animal and human cell line studies have found that *in utero* chlorpyrifos exposure changed epigenetics-associated gene expression (Kim et al., 2016; Moreira et al., 2010). Prenatal exposures can also induce transgenerational effects and determine

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disease susceptibility in later-life (Gluckman et al., 2008; Nelissen et al., 2011). To our knowledge, epidemiological evidence of the effects of prenatal chlorpyrifos exposure in association with epigenetic alterations is still lacking.

2.1.5. Study aims

The aims of the study were to study how prenatal chlorpyrifos exposure is associated with H3K4me3 levels of the *PPARγ* gene in the placenta and whether prenatal chlorpyrifos exposure is associated with birth outcomes and development in a birth cohort in Taiwan.

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2.2. Materials and methods

2.2.1. Study participants and questionnaire data

Details of the enrollment of study participants have been described previously (C. J. Hsieh et al., 2011). In brief, a total of 486 mother-infant pairs were enrolled in the Taiwan Birth Panel Study (TBPS), a birth cohort study that was conducted at one medical center in Taipei and one local hospital and two clinics in New Taipei City from April 2004 to January 2005. An in-person interview was administered by trained interviewers within three days after delivery by using structured questionnaires to obtain parental sociodemographic characteristics, residential address during pregnancy, and potential environmental exposures. Medical records were used to extract information on infant sex, gestational age, parity, and type of delivery (vaginal delivery or cesarean section). A follow-up postnatal questionnaire was administered by trained interviewers to collect children's anthropometric measurements, medical history, neurodevelopment, lifestyle, and residential environment when the children were 2 years of age. The study was approved by the Independent Ethics Committee of National Taiwan University Hospital (201307078RINB). Informed consent to participate in the study and follow-up was obtained from the pregnant women before giving birth.

2.2.2. Outcome assessments

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Medical records were used to extract information on birth outcomes, including gestational age, birth weight, and birth length. We defined a gestational age < 37 weeks as preterm birth and a birth weight < 2500 grams as low birth weight. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for gestational age according to the percentile scale derived from national Taiwanese data (W. S. Hsieh et al., 2006).

At 2 years of age, childhood neurodevelopment was evaluated by a trained physical therapist using the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT). The CDIIT was designed and standardized by Wang et al. in Taiwan (Wang et al., 1998) and was validated by Liao et al. (H. F. Liao et al., 2005). The whole CDIIT test has 343 items in five domains, namely cognitive, language, motor, social, and self-help. The cognitive domain was designed to examine the children's attention, perception, memory, reasoning, and concepts of number, color, size, and shape. The motor domain contains gross-motor and fine-motor subdomains. The social domain includes concepts of interpersonal interaction, affection, personal responsibility, and environmental adaptation. The self-help domain contains items regarding self-feeding, dressing, and hygiene skills. Each item was evaluated as either success or failure and was scored as 1 or 0 to represent success or failure, respectively. The scores were

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summed to represent each subdomain, domain, and the total score, and then each was transformed to developmental quotients to adjust for chronological age effects (M. H. Chen et al., 2013; H. F. Liao & Pan, 2005; Wang et al., 1998).

2.2.3. Sample collection

Placental (3 × 3 × 3-cm) and umbilical cord blood (10 mL) samples were collected immediately following delivery in the four aforementioned medical institutions by physicians trained with sample collection. Maternal and fetal sides of placental samples by the umbilical cord were collected. EDTA was added to blood samples to avoid clotting. The collected samples were then frozen at −80°C until the laboratory analyses were performed.

2.2.4. Chlorpyrifos exposure measurements

Prenatal chlorpyrifos exposure levels were measured in plasma samples from cord blood. The analyses and results are detailed in a prior publication (H. T. Liao et al., 2011). In brief, 300 μL of methanol was added to cord blood plasma at the same volume, vigorously shaken and centrifuged at 12,000 rpm for 10 minutes. The supernatant was transferred into a sample vial, and chlorpyrifos was measured by using online solid-phase extraction coupled with liquid chromatography-heated electrospray ionization tandem mass spectrometry (online SPE-LC/HESI/MS/MS). High linearity

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was demonstrated in the calibration curve of the standard solution ($r^2 = 0.9988$). The recovery tests were conducted by spiking the sample with 1 ppb chlorpyrifos, and the recovery rate was 97.2 ± 4.8%. The limit of detection (LOD) was 0.01 ng/mL, and 82.81% of cord blood samples had chlorpyrifos concentrations above the LOD. The investigators conducted all laboratory experiments blinded to the characteristics of the study participants.

2.2.5. Histone modification measurements of H3K4me3 — Chromatin immunoprecipitation coupled with quantitative polymerase chain reaction (ChIP-qPCR)

Twenty milligrams of placental samples were treated with 1% formaldehyde for 8 minutes at room temperature for DNA-protein crosslinking. Excess formaldehyde was then quenched, and crosslinked chromatin was released by cell lysis following the protocols for the Magna ChIP™ HiSens Chromatin Immunoprecipitation Kit (Millipore, cat. No. 17-10460). Chromatin extracts were sheared by sonication (Bioruptor Plus, Diagenode) at low power, with a 30 second ON/OFF setting, for 40 cycles. To confirm the optimal DNA fragment size of the sheared chromatin (i.e., DNA ranging from 200 to 1000 bp) (Haring et al., 2007; Lin et al., 2012), DNA samples were run on a 2% agarose gel.

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During immunoprecipitation (IP), 10 μL of Magna ChIP™ protein A+G Magnetic Beads (Millipore, cat. No. 16-663) were incubated with 3 μL of anti-H3K4me3 antibody (Millipore, cat. No. 05-745R) at 4°C with 75 rpm rotation for 1 hour. Then, 5 μL of sheared chromatin was added and incubated at 4°C with 75 rpm rotation overnight. The next day, the DNA-bead-antibody complexes were washed with an ice-cold Low Salt Wash Buffer, High Salt Wash Buffer, LiCl Wash Buffer, and TE Buffer in sequence following the protocol by Lin et al. (Lin et al., 2012). Finally, ChIPed DNA was de-crosslinked by incubating it with 50 μL of elution buffer and 1 μL of proteinase K at 65°C on a vortex platform for 2 hours and then purifying with a ChIP DNA Clean & Concentrator kit (Zymo Research, cat. No. D5205, USA).

The input samples were eluted and purified without IP procedures to represent the total amount of chromatin used in the IP reaction. Samples that were not incubated with antibody were used as negative controls following the same processes as used for the IP samples.

PPARγ H3K4me3 levels were evaluated by qPCR (LightCycler 480, Roche, Switzerland). Primer and TaqMan probe sets were designed within 1.5 kb upstream or downstream from the TSS, which was defined as the first position of protein coding in the genes (Ensembl, GRCh37). Sequences of primers and probes are shown in **Table**

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S1- 1. The qPCR program started at with 95°C for 10 minutes and then 50 cycles of 95°C for 10 seconds, 60°C for 30 seconds, and 72°C for 1 second. The results were obtained from the crossing point (Cp) of the 2nd derivative max; the smaller the Cp, the higher the DNA enrichment.

2.2.6. Statistical analysis

A total of 486 mother-infant pairs were enrolled in the TBPS. Since our primary aim was to evaluate the epigenetic effects, placental samples were required. Accordingly, 425 out of the 486 mother-infant pairs with placental samples collected were included in the analyses. Maternal educational level, type of delivery, parity, and infant sex were evaluated by χ^2, and chlorpyrifos levels, maternal age, maternal body mass index (BMI), birth outcomes, and CDIIT were evaluated by Student's t-tests between total participants and included participants. H3K4me3 levels were calculated by the percent of input method by the following equation: % Input = 2 ^ [Cp (Input) – Cp (ChIP)] * 100 (Haring et al., 2007). Pearson's correlation coefficient was used to calculate the correlation among H3K4me3 levels in *PPARγ*. Chlorpyrifos exposure levels were natural log-transformed due to the right-skewed distribution. Chlorpyrifos levels below the LOD were substituted with 1/2 LOD. Chlorpyrifos exposure effects were evaluated with the data evaluated as continuous and dichotomous (i.e., below or

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above median).

Univariable and multivariable linear regression models were used to study the following associations: prenatal chlorpyrifos exposure and H3K4me3 levels in *PPARγ*, prenatal chlorpyrifos exposure and health outcomes including birth outcomes and the development status at 2 years old, and H3K4me3 levels in *PPARγ* and health outcomes. If the point estimate before and after adjusting for a potential confounder had a 10% change or more, the variable was considered a confounder and was adjusted in the final model. Some variables representing potential determinants of early childhood development were also selected based on prior knowledge. The variables considered potential confounders were adjusted in the multivariable regression models, including maternal age, maternal BMI, maternal educational level, infant sex, gestational age, parity, and type of delivery (vaginal delivery or cesarean section). Previous studies have reported that chlorpyrifos exposure effects were different between boys and girls (Silver et al., 2017; Silver et al., 2018; Till et al., 2019). Likelihood ratio tests (LRTs) were used to measure the interaction effects between sex and chlorpyrifos exposure levels. We also conducted mediation analysis stratified by sex to investigate the sexual difference mediation effects of H3K4me3 levels in *PPARγ* within the relationships of chlorpyrifos exposure and health outcomes.

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Sensitivity analysis was conducted by removing participants if their mothers smoked during pregnancy or had preeclampsia, gestational hypertension (GHT), or gestational diabetes mellitus (GDM) to confirm whether smoking, preeclampsia, GHT, and GDM affect chlorpyrifos exposure-related effects. In addition, gestational age may be on the path of the exposure-health outcome association and associated with exposure and several health outcomes. Therefore, multivariable regression models with and without adjusting for gestational age were also conducted.

Since multiple neurodevelopmental performance outcomes were tested, permutation tests for linear models by lmPerm in R were used to adjust for multiple testing. All tests assumed a two-sided type I error of 0.05 and were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC) and R 3.5.2 (R Core Team, Vienna, Austria).

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2.3. Results

2.3.1. Characteristics of the study participants

Among the 486 mother-infant pairs in the TBPS, 425 of those with placental samples were included in the analyses. There were no significant differences in chlorpyrifos concentrations, maternal age, maternal BMI, maternal education level, type of delivery, parity, infant sex, gestational age, birth weight, birth length, or all domains in the CDIIT at 2 years old between the total participants in TBPS and the participants in the current analyses (**Table 1- 1**). Among the participants included in the analyses, the geometric mean chlorpyrifos concentration in cord blood was 0.13 (ng/mL) (geometric SD = 5.29) (**Table S1- 2**). The mothers' average age at delivery was 30.75 years old (SD = 4.59), and 74% of the mothers had a normal BMI. Most of the mothers received education from high school or above. Half of the infants were boys (50.12%), and 48.35% were firstborn. The vaginal delivery rate was 61.41%, which was similar to the results of a previous study in Taiwan (T. C. Liu et al., 2007). Regarding birth outcomes, the average gestational age, birth weight, and birth length were 38.47 weeks (SD = 1.63), 3154.02 g (SD = 449.11), and 48.98 cm (SD = 2.12), respectively.

Two hundred nineteen children were followed at 2 years old (follow-up rate = 51.53%). The follow-up participants had a higher maternal age and maternal education

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level, but no significant differences were shown in chlorpyrifos concentrations, maternal BMI, type of delivery, parity, infant sex, or placental *PPARγ* H3K4me3 levels (**Table 1-2**). The average scores of the CDIIT total score and the cognitive, language, motor, social, and self-help domain scores at 2 years old were 98.66 (SD = 13.04), 93.96 (SD = 12.54), 100.45 (SD = 13.08), 87.43 (SD = 12.44), 108.2 (SD = 16.87), and 100.94 (SD = 15.88), respectively.

2.3.2. Prenatal chlorpyrifos exposure and placental H3K4me3 levels in the *PPARγ* gene

The mean H3K4me3 levels around the *PPARγ* TSS were between 10.37 and 14.01 (% Input) (**Table S1- 3**). The correlations of the measured H3K4me3 levels between the 3 sites at the *PPARγ* TSS were high and statistically significant (Pearson's correlation coefficient r ranged from 0.67 to 0.73, $p < 0.0001$) (**Table S1- 4**).

The associations between chlorpyrifos exposure and H3K4me3 levels in *PPARγ* are summarized in **Table 1- 3**. The crude univariable regression models depict the associations without adjusting for potential confounders. In the univariable models, each unit increase in the natural log-transformed chlorpyrifos exposure level was associated with 0.97, 1.13, and 1.15 (% Input) increase in the *PPARγ* H3K4me3 levels, but the associations were not statistically significant. In the multivariable models, after adjusting for maternal age, maternal BMI, maternal educational level, type of delivery

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(vaginal delivery or cesarean section), parity, infant sex, and gestational age (week), similar chlorpyrifos exposure effects on *PPARγ* H3K4me3 level changes were observed (adjusted β (aβ) = 0.87, 1.34, and 1.16). The associations in multivariable models were not statistically significant (**Table 1- 3**).

2.3.3. Prenatal chlorpyrifos exposure and health outcomes

Chlorpyrifos exposure was associated with poor performance in the cognitive and language domains at 2 years old in the multivariable models (aβ = -1.20, 95% confidence interval (CI) = (-2.25, -0.15), p = 0.025, permutation p = 0.049, and aβ = -1.14, 95% CI = (-2.25, -0.03), p = 0.044, permutation p = 0.034, respectively) and the association has borderline significance in the univariable models (β = -1.01, 95% CI = (-2.10, 0.08), p = 0.07, and β = -0.95, 95% CI = (-2.10, 0.21), p = 0.11, respectively) (**Table 1- 4**). When chlorpyrifos levels were dichotomized at the median, scores of cognitive and motor domains were lower by approximately 3 points in the high chlorpyrifos exposure group than in the low exposure group (p = 0.14 and 0.09, respectively) (**Table S1- 5**). We did not observe significant effects of chlorpyrifos exposure in association with birth outcomes or performance in the motor, social, and self-help domains (**Table 1- 4**). We found that there was a borderline significant interaction effect of sex and exposure to birth weight (LRT, p = 0.094) (**Table S1- 6**). In

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boys, each unit increase in chlorpyrifos was associated with an increased birth weight of 22.74 g (95% CI = (-18.92, 64.40), p = 0.28) in the univariable model and a 25.33 g (95% CI = (-11.34, 62.01), p = 0.17) increase in the multivariable model (**Figure 1- 1** and **Table S1- 7**), whereas in girls, each unit increase in chlorpyrifos was associated with a decrease in birth weight of 9.45 g (95% CI = (-45.68, 26.78), p = 0.61) in the univariable model and a 12.83 g (95% CI = (-41.26, 15.6), p = 0.37) decrease in the multivariable model (**Figure 1- 1** and **Table S1- 8**). In association with the cognitive and language domains, both boys and girls showed poorer performances in the cognitive and language domains with chlorpyrifos exposure, but the associations were only significant among boys (aβ = -1.66, 95% CI = (-3.02, -0.31), p = 0.016, permutation p = 0.017, and aβ = -1.79, 95% CI = (-3.33, -0.26), p = 0.023, permutation p = 0.036) (**Figure 1- 1** and **Table S1- 7**). We did not find significant interaction effects of sex and exposure to development status including cognitive and language performances by LRTs (**Table S1- 6**).

2.3.4. H3K4me3 levels in the *PPARγ* gene and health outcomes

The associations between H3K4me3 levels in the *PPARγ* and health outcomes are summarized in **Figure 1- 2** and **Table S1- 9**. Birth outcomes were positively related to all 3 sites of H3K4me3 at *PPARγ*, although the significance values of the 3 sites were

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different. Each unit increase in H3K4me3 (log-% Input) in *PPARγ* R1 was associated with a 0.15-week (95% CI = (0.03, 0.28), $p = 0.016$) increase in gestational age in the crude univariable model and was associated with a 0.16-week (95% CI= (0.04, 0.29), $p = 0.011$) increase in gestational age after adjusting for potential confounders. In terms of birth weight, each unit increase in H3K4me3 in *PPARγ* R2 was associated with a 49.45 g (95% CI = (19.37, 79.53), $p = 0.001$) increase in the crude univariable model and was associated with a 30.52 g (95% CI= (6.36, 54.67), $p = 0.013$) increase after adjusting for potential confounders. In terms of birth length, each unit increase in H3K4me3 in *PPARγ* R2 and *PPARγ* R3 was associated with 0.26 cm (95% CI = (0.11, 0.40), $p < 0.001$) and 0.22 cm (95% CI = (0.06, 0.39), $p = 0.009$) increases in birth length in the crude univariable model, respectively, and with 0.18 cm (95% CI = (0.06, 0.30), $p = 0.003$) and 0.15 cm (95% CI = (0.01, 0.29), $p = 0.042$) increases, respectively, after adjusting for potential confounders. Comparing the SGA and appropriate for gestational age (AGA) groups, the average H3K4me3 level at *PPARγ* R2 was 5.44 in the SGA group and 14.66 in the AGA group. Each unit increase in the H3K4me3 level at *PPARγ* R2 was associated with an OR of 0.93 (95% CI = (0.86, 0.99), $p = 0.031$) in the univariable model and an adjusted OR (aOR) = 0.93 (95% CI = (0.86, 0.99), $p = 0.03$) in the multivariable model in association with SGA (with AGA as the reference group),

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as the *PPARγ* R2 H3K4me3 level was associated with increased birth weight and birth length. In association with 2-year-old development status, *PPARγ* R3 was associated with a 1.67-point (95% CI = (0.11, 3.23), $p = 0.036$, permutation $p = 0.34$) increased score in the gross-motor subdomain after adjusting for potential confounders.

2.3.5. Mediation analysis

Since our results indicated that the effects of chlorpyrifos exposure were different between boys and girls, we conducted mediation analysis stratified by sex to study the mediation effects of H3K4me3 levels in *PPARγ* within the relationships of chlorpyrifos exposure and health outcomes. In boys, the mediation effects of H3K4me3 levels in *PPARγ* R2 and R3 were statistically significant that the increase of chlorpyrifos exposure levels could increase H3K4me3 levels in *PPARγ* R2 and R3, and the increase of H3K4me3 levels in *PPARγ* R2 and R3 could increase birth length and the performance in the motor and gross-motor domains at 2 years old (**Figure 1- 3**). However, the total and direct effects were not significant in mediation analyses in boys. In girls, the mediation effects of H3K4me3 levels in *PPARγ* were not statistically significant within the relationships of chlorpyrifos exposure and health outcomes (data not shown).

2.3.6. Sensitivity analysis

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To determine whether maternal smoking and gestational diseases, including preeclampsia, GHT, and GDM, might influence the effect, $\chi 2$ and Student's t-tests were used to analyze the differences between included participants (n = 425) and participants excluding maternal smoking (n = 420) or gestational diseases (n = 415). There were no statistically significant differences among study participants with or without maternal smoking and gestational diseases in terms of baseline characteristics, chlorpyrifos levels measured, birth outcomes, development status at 2 years old, or *PPARγ* H3K4me3 levels. Analysis was conducted in the study participants without maternal smoking or gestational diseases, and similar results were found (data not shown). In addition, gestational age may be associated with exposure and several health outcomes. Multivariable regression models with or without adjustment for gestational age were also conducted, and similar results were found (data not shown).

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2.4. Discussions

Since residential use of chlorpyrifos was phased out in the USA in 2000, concentrations of chlorpyrifos in personal air samples, maternal blood, and umbilical cord blood have dropped rapidly since 2000 (USEPA, 2016; Whyatt et al., 2003). However, Taiwan has no such relevant regulations until 2024, and chlorpyrifos is ubiquitously detected in indoor and outdoor environments (C. C. Hung et al., 2018). Chlorpyrifos levels in cord blood in the present study (median = 0.17 ng/mL) were higher than those in studies conducted in New York City and California in the United States and in Zhejiang in China (median ranged from below the LOD to 0.003 ng/mL) (Huen et al., 2012; Silver et al., 2018; Whyatt et al., 2003). This might suggest that infants in Taiwan had a higher prenatal risk of chlorpyrifos exposure than infants in other areas.

In the present study, we examined the effects of prenatal chlorpyrifos exposure on birth outcomes, development status at 2 years old, and H3K4me3 levels of *PPARγ* in a birth cohort study in Taiwan. We found that prenatal chlorpyrifos exposure was associated with poor performance in the cognitive and language domains at 2 years old, especially in boys. *PPARγ* H3K4me3 levels were increased with increasing prenatal chlorpyrifos exposure, but the associations were not statistically significant.

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Although most of the studies in rodents found that low levels of prenatal chlorpyrifos exposure caused sex differences and poorer cognitive performance, the studies by Levin et al. (Levin et al., 2002) and Icenogle et al. (Icenogle et al., 2004) showed increased cognition in the T-maze and decreased cognition in the radial arm maze in both sexes (reviewed in (Silva, 2020)). In epidemiological studies, Rauh et al. found that prenatal chlorpyrifos exposure was associated with changes in brain structure in 5- to 11-year-old children by using magnetic resonance imaging (V. A. Rauh et al., 2012). Silver et al. reported that chlorpyrifos exposure levels measured in cord blood were associated with lower grating visual acuity in 9-month-old infants (Silver et al., 2018). Rauh et al. reported that compared with children with lower prenatal chlorpyrifos exposure, those with higher exposure (chlorpyrifos levels of > 6.17 pg/g plasma) had a significantly greater risk of mental and motor delays by 3 years old and were significantly more likely to have attention problems, attention deficit/hyperactivity disorder (ADHD) problems, and pervasive developmental disorder problems at 3 years old (V. A. Rauh et al., 2006). In their follow-up study, Rauh et al. reported that each standard deviation increase in prenatal chlorpyrifos exposure (4.61 pg/g) was associated with a 1.4% decline in the full-scale intelligence quotient (IQ) and a 2.8% decline in working memory in 7-year-old children (V. Rauh et al., 2011). Horton et al. reported a

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borderline significant interaction between prenatal chlorpyrifos exposure and child sex in which prenatal chlorpyrifos exposure was associated with a working memory decrease in boys but not in girls (Horton et al., 2012). The aforementioned studies indicated that prenatal chlorpyrifos exposure could affect brain development differently by sex, which was consistent with our results.

Among the studies using 3,5,6-trichloro-2-pyridinol (TCPy), a metabolite of chlorpyrifos in maternal urine, to represent prenatal chlorpyrifos exposure, Fluegge et al. reported that exposure was associated with adverse neurodevelopment among 3-months-old children (Fluegge et al., 2016). Fortenberry et al. reported an increase in the ADHD index with exposure tertiles among 6- to 11-year-old boys (Fortenberry et al., 2014), while an association with neurodevelopment was not found by Eskenazi et al. among 2-year-old children (Eskenazi et al., 2007), by Guo et al. among 3-year-old children (J. Guo et al., 2019), or by Dalsager et al. among 2- to 4-year-old children (Dalsager et al., 2019).

PPARγ is essential for placental development and plays an important role in energy metabolism, modulation of inflammatory and immune responses (Janani & Ranjitha Kumari, 2015), early brain development (Villapol, 2018), and cognitive performance (d'Angelo et al., 2019). A study in the human cell line SH-SY5Y showed

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that PPARγ expression was decreased by chlorpyrifos treatment (Lee et al., 2014). In association with epigenetic alterations, a study in human neural progenitor cells found that global histone modification levels were altered by chlorpyrifos exposure (Kim et al., 2016).

To our knowledge, only limited epidemiological studies have reported prenatal chlorpyrifos exposure effects in association with epigenetic alterations. Among 48 children whose mothers were occupationally unexposed or exposed to pesticides early in pregnancy, Declerck et al. investigated the prenatal pesticide exposure effects (yes/no) on DNA methylation when the children were between 6 and 11 years old. Declerck et al. reported that chlorpyrifos was one of the most frequently used organophosphate pesticides in their study, and there was no association between maternal occupational pesticide exposure and the DNA methylation levels at the region of Illumina probe cg01412654 of *PPARγ* in whole blood (Declerck et al., 2017). In our previous study, we selected the region to measure *PPARγ* DNA methylation based on the known effects linked with gene expression (Chiu et al., 2021; Dave et al., 2015), and the region differed with Declerck et al. (Declerck et al., 2017). We found that prenatal chlorpyrifos exposure was positively associated with *PPARγ* DNA methylation level (Chiu et al., 2021), which could decrease the expression level of PPARγ (Dave et al., 2015).

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We also found that *PPARγ* H3K4me3, an epigenetic marker of transcriptional activation, in the human placenta had positive associations with gestational age, birth weight, and birth length. Previous studies indicated that the expression level of *PPARγ* in the human placenta was positively associated with birth weight and birth length (Diaz et al., 2012; Meher et al., 2016), which is consistent with our findings.

There were several strengths of the present study, including the prospective cohort design to minimize recall bias and the measurement of chlorpyrifos levels directly in the blood instead of using questionnaire data or measuring its metabolite, either of which may have led to an overestimation of the chlorpyrifos exposure (Eaton et al., 2008). This study collected comprehensive information to enable adjustment for several potential confounders/effect modifiers reported in previous studies. Only a few epidemiological studies have investigated the effects of prenatal chlorpyrifos exposure on epigenetics, and our findings add to the understanding of chlorpyrifos exposure mechanisms. The study has several potential limitations. First, the participants included in the current analyses had higher cord blood chlorpyrifos levels than studies in the United States and in China. Our results may not be generalizable to populations with lower exposure levels. Second, the epigenetic alterations may be tissue-specific, and our findings that prenatal chlorpyrifos exposure was not associated with *PPARγ* H3K4me3

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levels in the placenta may not apply to other organs. Third, even though we conducted several sensitivity analyses and adjusted for potential confounders based on the literature, we still cannot rule out the potential of residual confounding effects. For example, some other exposures, such as other pesticide exposure, that are correlated with chlorpyrifos may confound our results. Further research controlling for other pesticide exposures is required to confirm the chlorpyrifos effects.

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2.5. Conclusions

Our results suggested that prenatal chlorpyrifos exposure was associated with poor performance in cognitive and language domains among 2-year-old children, particularly in boys. We also found that prenatal chlorpyrifos exposure was not associated with placental *PPARγ* H3K4me3 modifications. Although chlorpyrifos was banned in April 2024 in Taiwan, pregnant women still have the potential to be exposed to chlorpyrifos from the environment. Monitoring of prenatal chlorpyrifos exposure and related health outcomes, especially child development, is still needed in the following years.

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Chapter 3. Ambient temperature exposures and DNA methylation aging in adults

3.1. Introduction

3.1.1. Ambient temperature

Climate change has led to rising ambient temperature and the occurrence of more frequent and prolonged extreme high-temperature events (M. Romanello et al., 2022). Between 1990 and 2019, the population attributable fraction of global mortality attributable to high temperature was increased, from 0.44% in 1990 to 0.63% in 2019 (Burkart et al., 2021). In 2019, there were around 11 million disability-adjusted life years (DALYs) and over 300 thousand deaths worldwide due to high temperature exposure (Burkart et al., 2021; J. Song et al., 2021). Exposure to high ambient temperature is associated with increased risks of heat stroke, cardiovascular disease (CVD), respiratory disease, renal disease, neurodegenerative disease morbidity and mortality (Bongioanni et al., 2021; Ebi et al., 2021; J. Liu et al., 2022; Zanobetti & O'Neill, 2018), and biological aging including telomere shortening (Martens et al., 2019) and DNA methylation age acceleration (Ni et al., 2023).

3.1.2. DNA methylation age and biological aging

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DNA methylation is a methyl group covalent binding to the cytosine ring in the cytosine-guanine dinucleotide (CpG) (Dor & Cedar, 2018). DNA methylation can regulate gene expression and chromosome stability (Robertson, 2005). DNA methylation is strongly associated with aging (Dor & Cedar, 2018; Yousefi et al., 2022), and DNA methylation age has been developed to predict chronological age by using DNA methylation levels at specific CpG sites across the genome (Garagnani et al., 2012; Hannum et al., 2013; Horvath, 2013; Weidner et al., 2014). In addition, DNA methylation age was associated with CVD, age-related diseases, and mortality (Horvath & Raj, 2018; Jylhava et al., 2017; Marioni et al., 2015a; Oblak et al., 2021). Thus, DNA methylation age was widely used to evaluate biological aging (Galow & Peleg, 2022; Jylhava et al., 2017; Oblak et al., 2021). The Horvath's and Hannum's DNA methylation age (Hannum et al., 2013; Horvath, 2013) are the most widely used methods in environmental epidemiology studies (Dhingra et al., 2018). The Horvath's and Hannum's DNA methylation age were estimated by using 353 CpGs and 71 CpGs from the Illumina Methylation array, respectively. The Skin & blood clock, which was later developed by Horvath et al. based on 391 CpGs, has been shown to be more accurate in estimating chronological age by using blood than the Horvath's and Hannum's methods (Horvath et al., 2018). Measurements based on fewer CpGs were

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also developed. The Weidner's DNA methylation age used three CpGs (Weidner et al., 2014), and the *ELOVL2* and *FHL2* methods used single CpG (Garagnani et al., 2012). More recently, the phenotypic DNA methylation age and GrimAge2, the second-generation methods, were developed by using 513 CpGs and 1030 CpGs and including clinical markers, age-related morbidity and mortality risk into biological age measurements (Levine et al., 2018; A. T. Lu et al., 2022).

3.1.3. Ambient temperature and DNA methylation aging

Ambient temperature has been found to affect DNA methylation levels based on epidemiological studies conducted in areas with relatively low temperature (M. A. Bind et al., 2014; M. C. Bind et al., 2016; Ni et al., 2023; Xu et al., 2020; Xu et al., 2021). When co-exposure to high humidity, the heat risk is more dangerous due to the less effective evaporation and ventilation (Sherwood & Huber, 2010). The high humidity increases the heat-induced thermoregulatory strain, including apparent and core body temperatures (Che Muhamed et al., 2016; Steadman, 1979). Heat index (HI) calculated from ambient temperature and relative humidity is an approximation of apparent temperature. People live in the hot and humid areas, such as Taiwan, have a high tendency to expose to dangerous HI levels. HI is also used to prevent outdoor workers' heat injuries according to Taiwan's Ministry of Labor guidelines. The epidemiological

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evidence of how hot and humid climates affect DNA methylation is limited.

3.1.4. Study aims

The aim of the study was to study DNA methylation age in relation to ambient temperature exposures in adults, using a nationwide population-based cohort in Taiwan.

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3.2. Materials and methods

3.2.1. Study participants

Taiwan Biobank (TWB) recruited cancer-free general population in Taiwan to investigate the interactions among genes, environmental factors, and diseases. Details of the study scheme and participant recruitment of TWB were described elsewhere (Fan et al., 2008). In this study, a total of 2,084 participants aged between 30 and 70 years old recruited from 2008 to 2016 were included. Most of the study participants are Han Chinese (Feng et al., 2022). Sociodemographic characteristics, residential county and township, and smoking status were collected by using a structured questionnaire. BMI was obtained through anthropometric measurement. Whole blood samples were also collected. This study was approved by the Research Ethics Committee of National Taiwan University (202106HM010).

3.2.2. Exposure assessment of ambient temperature and apparent temperature

Daily minimum temperature, mean temperature, maximum temperature, and relative humidity were obtained from weather monitoring stations from the Central Weather Bureau (CWB) Observation Data Inquire System, Taiwan (https://e-service.cwb.gov.tw/HistoryDataQuery/index.jsp). Weather monitoring stations with altitudes more than 1,000 meters or located in offshore islands were

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excluded since there were no study participants lived in these areas. A total of 368 weather monitoring stations were used. Unrealistic values in daily temperature and RH were removed by the following criteria: temperature < 0°C or > 40°C (Tan & Tseng, 2012), maximum temperature ≤ mean temperature, minimum temperature ≥ mean temperature, and relative humidity < 0% or > 100%. We mapped median centers of participants' residential townships by using ArcMap 10.8.1 (ESRI, Redlands, CA) as exposure surrogates. Ordinary kriging with automatic fitting of semivariogram by the sp (Pebesma & Bivand, 2005), gstat (Pebesma, 2004), and automap (Hiemstra et al., 2009) R packages were used to estimate residential daily minimum temperature (T(min)), mean temperature (T(mean)), maximum temperature (T(max)), and mean relative humidity (RH) in the level of township. To validate the model performance of ordinary kriging, we calculated normalized root mean square errors (NRMSEs) of leave-one-out cross-validation. NRMSEs were calculated as root mean square errors (RMSEs) between observations and leave-one-out cross-validation divided by corresponding means of daily T(min), T(mean), T(max), and RH. Ordinary kriging models with NRMSEs ≥ 0.3 were considered poor estimation models and would not be included in further analyses (He et al., 2018). We then removed unrealistic interpolated values followed by the criteria of unrealistic values mentioned above.

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To approximate apparent temperature, daily HI of HI(min), HI(mean), and HI(max) were calculated using weathermetrics R package based on the U.S. National Weather Service (NWS) heat index algorithm to combine RH and daily T(min), T(mean), and T(max), respectively (Anderson et al., 2013; Rothfusz, 1990). Five categories of heat stress day, including no warning (lower than 80˚F), caution (80 to 90˚F), extreme caution (90 to 103˚F), danger (103 to 124˚F), and extreme danger (higher than 124˚F) were defined by daily HI according to the NWS's criteria (https://www.weather.gov/ama/heatindex).

3.2.3. Estimation of DNA methylation age

Genome-wide DNA methylation profiles in whole blood samples were measured by Infinium MethylationEPIC BeadChip (850K, Illumina Inc., CA, USA), and data processing steps were conducted by ChAMP R package (Tian et al., 2017). A total of 865,918 β-values indicating methylation levels from each CpG site were extracted from idat files. Data quality control was accomplished in the following steps: normalization of type-I and type-II probe design on 850K by using Peak Based Correction (Dedeurwaerder et al., 2011), cell type composition correction by using a reference-based method derived from white blood cell type-specific methylation patterns (Houseman et al., 2012), and batch effect adjustment of array chips and

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positions of sample loaded on chip (Johnson et al., 2007).

After data quality control, we used cell type heterogeneity corrected- and batch effect corrected-β-values to calculate the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, phenotypic (Pheno), Skin & blood, and GrimAge2 (Grim2) DNA methylation age. The Horvath's, Hannum's, Skin & blood, and Grim2 DNA methylation age could be obtained from online DNA Methylation Age Calculator (https://dnamage.genetics.ucla.edu/) (Hannum et al., 2013; Horvath, 2013; Horvath et al., 2018; A. T. Lu et al., 2022). Three CpGs of cg02228185, cg25809905, and cg17861230 were used for the Weidner's DNA methylation age calculation (Weidner et al., 2014). Single CpGs of cg16867657 and cg06639320 were used to compute the *ELOVL2* and *FHL2* DNA methylation age, respectively (Durso et al., 2017; Garagnani et al., 2012). The Pheno DNA methylation age was calculated using 513 CpGs (Levine et al., 2018).

Age acceleration was defined as the difference between DNA methylation age and chronological age; in other words, a positive age acceleration indicated one's DNA methylation age was older than chronological age, which denoted biological aging (Mendelson, 2018).

3.2.4. Statistical analysis

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In baseline characteristics, continuous and categorized variables were described as mean (standard deviation (SD)) and frequency (percentage), respectively. None or no more than six months smokers were defined as non-smokers. Individual moving averages of T(min), T(mean), T(max), RH, HI(min), HI(mean), and HI(max) were calculated in multiple exposure windows including mean exposure during 1, 3, 7, 15, 30, 60, 90, and 180 days prior to enrollment of each participant. The 365-day (annual) averages of exposures were calculated to describe climate characteristics in Taiwan. We also calculated the number of heat stress days in each HI category (i.e. no warning, caution, extreme caution, danger, and extreme danger) within multiple exposure windows.

Univariable and multivariable models were used to study the exposure effects of ambient temperature and HI in multiple exposure windows in relation to age acceleration. In the analyses to study the effects of heat stress days, we used "no warning" HI category as reference. Linear regression and non-linear models have been used to evaluate the effect of ambient temperature on DNA methylation levels (Ni et al., 2023; Xu et al., 2020; Xu et al., 2021). To test for linearity between the effects of temperature exposures and age acceleration, we compared Akaike's Information Criterion (AIC) of the linear regression models and generalized additive models (GAMs)

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with three to five degrees of freedom (df). The exposure-response effects were assumed to be linear when the estimated degrees of freedom (edf) of GAM was approximated one and AIC was worse in GAM than the corresponding linear regression model. For the exposure-response effects appeared to be non-linear, we used GAMs to study the effects. GAMs using quadratic B-splines with one internal knot were selected due to the lower AIC (**Figure S2- 1**). The references of exposures for each GAM were the mean annual averages of corresponding exposures. The effect sizes in GAMs were estimated through the dlnm R package.

To better understand the exposure-response and lag-response relationships between ambient temperature and age acceleration, we calculated the participant’s exposure history of 1- to 52-week (1-year) averages before enrollment and conducted distributed lag non-linear models (DLNMs) by the dlnm R package (Gasparrini, 2011). We used AIC to optimize the df and degrees used in DLNMs (Gasparrini et al., 2015a; Gasparrini et al., 2015b; Luo et al., 2013), and a quadratic B-spline with one internal knot for the exposure-response function and a natural cubic B-spline with an intercept and one internal knot for the lag-response function were selected (**Figure S2- 2**). The references of exposures for each DLNM were the mean annual averages of corresponding exposures.

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In the adjustment of covariates, we calculated the generalized variance inflation factor (GVIF) to assess the collinearity of variables included in models, and a variable with $(GVIF^{1/(2df)})^2 > 5$ indicated that collinearity with other variables could not be negligible (Pedersen et al., 2016) and would not be adjusted in the model. Potential confounders, including sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$, were adjusted in multivariable models. The $PM_{2.5}$ data were collected from air quality monitoring stations from Taiwan Environmental Protection Administration, and we used ordinary kriging to estimate participants' residential daily exposure levels. For the 1- to 7-day exposure windows, we additionally adjusted for time trend (natural cubic B-spline with five df per year) (Ni et al., 2023) and weekend/holiday. For the 15- to 180-day exposure windows, we additionally adjusted for year and season (warm season, May to October; cold season, November to April) (Tran et al., 2023) of enrollment. In DLNMs, sex, chronological age, BMI, educational level, smoking status, and year of enrollment were adjusted. $PM_{2.5}$, time trend, and weekend/holiday were not adjusted in DLNMs because of the strong collinearity with other variables. RH was further adjusted in the models studying exposure effects of T(min), T(mean), and T(max) in linear regression models, GAMs, and DLNMs.

We investigated the interaction effects between temperature exposures and seasons

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(warm and cold seasons), geographical areas of participants' residential townships (the northern, central, southern, and eastern areas in Taiwan, according to Central Weather Administration (https://www.cwa.gov.tw/V8/C/P/Rainfall/Rainfall_Area.html)), and sex by using LRTs. The interaction effects were observed between temperature exposures and seasons and geographical areas. Thus, we conducted the analyses stratified by seasons in the exposure windows up to 90-day and geographical areas in the exposure windows up to 180-day to enhance understanding of seasonal and geographical variations on age acceleration, respectively. The interaction effects were also found between temperature exposures and sex among Skin & blood and Grim2 age acceleration in the 15-day exposure window in multivariable linear regression models. The stratification analyses were performed according to the interaction effects to understand sexual differences of temperature exposures on age acceleration.

All tests assumed a two-sided type I error of 0.05 and were performed with R 4.1.0 (R Core Team, Vienna, Austria).

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3.3. Results

3.3.1. Baseline characteristics of participants

A total of 2,084 TWB participants with mean age of 50.44 years (SD = 11.08) and almost equal males and females (49.52% and 50.48%) were included in the analysis. The mean BMI was 24.41 kg/m^2 (SD = 3.65). The majority of participants received education from university or above (61.91%), and over 70% of participants were non-smokers. More participants enrolled in the warm season (57.63%) than the cold season (42.37%). The participants' residential townships were categorized into northern (49.62%), central (22.98%), southern (23.46%), and eastern areas (3.93%) (**Table 2- 1**). Among all age acceleration methods, the means ranged from -8.2 to 7.83 years (**Table 2- 1**), and they positively correlated with each other in moderate to high degrees (Pearson's correlation coefficient *r* ranged from 0.36 to 0.81) (**Figure 2- 1**).

3.3.2. Moving averages of ambient temperature, RH, and HI exposure assessments

NRMSEs of ordinary kriging models for T(min), T(mean), T(max), and RH were 0.034-0.29, 0.03-0.25, 0.032-0.23, and 0.028-0.16, respectively, which meant estimation performance was acceptable in the present study (He et al., 2018). Individual exposures were assessed by using moving averages from 1 day to 365 days (1 year) prior to participant enrollment. The average daily temperature was from 8.31°C to 32.2

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˚C between 2007 and 2016. Moving averages of each exposure across all exposure windows had similar mean values, whereas their SD decreased with prolonged exposure windows (**Figure 2- 2** and **Table S2- 1**). The mean 365-day moving average was 23.16 ˚C (SD = 0.97) for T(mean), 77.74% (SD = 2.92) for RH, and 24.81˚C (SD = 1.35) for HI(mean), which showed our participants resided in a warm and humid environment. The 365-day T(mean) was highly correlated with the 365-day HI(mean) (Pearson's correlation coefficient $r = 0.99$).

In the warm season, the mean 90-day moving average was 26.08˚C (SD = 2.64) for T(mean), 78.67% (SD = 3.42) for RH, and 28.91˚C (SD = 4.14) for HI(mean); and in the cold season, the mean 90-day moving average was 21.13˚C (SD = 3.58) for T(mean), 76.29% (SD = 3.65) for RH, and 21.77˚C (SD = 4.52) for HI(mean) (**Figure S2- 3**). As stratified by geographical areas, the mean 365-day moving averages of T(mean) were 22.67˚C (SD = 0.66), 23.02˚C (SD = 0.54), 24.44˚C (SD = 0.67), and 22.46˚C (SD = 0.62) in northern, central, southern, and eastern areas, respectively (**Figure S2- 4**).

3.3.3. Distributions of the number of heat stress days

In general, across all exposure windows, more than half of the days had HI(max) as either no warning or danger (**Figure 2- 3** and **Table S2- 2**). For example, within the

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365-day exposure window, the study participants had on average 129.53 no warning days, 49.28 caution days, 56.14 extreme caution days, 107.42 danger days, and 21.54 extreme danger days in HI(max). In the distributions of HI(mean) and HI(min), more than half of the days had no warning across all exposure windows. For example, within the 365-day exposure window, the study participants had on average 215.08 no warning days, 76.47 caution days, 73.19 extreme caution days, 0.26 danger days, and 0 extreme danger days in HI(mean); and 313.89 no warning days, 49.41 caution days, 0.67 extreme caution days, 0 danger or extreme danger days in HI(min). The occurrences of danger or extreme danger heat stress days were rare in HI(mean) and HI(min) as compared to HI(max). Therefore, we focused on HI(max) to study the number of heat stress days in association with age acceleration in the following analyses.

Compared the numbers of heat stress days in HI(max) between the warm and cold season, around half of the days in the warm season had HI(max) as danger and half of the days in the cold season as no warning (**Figure S2- 5**). For example, within the 90-day exposure window, the study participants enrolled in the warm season had on average 11.84 no warning days, 8.49 caution days, 17.11 extreme caution days, 42.81 danger days, and 9.58 extreme danger days in HI(max); and the study participants enrolled in the cold season had on average 45.53 no warning days, 16.87 caution days,

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13.84 extreme caution days, 12.20 danger days, and 1.34 extreme danger days in HI(max). In the geographical variation within 365-day exposure windows, study participants from the northern area had more no warning and extreme danger days than participants from the central and southern areas (**Figure S2- 6**). The pattern of heat stress days in HI(max) among participants from the eastern area was similar to participants from the northern area. The number of high to low caution, extreme caution, and danger days were participants from the southern, central, eastern, and northern areas.

3.3.4. Ambient temperature and HI exposures in relation to age acceleration

Non-linear associations were found in the Weidner's and *FHL2* age acceleration in relation to ambient temperature and HI exposures in the 3- to 90-day and 60- to 90-day exposure windows, respectively (**Figure S2- 7**). As there were no significant deviations from linearity for the Horvath's, Hannum's, *ELOVL2*, Pheno, Skin & blood, and Grim2 age acceleration, we demonstrated the Horvath's, Hannum's, *ELOVL2*, Pheno, Skin & blood, and Grim2 age acceleration in linear regression models. The Weidner's and *FHL2* age acceleration in relation to ambient temperature were estimated in the GAMs.

In the linear regression models, we found that age acceleration was increased with increasing T(min), T(mean), and T(max) exposures, particularly in the Pheno and Skin

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& blood age acceleration, and the effect sizes were increased with a prolonged exposure window (**Figure 2- 4** and **Table S2- 3**). The 365-day moving averages were not used in the analyses in association with age acceleration due to their low variation among study participants (**Figure 2- 2** and **Table S2- 1**) and limited statistical power (Zanobetti & O'Neill, 2018). With exposure windows ranging from 1- to 180-day, each unit (˚C) increase in T(min), T(mean), and T(max) exposures were significantly associated with increased age acceleration by 15.95 to 72.06 days, 16.77 to 76.37 days, and 16.2 to 78.75 days, respectively, by using the Horvath's, Hannum's, *ELOVL2*, Pheno, Skin & blood, and Grim2 DNA methylation age estimators in univariable linear regression models. In multivariable linear regression models, each unit (˚C) increase in the 60- to 90-day T(min), T(mean), and T(max) exposures were significantly associated with increased age acceleration by 41.14 days, 42.71 to 44.34 days, and 38.91 to 40.34 days, respectively, in the Pheno age acceleration (**Figure 2- 4** and **Table S2- 3**). The Skin & blood age acceleration had similar patterns to the Pheno age acceleration, but the effect sizes were smaller, with 36.49 to 41.66 days and 36.52 to 41.68 days increases in association with each unit (˚C) increase in the 60- to 90-day T(min) and T(mean) exposures, respectively. The Horvath's, Hannum's, *ELOVL2*, and Grim2 age acceleration were also increased in association with an increase in T(min), T(mean), and

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T(max) in the 15- to 180-day, 1- to 180-day, 3- to 90-day, and 15- to 180-day exposure windows, respectively, but the results were not statistically significant.

Regarding the effects of HI, the patterns were similar among HI(min), HI(mean), and HI(max). Increasing HI(min), HI(mean), and HI(max) were associated with increasing age acceleration, and their effect sizes were also increased with a prolonged exposure window, especially in the Pheno and Skin & blood age acceleration. Each unit (˚C) increase in the 1- to 180-day HI(min), HI(mean), and HI(max) exposures were significantly associated with 13.81 to 62.18 days, 11.63 to 53.42 days, and 7.93 to 33.68 days increase in age acceleration, respectively, in univariable linear regression models (**Table S2- 3**). In multivariable linear regression models, each unit (˚C) increase in the 90-day HI(mean) and 60- to 90-day HI(max) exposures were significantly associated with 27.06 days and 18.08 to 18.29 days increase in the Pheno age acceleration, respectively (**Figure 2- 4** and **Table S2- 3**). Each unit (˚C) increase in the 60-day HI(min) and HI(mean) exposures were also significantly associated with 33.62 days and 26.7 days increase in the Skin & blood age acceleration, respectively. The Horvath's, Hannum's, *ELOVL2*, and Grim2 age acceleration were also increased in association with increases in HI(min), HI (mean), and HI (max) in the 15- to 180-day, 15- to 180-day, 3- to 60-day, and 15- to 180-day exposure windows, respectively, but the

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results were not statistically significant. Notably, the effect sizes of HI(min) were similar to HI(mean), and the effect sizes of HI(min) and HI(mean) were larger than HI(max).

In the GAMs, we found that the Weidner's age acceleration was increased with increasing T(mean), particular in the 15- to 60-day exposure windows (**Figure 2- 5A**). Compared to T(mean), similar patterns were observed among T(min) in the 60- to 90-day exposure windows and T(max) in association with the Weidner's age acceleration (**Figure S2- 8**). The patterns of HI exposures in relation to the Weidner's age acceleration were similar to corresponding ambient temperature in the 60- to 180-day exposure windows. In relation to the *FHL2* age acceleration, the patterns of 7- to 90-day T(mean) exposures were similar to the Weidner's age acceleration, but had wider confidence intervals and less significant results (**Figure 2- 5B**). The exposure-response curves appeared to be U-shaped in the 1- and 3-day exposure windows, particularly HI(max) (**Figure 2- 5B** and **Figure S2- 9**).

The three-dimensional plots summarized the exposure-lag-response associations between T(mean) exposure and age acceleration in DLNMs (**Figure 2- 6**). In general, the patterns were similar in the Horvath's, Hannum's, Weidner's, *ELOVL2*, Pheno, and Skin & blood age acceleration, and the strongest positive associations in relation to age

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acceleration were at 17- to 27-week lags and 32˚C of T(mean). The overall cumulative associations indicated that 19.5 to 22.5˚C and 32˚C of T(mean) were positively associated with the Horvath's, Hannum's, Weidner's, *ELOVL2*, Pheno, and Skin & blood age acceleration compared to 23˚C as reference, and the strongest effect were at 32˚C (11.14 to 23.42 years age acceleration) (**Figure 2- 7**). Our results also showed that 23.5 to 25˚C were negatively associated with the Horvath's, Hannum's, Weidner's, *ELOVL2*, and Skin & blood age acceleration. The overall cumulative associations of HI(mean) had similar patterns with T(mean) (**Figure S2- 10**). HI(mean) exposure at 37.5 to 40˚C were associated with 6.15 to 17.96 years increases of the Horvath's, Hannum's, Weidner's, *ELOVL2*, Pheno, and Skin & blood age acceleration.

3.3.5. Heat stress days in association with age acceleration

We found that the associations between heat stress days and age acceleration were non-linear in the 90- and 180-day exposure windows, so only the results of 1- to 60-day exposure windows were shown. The heat stress days with HI(max) in caution, extreme caution, danger, and extreme danger were associated with increased age acceleration, especially in the danger and extreme danger days. For example, in the 1-day exposure window by univariable linear regression models, each HI(max) danger day and extreme danger day were significantly associated with 311.44 (95% CI = (46.72, 576.15), p =

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0.021) and 524.37 (95% CI = (87.97, 960.76), $p = 0.019$) days increase in the Hannum's age acceleration, respectively. Significant results were also observed between HI(max) danger day in relation to the Weidner's and Grim2 age acceleration, and HI(max) extreme danger day in relation to the Pheno and Skin & blood age acceleration. In multivariable linear regression models, each HI(max) extreme danger day in the 1-day exposure window was significantly associated with 571.38 (95% CI = (42.63, 1100.13), $p = 0.034$) and 528.02 (95% CI = (36.16, 1019.87), $p = 0.035$) days increases in the Horvath's and Hannum's age acceleration, respectively (**Figure 2- 8** and **Table S2- 4**). Each HI(max) extreme danger day in the 15- and 30-day exposure windows were significantly associated with 43.9 (95% CI = (0.28, 87.52), $p = 0.049$) and 24.78 (95% CI = (0.09, 49.46), $p = 0.049$) days increases in the Weidner's age acceleration, respectively, and each HI(max) extreme danger day in the 60-day exposure window was significantly associated with 16.82 (95% CI = (2.36, 31.28), $p = 0.023$) and 15.52 (95% CI = (2.17, 28.88), $p = 0.023$) days increases in the Pheno and Skin & blood age acceleration. Significant effects of caution, extreme caution, and danger day were also observed in the Weidner's and Grim2 age acceleration.

3.3.6. Seasonal variation of ambient temperature, HI, and heat stress days exposures

Non-linear associations were found in all exposure windows in exposure-age

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acceleration associations stratified by season; for this reason, the stratified results were presented by GAMs. In general, T(mean) with the temperature higher than the reference of 23˚C in the warm season were associated with increasing age acceleration compared to the reference (**Figure 2- 9**). Low temperature of T(mean) in the warm season was associated with increasing age acceleration, but the results were not statistically significant and with wide confidence intervals. In cold season, high temperature of T(mean) was associated with increasing age acceleration in the 60- and 90-day exposure windows compared to the reference. In the exposure windows of 30-day and less, the patterns of exposure-response curves at high temperature were not consistent between the age acceleration methods (**Figure 2- 10**). Low temperature of T(mean) in the cold season were associated with decreasing age acceleration in the 15- to 60-day exposure windows.

The overall cumulative associations among 90-day exposure window showed that compared to the reference of mean annual average 23˚C, T(mean) exposure in the warm season was associated with increasing age acceleration by 2.98 to 3.94 years in the *ELOVL2* methods at 30 to 31˚C (**Figure 2- 11**). Low temperature of T(mean) exposure in the warm season had wide confidence intervals in relation to DNA methylation age. In the cold season, T(mean) was associated with 1.02 to 25.26 years increases in the

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ELOVL2 age acceleration at 24.5 to 32˚C. Low temperature of T(mean) in the cold season was associated with 1.74 to 2.74 years decreases in the Grim2 age acceleration at 12 to 14.5˚C.

In the analyses of heat stress days stratified by season, since half of the days in the warm season had HI(max) as danger and most of the days in the cold season as no warning. There were lack of the other categories of heat stress days in the 1- and 3-day exposure windows. In addition, the associations between heat stress days and age acceleration were non-linear in the 90-day exposure windows. As a result, we performed the analyses of heat stress days stratified by season within the 7- to 60-day exposure windows (**Figure 2- 12** and **Table S2- 5**). We found that heat stress days in the warm season were not associated with age acceleration. In the cold season, heat stress days with HI(max) in extreme danger in the 60-day exposure window and HI(max) in danger in the 15- to 60-day exposure windows were significantly associated with the Skin & blood and Weidner's age acceleration, respectively.

3.3.7. Geographical variation of ambient temperature, HI, and heat stress days exposures

Due to the non-linear associations in exposure-age acceleration associations stratified by area, we presented the results by GAMs. We found geographical variation

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in the results that T(mean) with the temperature higher than the reference of mean annual average 23˚C was associated with increasing age acceleration in the northern, central, and eastern areas but not in the southern area. High temperature of T(mean) was associated with increasing age acceleration compared to the reference in the northern area, as low temperature of T(mean) was associated with decreasing age acceleration (**Figure 2- 13**). The patterns of exposure-response curves were consistent in the 60- to 180-day exposure windows in the northern area. High temperature of T(mean) was associated with increasing age acceleration in the 7- to 30-day exposure windows in the central area, but the patterns of exposure-response curves were not consistent across age acceleration methods (**Figure 2- 14**). In the southern area, high temperature of T(mean) was associated with decreasing age acceleration in the 1- to 15-day exposure windows, and inconsistent results were found in the low temperature of T(mean) (**Figure 2- 15**). In the 7- to 60-day exposure windows in the southern area, high temperature of T(mean) was associated with increasing age acceleration; in contrast, low temperature of T(mean) was associated with decreasing age acceleration (**Figure 2- 16**).

In DLNM results, the overall cumulative associations among 365-day exposure window demonstrated that compared to the reference of mean annual average 23˚C, high temperature of T(mean) exposure in the northern area was associated with

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increasing age acceleration by 17.3 to 29.75 years in the Weidner's method at 30.5 to 32 ˚C, 19.46 to 26.32 years in the *ELOVL2* method at 31 to 32˚C, and 3.46 to 19.38 years in the *FHL2* method at 23.5 to 29˚C, respectively (**Figure 2- 17A**). Low temperature of T(mean) was associated with 3.51 to 9.63 years decreases in the *FHL2* age acceleration at 21.5 to 22.5˚C in the northern area. In the southern area, high temperature of T(mean) was associated with increasing age acceleration by 35.9 to 38.39 years in the *FHL2* age acceleration at 29 to 30˚C, whereas high temperature of T(mean) was associated with decreasing age acceleration by 19.66 to 33.66 years in the Weidner's age acceleration at 27.5 to 31˚C (**Figure 2- 17C**). Low temperature of T(mean) was associated with 31.51 to 60.68 years decreases in the Weidner's age acceleration at 12.5 to 15˚C in the southern area. In the eastern area, high temperature of T(mean) was associated with 23.87 to 29.37 years decreases in the Grim2 age acceleration at 30 to 30.5˚C (**Figure 2- 17D**). However, T(mean) was not associated with age acceleration in the central area (**Figure 2- 17B**).

Our results showed that the increase of heat stress days with HI(max) in caution, extreme caution, danger, and extreme danger was significantly associated with increasing age acceleration in the northern, southern, and eastern areas (**Figure 2- 18**). Inconsistent results of heat stress days with HI(max) were found among age acceleration

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methods in the central area.

3.3.8. Sexual differences of ambient temperature exposures

The sex stratification analyses were performed by GAMs. Sexual differences were observed in T(mean) with the temperature lower than the reference of mean annual average 23˚C among Skin & blood and Grim2 age acceleration in the 15-day exposure window, while the results were not statistically significant in high temperature of T(mean) in both sexes (**Figure 2- 19**). Low temperature of T(mean) was associated with decreasing Skin & blood age acceleration in males. In females, low temperature of T(mean) was not associated with Skin & blood age acceleration, but low temperature of T(mean) was associated with decreasing Grim2 age acceleration.

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3.4. Discussions

Our results suggest that exposure to high ambient temperature and HI were associated with increasing age acceleration in Han Chinese adults, who resided in a warm and humid environment with the mean 365-day (annual) moving average temperature being 23.16°C (SD = 0.97). To our knowledge, this is the first study to investigate the effect of ambient temperature on DNA methylation age in a warm environment. Recently, the Cooperative Health Research in the Region of Augsburg (KORA) in Germany reported that the 4- and 8-week moving averages were associated with age acceleration, and every 1°C increase in annual average was also associated with increased the Horvath's, Hannum's, and Pheno age acceleration by 0.32 to 2.24 years in adults who were mostly Caucasians residing in areas with the mean annual temperature being 9.3°C (SD = 0.8) (Ni et al., 2023). Our results demonstrated that every 1°C increase in the 180-day moving average was associated with 0.04 to 0.08 years increase in the Horvath's, Hannum's, and Pheno age acceleration.

In animal models, lifespan was reduced with increasing environmental and body temperature (Conti, 2008; Keil et al., 2015). In DNA methylation studies, the Normative Aging Study (NAS) from the USA and the Australian Mammographic Density Twins and Sisters Study (AMDTSS) reported that high ambient temperature was associated

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with DNA methylation levels in genes related to inflammatory responses and CVD in relatively cool areas (3-week median temperature was 13˚C for NAS and the 365-day average temperature was 17.7˚C for AMDTSS) (M. A. Bind et al., 2014; M. C. Bind et al., 2016; Xu et al., 2021). Metabolic pathways related to inflammation and oxidative stress were demonstrated to be perturbed by 1-year ambient temperature exposure (annual average temperature of 11˚C) in blood metabolome in NAS (Nassan et al., 2021). High ambient temperature and apparent temperature exposures could also elevate B-type natriuretic peptide (BNP) and C-reactive protein (CRP) levels, biomarkers of systemic inflammation (Wilker et al., 2012), and modify leukocyte counts and composition (Gao et al., 2019; S. C. Hung et al., 2021) in participants recruited from the USA and Taiwan. Hence, inflammation was one of the mechanisms of high ambient temperature exposure on human health and linking high ambient temperature exposure to age acceleration (Franceschi et al., 2018; Liberale et al., 2022).

The change in physical activity might be another mechanism in the relationship between high ambient temperature and age acceleration. A meta-analysis showed that physical activity was negatively associated with age acceleration in different methods of DNA methylation age (Oblak et al., 2021). The global trend of rising ambient temperature not only increased the loss of time available for safe physical activity but

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also reduced the frequency, duration, and desire to exercise (Marina Romanello et al., 2021). Therefore, high ambient temperature may lead to insufficient or inadequate physical activity and subsequently increase age acceleration.

Increment of age acceleration was associated with increased risks of many health outcomes (Horvath & Raj, 2018; Jylhava et al., 2017; Oblak et al., 2021). Increment of every year of age acceleration was suggested to increase the risk of all-cause mortality by 2 to 18% across multiple meta-analyses independent of several risk factors, including chronological age, BMI, smoking, and certain comorbidities (B. H. Chen et al., 2016; Marioni et al., 2015a; Oblak et al., 2021). Age acceleration and DNA methylation age were associated with increased CVD risk (Levine et al., 2018; Lind et al., 2018) and CVD mortality (Perna et al., 2016; Roetker et al., 2018) in participants from Sweden, Germany, and the USA. Age acceleration and DNA methylation age were also predictors of aging-related phenotypes, including cognitive dysfunction, low grip strength, and self-reported physical limitations, in cross-sectional and longitudinal analyses in New Zealand, the UK, and the USA (Belsky et al., 2018; Faul et al., 2023; Marioni et al., 2015b).

In general, the effect sizes of T(min) were greater than T(max), and the effect sizes of HI(min) were also greater than HI(max) in our results. Studies had shown that the

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global warming rate of the average T(min) was faster than the average T(max) in the past decades (C. Lu et al., 2022; Sun et al., 2018). Similar T(min) trend was observed in Taiwan, and the rates were higher in urban areas than in rural areas (Lai & Cheng, 2010). The increase of T(min) could affect nighttime core body temperature decreasing and sleep quality, disturb thermoregulation and circadian rhythm, and further cause or exacerbate adverse health outcomes (F. Guo et al., 2021; Luo et al., 2013; Weinert, 2010).

We found that the effect sizes of ambient temperature and HI exposures on age acceleration increased with an elongated exposure window, suggesting that the effects of exposures on DNA methylation age accumulated over time. Wilker et al. indicated that the effect sizes of BNP and CRP in relation to ambient temperature exposure were increased from the 1- to 4-day moving averages, suggesting a period of prolonged high temperature is needed to upregulate inflammation biomarkers (Wilker et al., 2012). In addition, Xu et al. suggested that the associations between ambient temperature exposure and CpGs were more robust with a prolonged exposure window (Xu et al., 2021).

In addition to the effects of ambient heat, the overall cumulative associations in DLNMs in the present study revealed that low T(mean) around 19.5 to 22.5°C (42nd to

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56th percentiles) was associated with increased age acceleration. Cold exposure, when temperature percentile was below threshold, has been found to be associated with increased risks of CVD, cerebrovascular disease, and respiratory disease morbidity (X. Song et al., 2017) and mortality (Burkart et al., 2021; Gasparrini et al., 2015b; X. Song et al., 2017). On the other hand, when T(mean) was slightly above the average, age acceleration was decreased in our DLNM results. Our results suggest an optimum temperature between 23.5 to 25˚C for Taiwanese population are in line with previous findings that the mean ambient temperature around 26˚C have the lowest mortality among individuals in Taiwan (Gasparrini et al., 2015b).

Our results revealed that high temperature exposure was associated with age acceleration, whether in the warm or cold season. The overall cumulative associations by high temperature exposure were larger in the cold season. In the cold season, the human body may be less adaptive to the high temperature. The different heat acclimatization by season may alter the physiological outcomes in response to heat exposure (Brown et al., 2022). The epigenetic regulations, including DNA methylation, have been found to participate in the thermoregulation and adaption processes to heat (Murray et al., 2022). Our results also indicated that cold exposure in the warm season could accelerate biological aging. Further research is needed to determine whether the

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seasonal variations in our findings are related to the adaptation processes.

In our geographical variation results, we found that the associations between high temperature exposure and age acceleration were more sensitive in participants from the northern area. Compared to other areas, participants from the northern area experienced more days with no warning and extreme danger in HI(max), which indicated higher temperature variability. Previous studies demonstrated that temperature variability was associated with increasing emergency department visits and mortality (Y. Guo et al., 2016; Rahman et al., 2022). More studies would be needed to understand the role of temperature variability in the relationship between ambient temperature exposure and age acceleration.

Sexual differences were demonstrated in this study regarding the effects of ambient temperature exposure on specific age acceleration. This finding might result from physiological differences between sexes in thermoregulation (Achebak et al., 2019). Men were reported to be more sensitive to cold exposure than women, whereas women were more sensitive to heat than men (Achebak et al., 2019; Bittel & Henane, 1975; Graham, 1988). However, our results were inconsistent with previous findings.

In the present study, we analyzed the effects of ambient temperature exposure in relation to biological aging by using DNA methylation age, which could be an indicator

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in quantifying the adverse health outcomes of ambient temperature exposure to humans. We investigated short- and long-term exposure windows simultaneously among participants resided in relatively warm areas, as compared to the aforementioned study conducted in Germany (Ni et al., 2023). The health effects of ambient high temperature exposure have been found to be different by climate zones (J. Liu et al., 2022). Our findings provide additional evidence of subtropical climate effects on DNA methylation age.

However, there were some limitations of this study. Firstly, participants' exposure levels were estimated by ambient temperature. The lack of detailed individual information such as time spent outdoors, outdoor land use, lifestyle, physical activity, behavior change due to ambient temperature, and indoor environment led to inaccurate estimation of exposure. We attempted to adjust for the effects of lifestyle and physical activity by including BMI in multivariable models and DLNMs and the ambient temperature exposure effects were remained. Secondly, the effects of co-exposure such as air pollution other than $PM_{2.5}$ and occupational exposures were not considered, which might confound our results. Thirdly, we calculated DNA methylation age based on Infinium MethylationEPIC BeadChip, while the Horvath's, Hannum's, Weidner's, *ELOVL2*, and *FHL2* DNA methylation age were established by using Infinium

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HumanMethylation450 BeadChip (Garagnani et al., 2012; Hannum et al., 2013; Horvath, 2013; Weidner et al., 2014). In addition, DNA methylation age methods used in this study were established based on non-Asian populations. The estimation accuracy of DNA methylation age might be influenced in our results. However, strong correlations (r = 0.91 to 0.96) were found between DNA methylation age calculated from both Infinium MethylationEPIC and Infinium HumanMethylation450 BeadChip platforms (McEwen et al., 2018). Lastly, we did not consider pre-existing health status and comorbidities, which could affect participants' DNA methylation age.

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3.5. Conclusions

This is the first study investigating the effect of ambient temperature on DNA methylation age among Han Chinese population in Taiwan, a subtropical island in Asia. Our results indicated that high ambient temperature and HI could accelerate DNA methylation age, a biomarker of biological aging, among people who lived in a warm and humid environment. Seasonal and geographical variations were also demonstrated in the relationships between high ambient temperature exposure and DNA methylation age acceleration in this study. According to the trend of ambient temperature in the past decades and climate change, the ambient temperature may rise in the upcoming years. This scenario can further accelerate biological aging. Furthermore, the aging population and urban heat island caused by urbanization worldwide may exacerbate the effects of ambient temperature on human health. Actions must be taken to mitigate the impact of ambient temperature and climate change on humans.

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Chapter 4. Conclusions

Our study suggests that environmental exposures can alter epigenetic marks, and epigenetic marks are associated with health outcomes in cohort studies. For this reason, epigenetic marks play important roles in studying the origins of diseases. Epigenetic marks can be used to monitor the effects of environmental exposures on humans and assess the risk of potential health outcomes in the early stages. Due to the changeable feature, epigenetic marks can also be applied to investigate the efficacy of decreasing environmental exposure levels, using personal protective equipment, and changing human behaviors. This dissertation provides additional evidence of the associations between environmental exposures, epigenetic marks, and health outcomes. However, more efforts are needed to mitigate the impact of environmental exposures on humans.

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Table 1- 1. Baseline characteristics of total and included study participants.

Characteristics	Total (*N* = 486)	Included (*N* = 425) [1]
Chlorpyrifos (ng/mL) (GM (GSD))	0.13 (5.29)	0.13 (5.29)
Mothers		
Age at delivery (year) (mean (SD))	30.99 (4.6)	30.75 (4.59)
Maternal BMI (mean (SD))	20.94 (2.92)	20.92 (2.87)
Educational level (n (%))		
Not senior high school graduated	44 (9.09)	43 (10.14)
Senior high school graduated	225 (46.49)	201 (47.41)
University and above	215 (44.42)	180 (42.45)
Infants		
Type of delivery, vaginal (n (%))	292 (60.08)	261 (61.41)
Parity (n (%))		
1	230 (47.52)	205 (48.35)
2	180 (37.19)	156 (36.79)
≧ 3	74 (15.29)	63 (14.86)
Boys (n (%))	246 (50.62)	213 (50.12)
Gestational age (week) (mean (SD))	38.47 (1.73)	38.47 (1.63)
Birth weight (g) (mean (SD))	3157.87 (476.64)	3154.02 (449.11)
Birth length (cm) (mean (SD))	48.98 (2.24)	48.98 (2.12)
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old (mean (SD))		
Whole test	98.03 (13.54)	98.66 (13.04)
Cognitive	93.52 (13.01)	93.96 (12.54)
Language	99.92 (13.63)	100.45 (13.08)
Motor	87.16 (12.44)	87.43 (12.44)
Gross-motor	84.65 (14.28)	84.85 (14.4)
Fine-motor	94.83 (12.59)	95.13 (12.57)
Social	107.92 (16.9)	108.2 (16.87)
Self-help	100.23 (16.78)	100.94 (15.88)

[1] Participants had placental samples collected. GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.

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Table 1- 2. Baseline characteristics of included and follow-up at 2 years old study participants.

Characteristics	**Included (*N* = 425)**	**Follow-up at 2 years old (*N* = 219)** [1]	***p***
Chlorpyrifos (ng/mL) (GM (GSD))	0.13 (5.29)	0.14 (5.21)	0.86
Mothers			
Age at delivery (year) (mean (SD))	30.75 (4.59)	32.08 (3.87)	0.0001*
Maternal BMI (mean (SD))	20.92 (2.87)	20.95 (2.7)	0.91
Educational level (n (%))			0.005*
Not senior high school graduated	43 (10.14)	10 (4.57)	
Senior high school graduated	201 (47.41)	91 (41.55)	
University and above	180 (42.45)	118 (53.88)	
Infants			
Type of delivery, vaginal (n (%))	261 (61.41)	144 (65.75)	0.32
Parity (n (%))			0.35
1	205 (48.35)	94 (42.92)	
2	156 (36.79)	85 (38.81)	
≧ 3	63 (14.86)	40 (18.26)	
Boys (n (%))	213 (50.12)	120 (54.79)	0.3
Placental H3K4me3 levels of *PPARγ* (% Input)			
R1	13.5 (20.63)	13.16 (21.18)	0.85
R2	14.01 (21.37)	14.07 (22.22)	0.97
R3	10.37 (18.25)	10.22 (18.48)	0.92

* $p < 0.05$. [1] Participants had the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) measurement.

GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.

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Table 1- 3. Associations between prenatal chlorpyrifos exposure and H3K4me3 levels in *PPARγ* gene.

H3K4me3 levels (% Input)	**Chlorpyrifos** [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI) [2]	Adjusted p [2]
R1	0.97 (-0.42, 2.35)	0.17	0.87 (-0.51, 2.26)	0.22
R2	1.13 (-0.25, 2.52)	0.11	1.34 (-0.05, 2.72)	0.06
R3	1.15 (-0.021, 2.32)	0.05	1.16 (-0.003, 2.32)	0.05

[1] Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). [2] Adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, infant sex, and gestational age (week).

p values before adjustment for multiple comparisons.

a*β*, adjusted *β*; CI, confidence interval.

Table 1- 4. Health effects in association with prenatal chlorpyrifos exposure.

Health outcomes	**Chlorpyrifos** [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI) [2]	Adjusted p [2]
Birth outcomes				
Gestational age (week)	-0.017 (-0.12, 0.08)	0.74	-0.0004 (-0.1, 0.1)	0.99
Birth weight (g)	6.0 (-21.85, 33.86)	0.67	7.88 (-15.28, 31.04)	0.50
Birth length (cm)	-0.03 (-0.16, 0.10)	0.65	-0.01 (-0.12, 0.1)	0.85
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old				
Whole test	-0.29 (-1.45, 0.87)	0.63	-0.44 (-1.55, 0.66)	0.43
Cognitive	-1.01 (-2.10, 0.08)	0.07	**-1.20 (-2.25, -0.15)**	**0.025***
Language	-0.95 (-2.10, 0.21)	0.11	**-1.14 (-2.25, -0.03)**	**0.044***
Motor	-0.59 (-1.64, 0.47)	0.27	-0.59 (-1.63, 0.46)	0.27
Gross-motor	-0.83 (-2.05, 0.39)	0.18	-0.69 (-1.91, 0.54)	0.27
Fine-motor	0.08 (-1.04, 1.20)	0.89	-0.08 (-1.18, 1.03)	0.89
Social	0.27 (-1.20, 1.74)	0.72	0.22 (-1.25, 1.69)	0.77
Self-help	0.90 (-0.53, 2.34)	0.21	0.86 (-0.46, 2.18)	0.20

* $p < 0.05$. [1] Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). [2] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, infant sex, and gestational age (week) except for the association with gestational age.

p values before adjustment for multiple comparisons. *p* values less than 0.05 shown in bold.

a*β*, adjusted *β*; CI, confidence interval.

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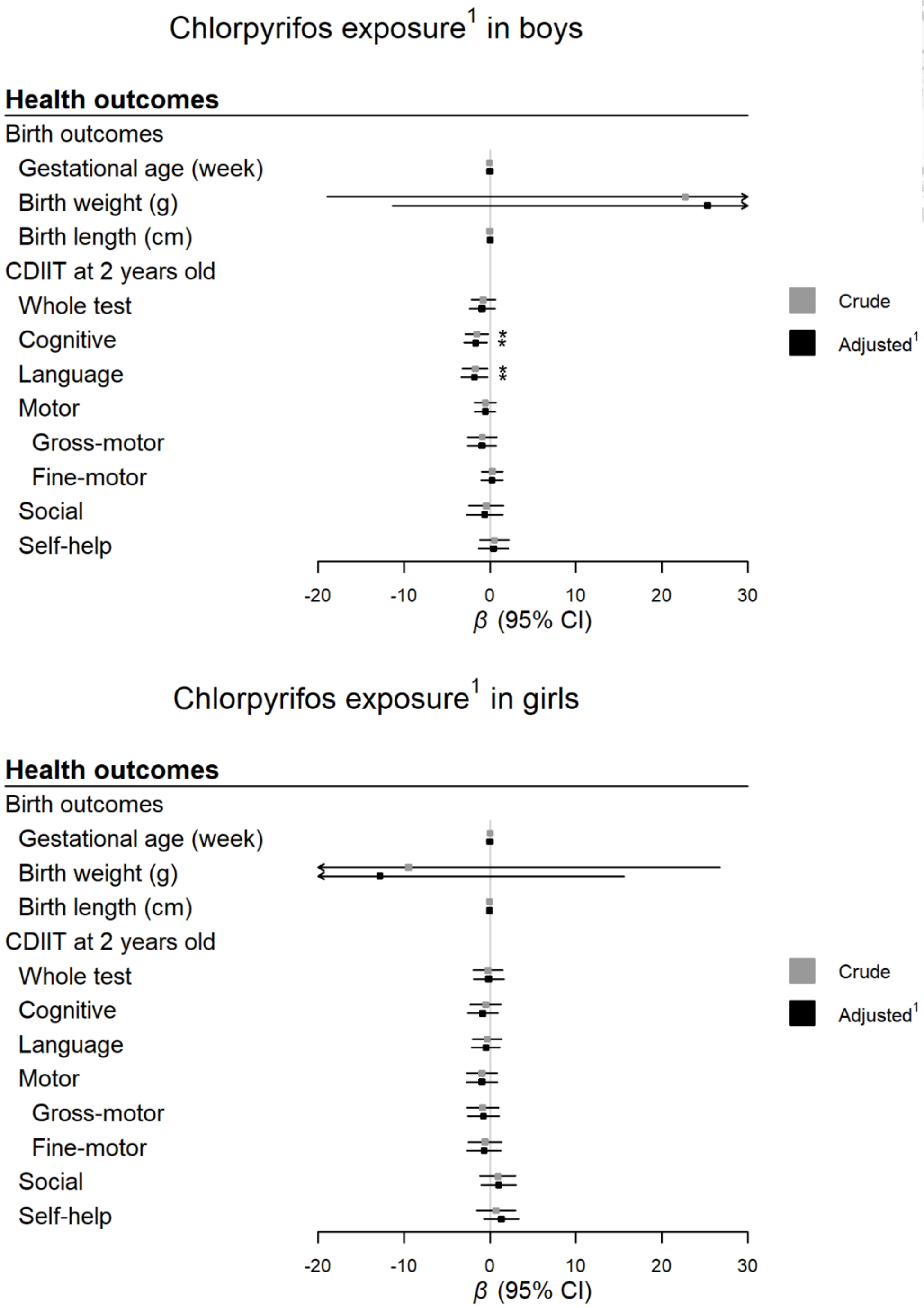

Figure 1- 1. Health outcomes in association with prenatal chlorpyrifos exposure in boys and girls.

* $p < 0.05$. [1] Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). [2] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, and gestational age (week) except for the association with gestational age.

The gray and black boxes represented the point estimates, and the black lines represented the 95% confidence intervals.

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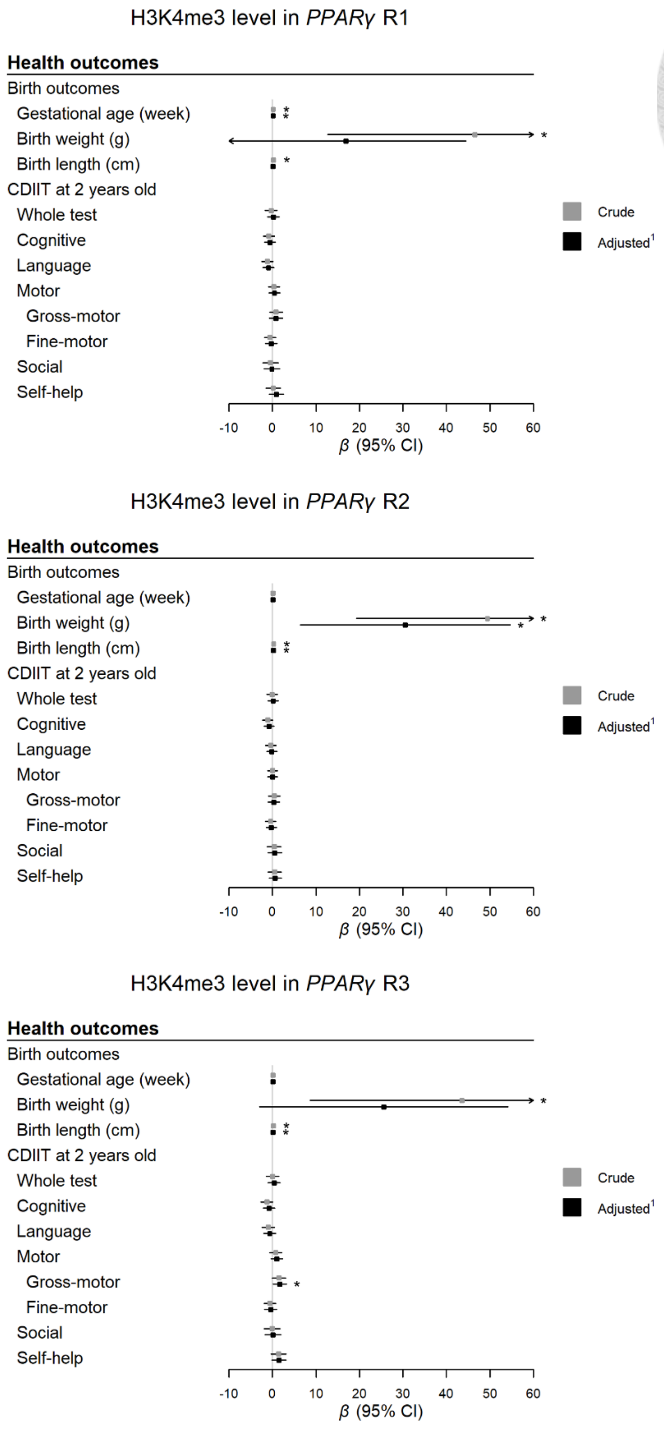

Figure 1- 2. The associations between H3K4me3 levels in *PPARγ* gene and health outcomes.

* $p < 0.05$. [1] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, infant sex, and gestational age (week) except for the association with gestational age.

The gray and black boxes represented the point estimates, and the black lines represented the 95% confidence intervals.

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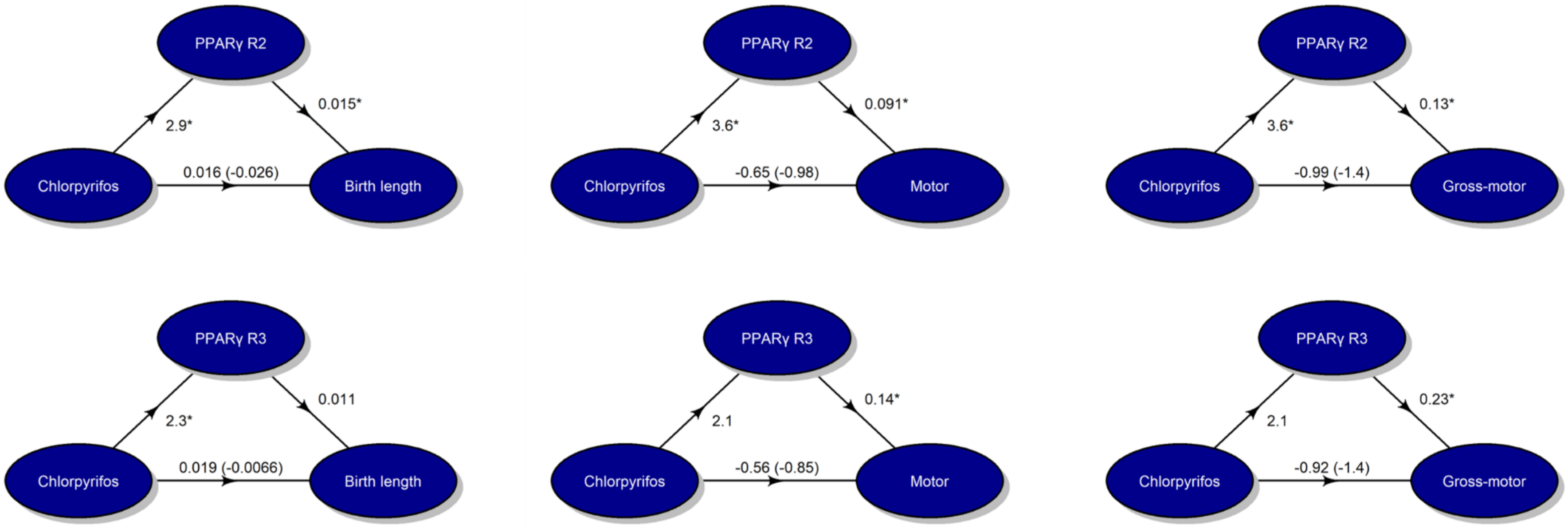

Figure 1- 3. Mediation analysis of H3K4me3 levels in *PPARγ* gene in the relationships of prenatal chlorpyrifos exposure and health outcomes in boys.

* $p < 0.05$. Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, and gestational age (week).

The upper left numbers were the effects of prenatal chlorpyrifos exposure on H3K4me3 levels in *PPARγ* gene, the upper right numbers were the effects of H3K4me3 levels in *PPARγ* gene on health outcomes, and the lower numbers were the total effects (direct effects) of prenatal chlorpyrifos exposure on health outcomes.

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Table 2- 1. Baseline characteristics of Taiwan Biobank participants.

Characteristics	Participants (N = 2,084)
Age (years, mean (SD))	50.44 (11.08)
Sex (n (%))	
Male	1032 (49.52)
Female	1052 (50.48)
BMI (mean (SD))	24.41 (3.65)
Educational level (n (%))	
Elementary school or below	83 (3.99)
Junior high school	113 (5.43)
High school	597 (28.67)
University or above	1289 (61.91)
Smoking status (n (%))	
Non-smokers	1540 (73.9)
Former	266 (12.76)
Seldom	31 (1.49)
Current	247 (11.85)
Season of enrollment (n (%))	
Warm	1201 (57.63)
Cold	883 (42.37)
Residential area (n (%))	
Northern	1034 (49.62)
Central	479 (22.98)
Southern	489 (23.46)
Eastern	82 (3.93)
Age acceleration (years, mean (SD))	
Horvath's	7.83 (7.18)
Hannum's	-6.2 (6.72)
Weidner's	-3.12 (8.79)
ELOVL2	6.71 (7.39)
FHL2	5.99 (10.19)
Pheno	-8.2 (7.29)
Skin & blood	-1.1 (6.46)
Grim2	4.61 (4.65)

SD, standard deviation.

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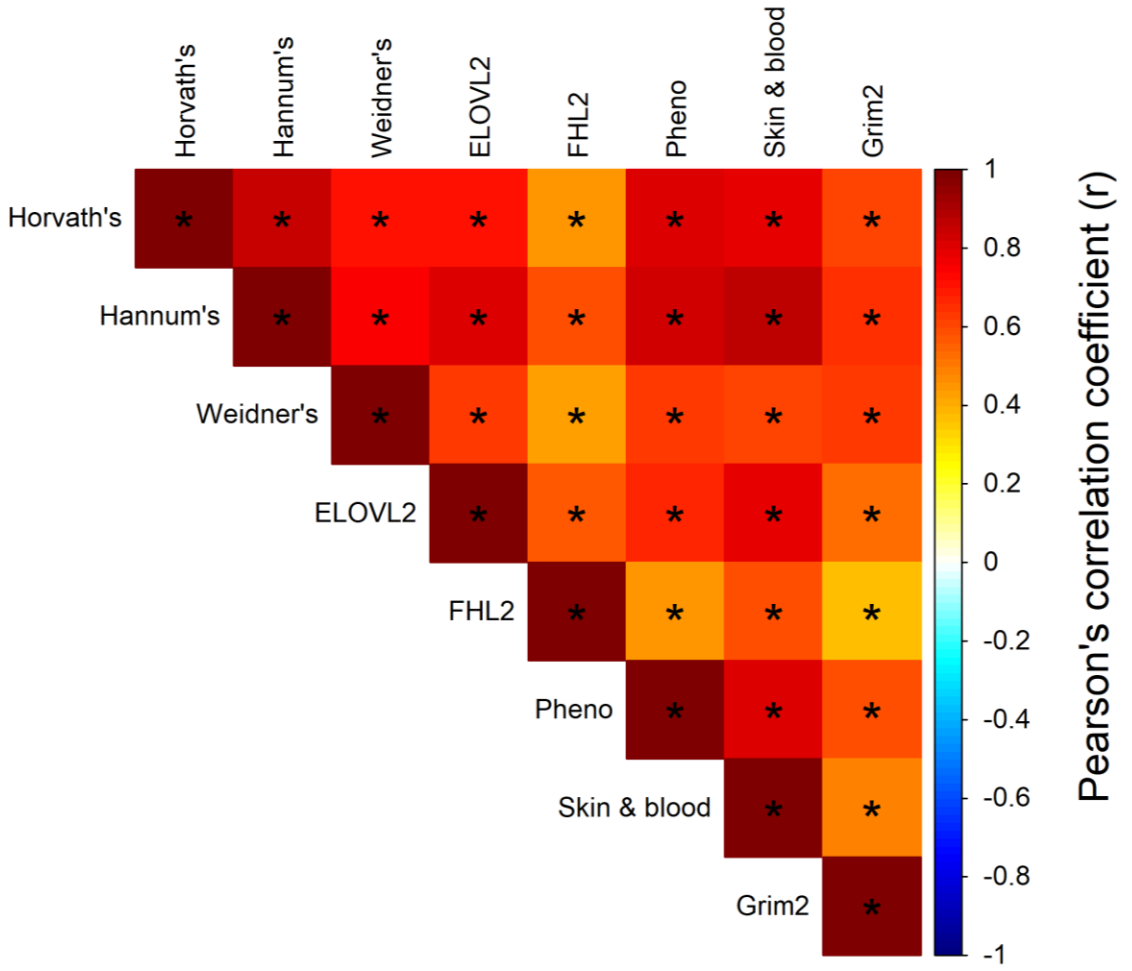

Figure 2- 1. Correlations among age acceleration in Taiwan Biobank participants.

* $p < 0.05$.

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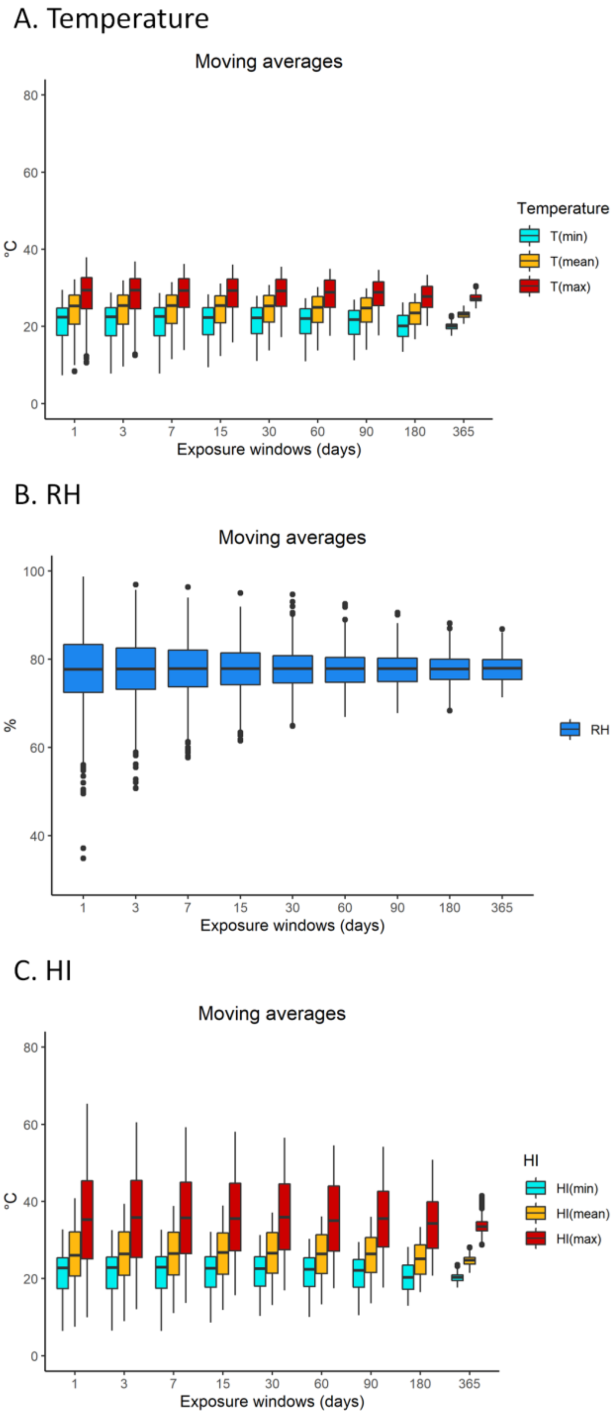

Figure 2- 2. Distributions of moving averages of A. temperature (˚C), B. RH (%), and C. HI (˚C) from 1 day to 365 days prior to participant enrollment.

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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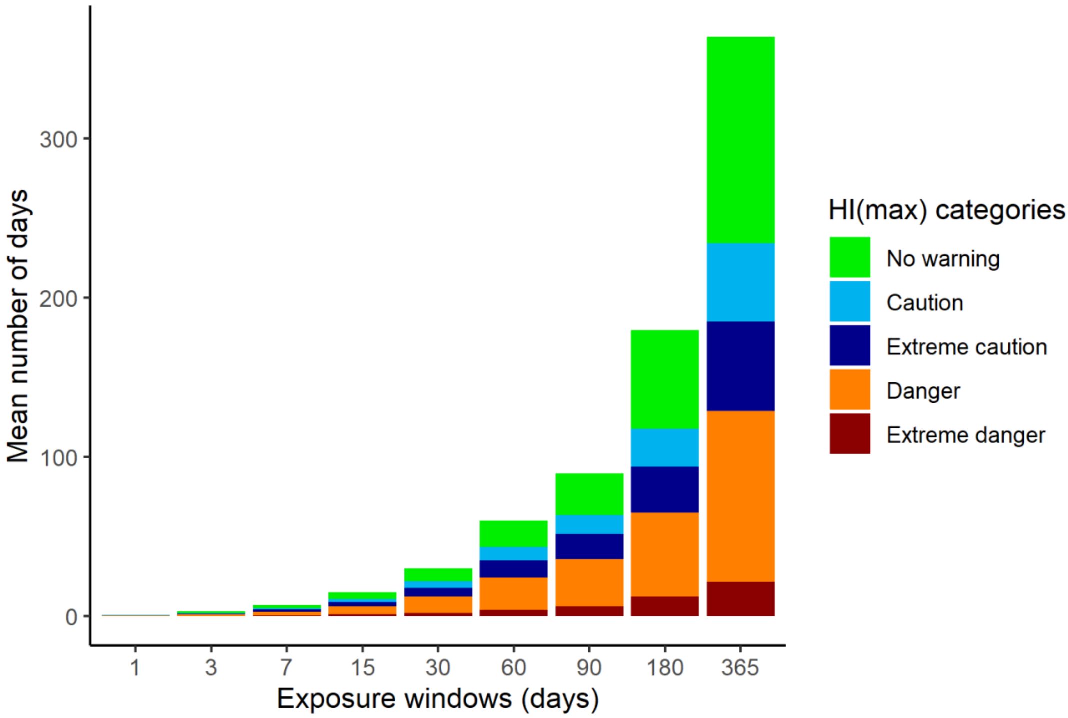

Figure 2- 3. Number of heat stress days in HI(max) in multiple exposure windows.

HI(max), heat index of maximum temperature.

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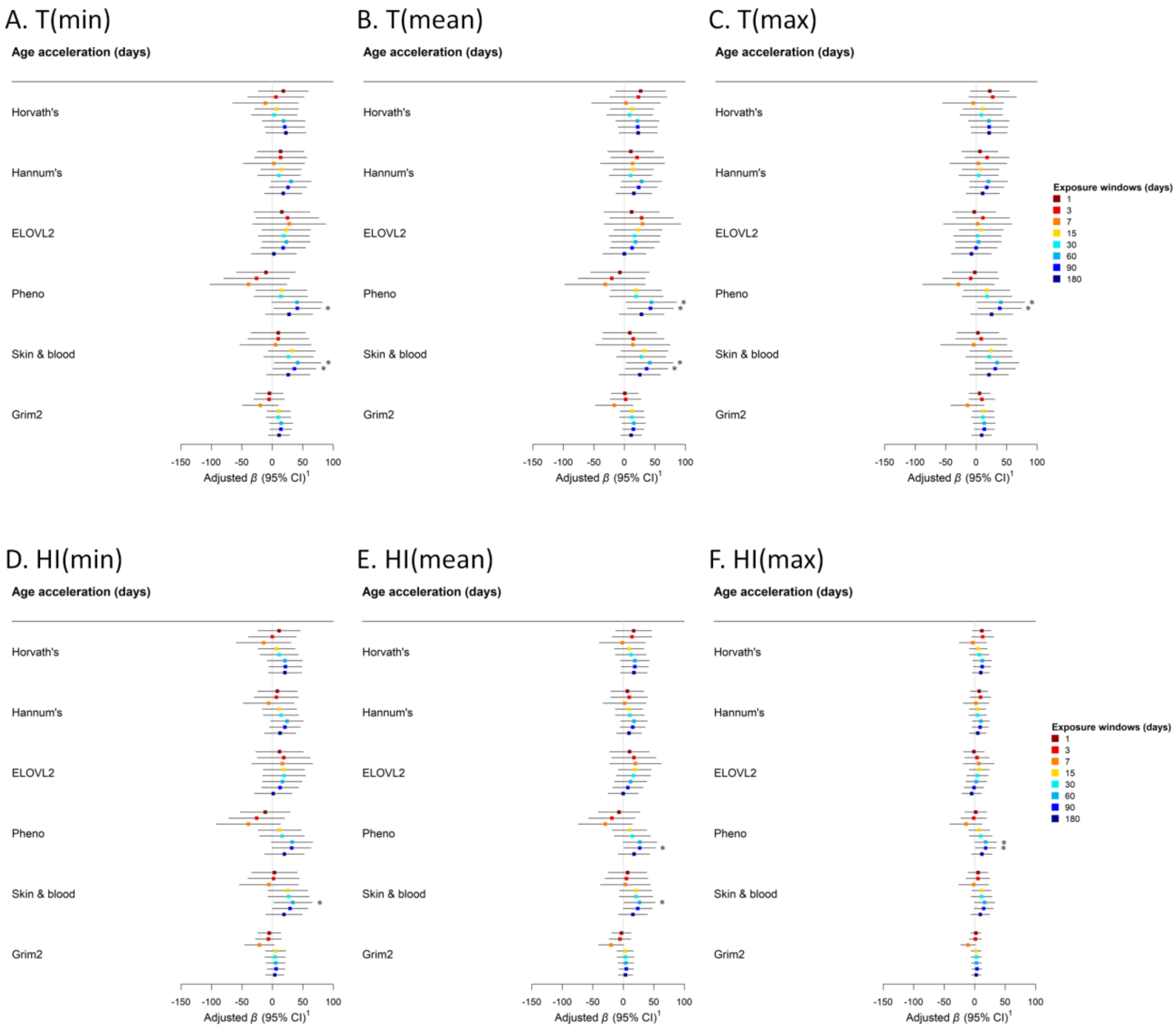

Figure 2- 4. The associations between A. T(min), B. T(mean), C. T(max), D. HI(min), E. HI(mean), F. HI (max) and DNA methylation age acceleration in multivariable linear regression models.

* $p < 0.05$. [1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. RH was further adjusted in the temperature models.

The colored boxes represented the point estimates, and the black lines represented the 95% confidence intervals.

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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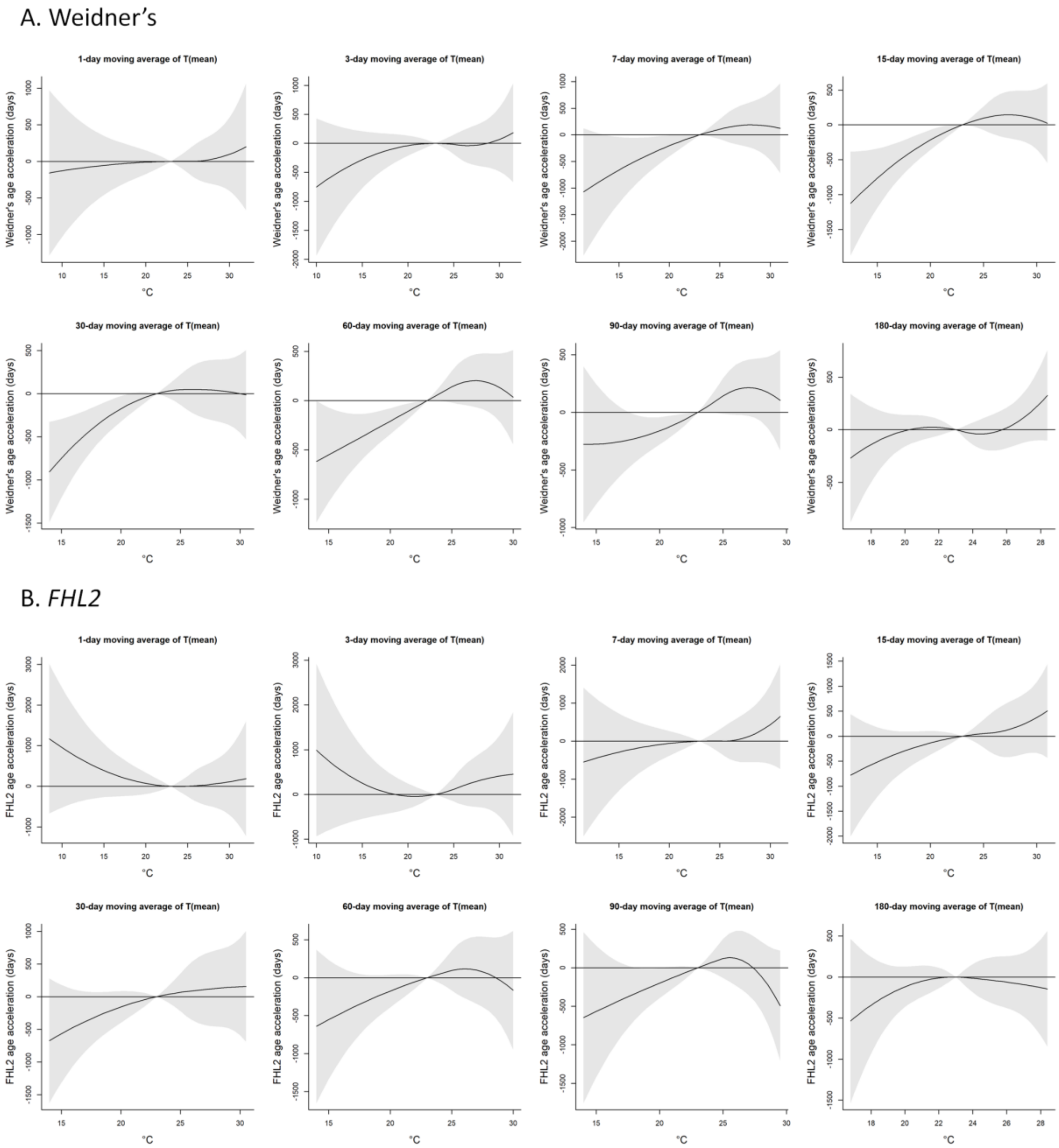

Figure 2- 5. The exposure-response curves between T(mean) and A. Weidner's and B. *FHL2* DNA methylation age acceleration in generalized additive models.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23 ° C.

T(mean), mean temperature; RH, relative humidity.

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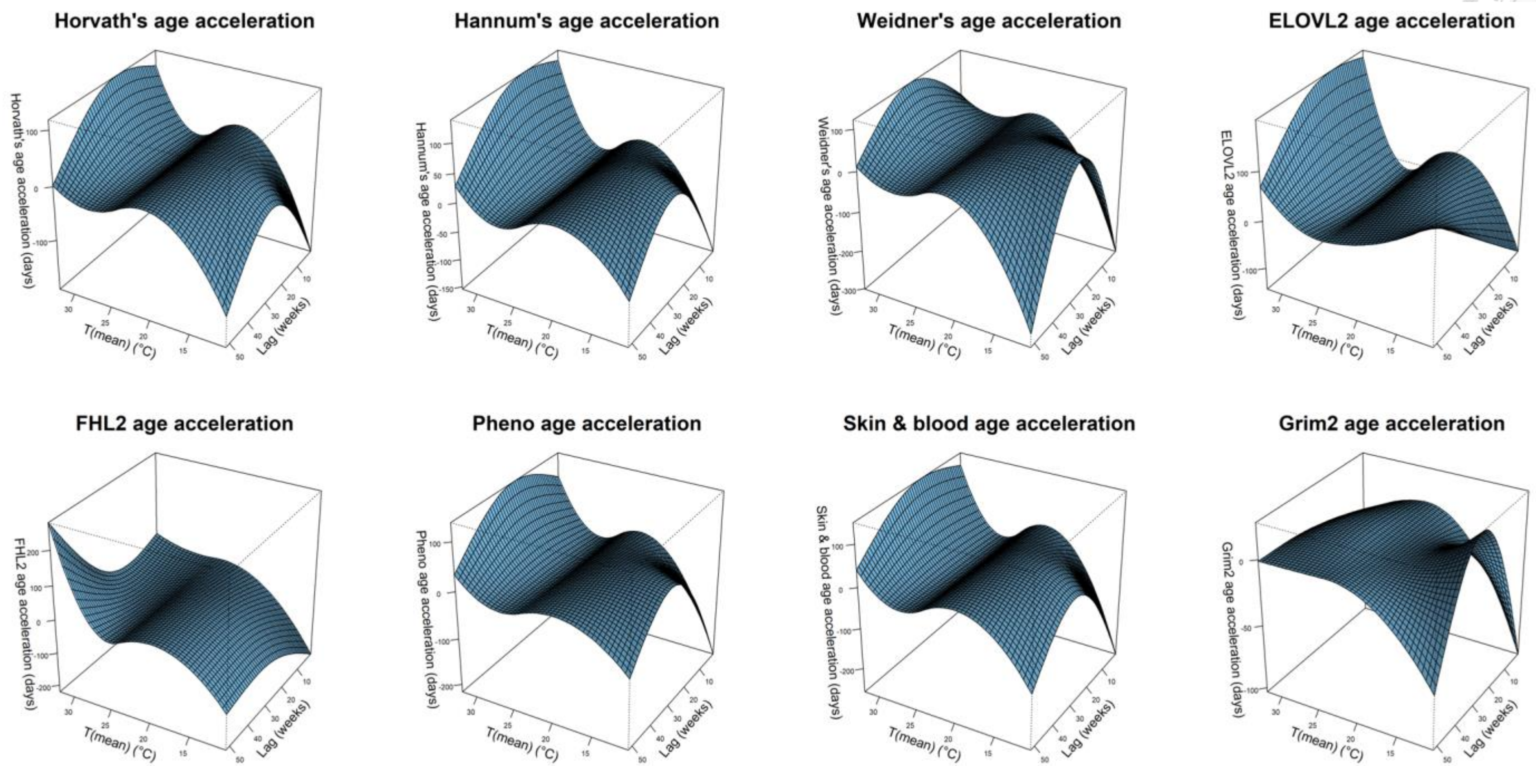

Figure 2- 6. Exposure-lag response surfaces for the association between T(mean) and DNA methylation age acceleration within 52 weeks exposure window in distributed lag non-linear models.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, year of enrollment, and RH. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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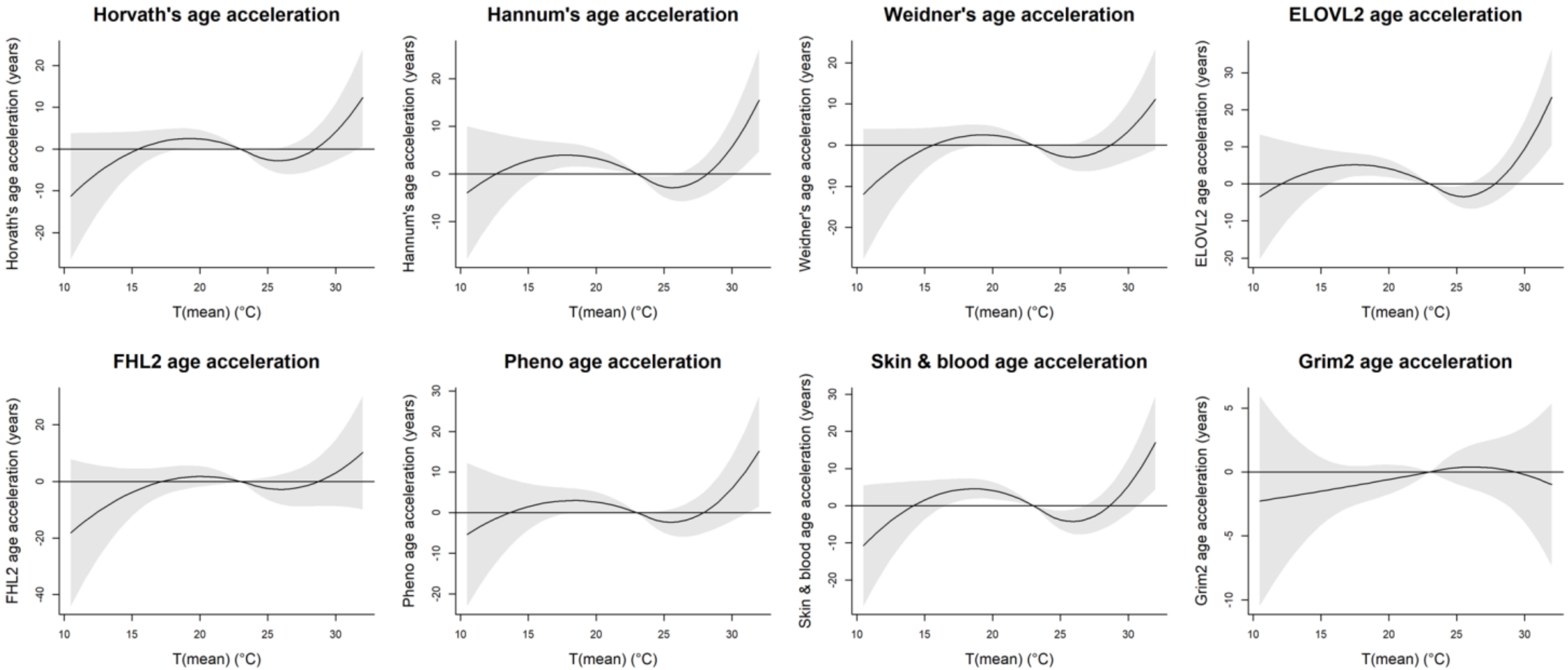

Figure 2- 7. Overall cumulative associations between T(mean) and DNA methylation age acceleration within 52 weeks exposure window in distributed lag non-linear models. Models were adjusted for sex, chronological age, BMI, educational level, smoking status, year of enrollment, and RH. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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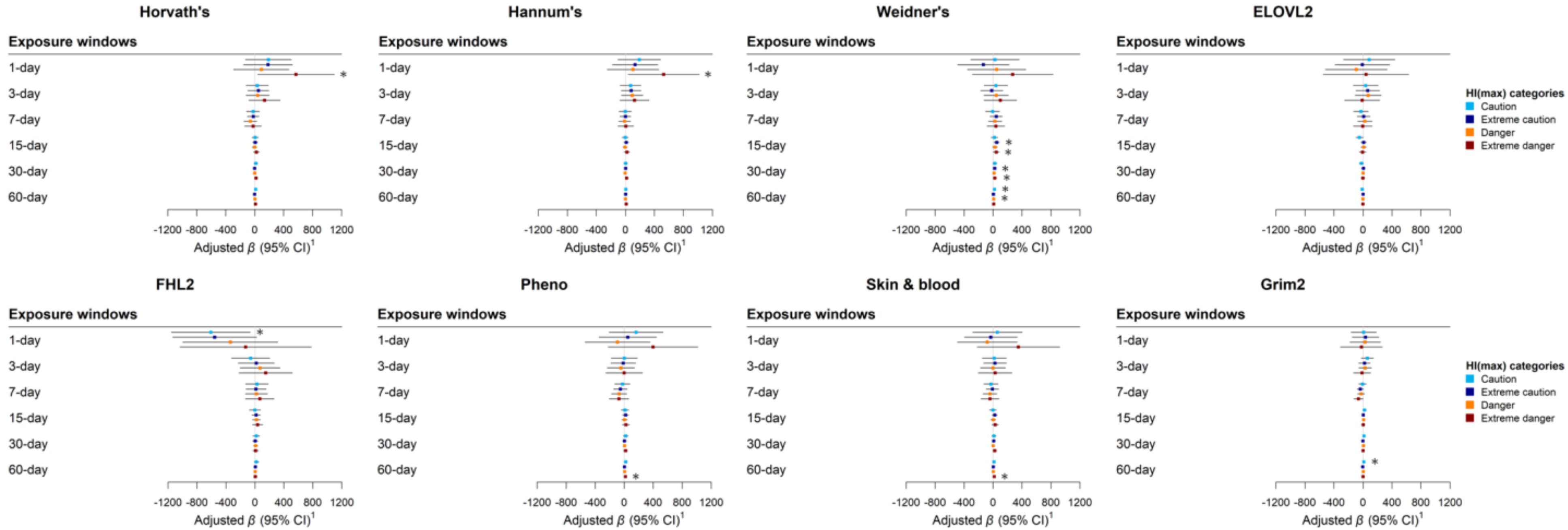

Figure 2- 8. The associations between number of heat stress days in a given exposure window and DNA methylation age acceleration in multivariable linear regression models.

* $p < 0.05$. [1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season of enrollment were additionally adjusted in models of 15- to 60-day exposure windows. The colored boxes represented the point estimates, and the black lines represented the 95% confidence intervals.

HI(max), heat index of maximum temperature.

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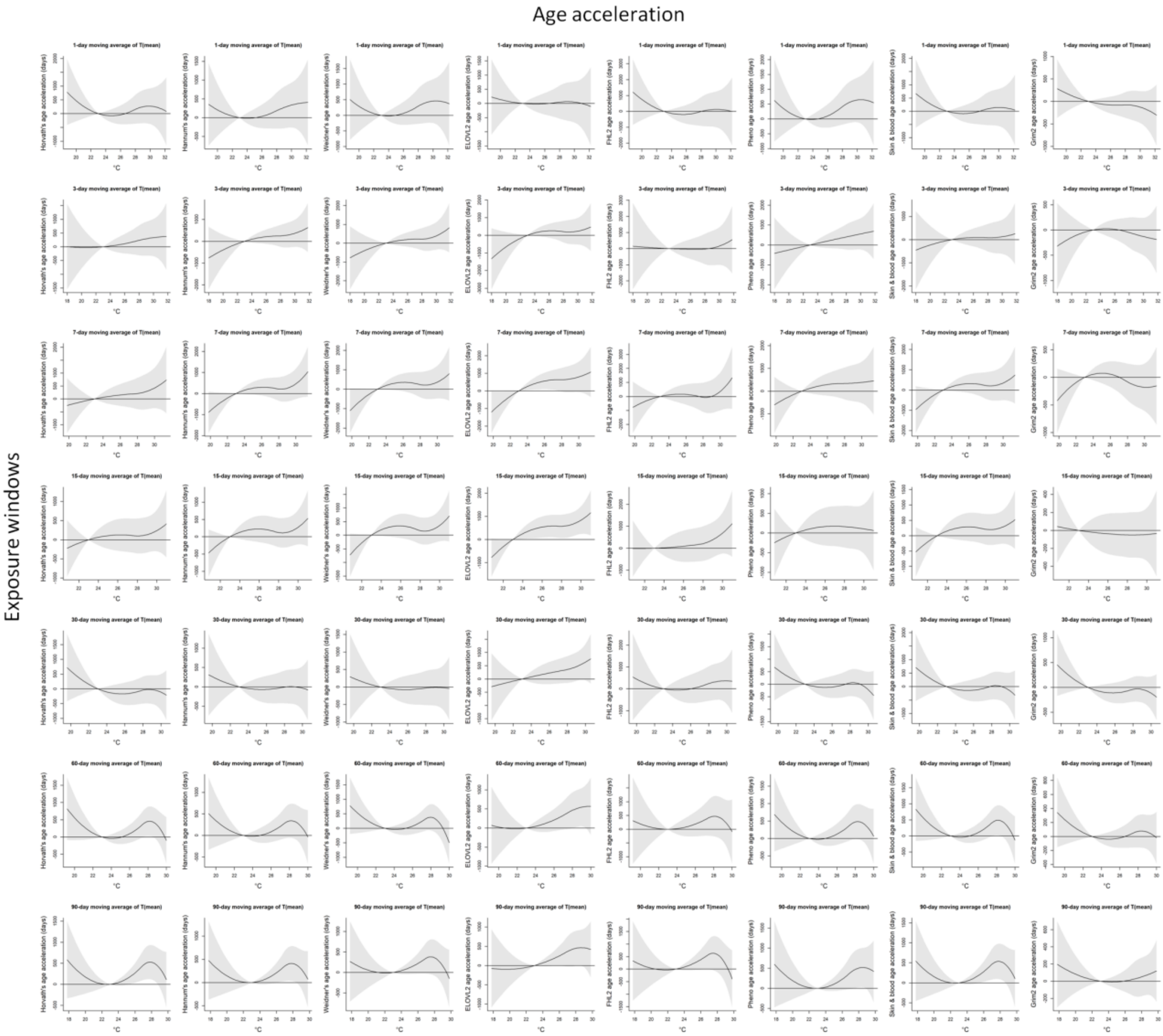

Figure 2- 9. The associations between T(mean) and DNA methylation age acceleration in generalized additive models among participants enrolled in the warm season.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year of enrollment was additionally adjusted in models of 15- to 90-day exposure windows. Results of the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin & blood, and Grim2 age accelerations were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, and 90-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23 ˚C.

T(mean), mean temperature; RH, relative humidity.

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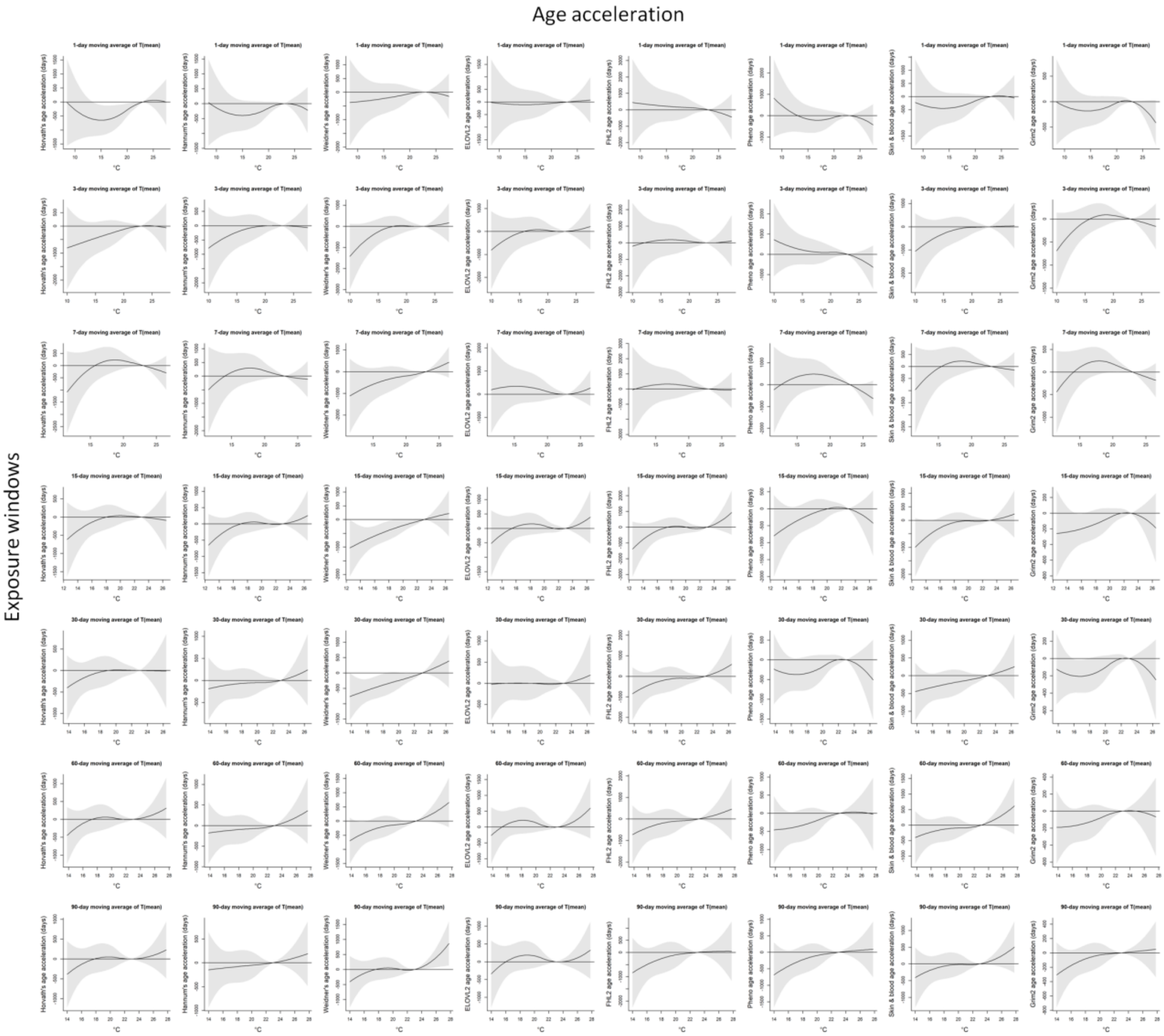

Figure 2- 10. The associations between T(mean) and DNA methylation age acceleration in generalized additive models among participants enrolled in the cold season.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year of enrollment was additionally adjusted in models of 15- to 90-day exposure windows. Results of the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin & blood, and Grim2 age accelerations were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, and 90-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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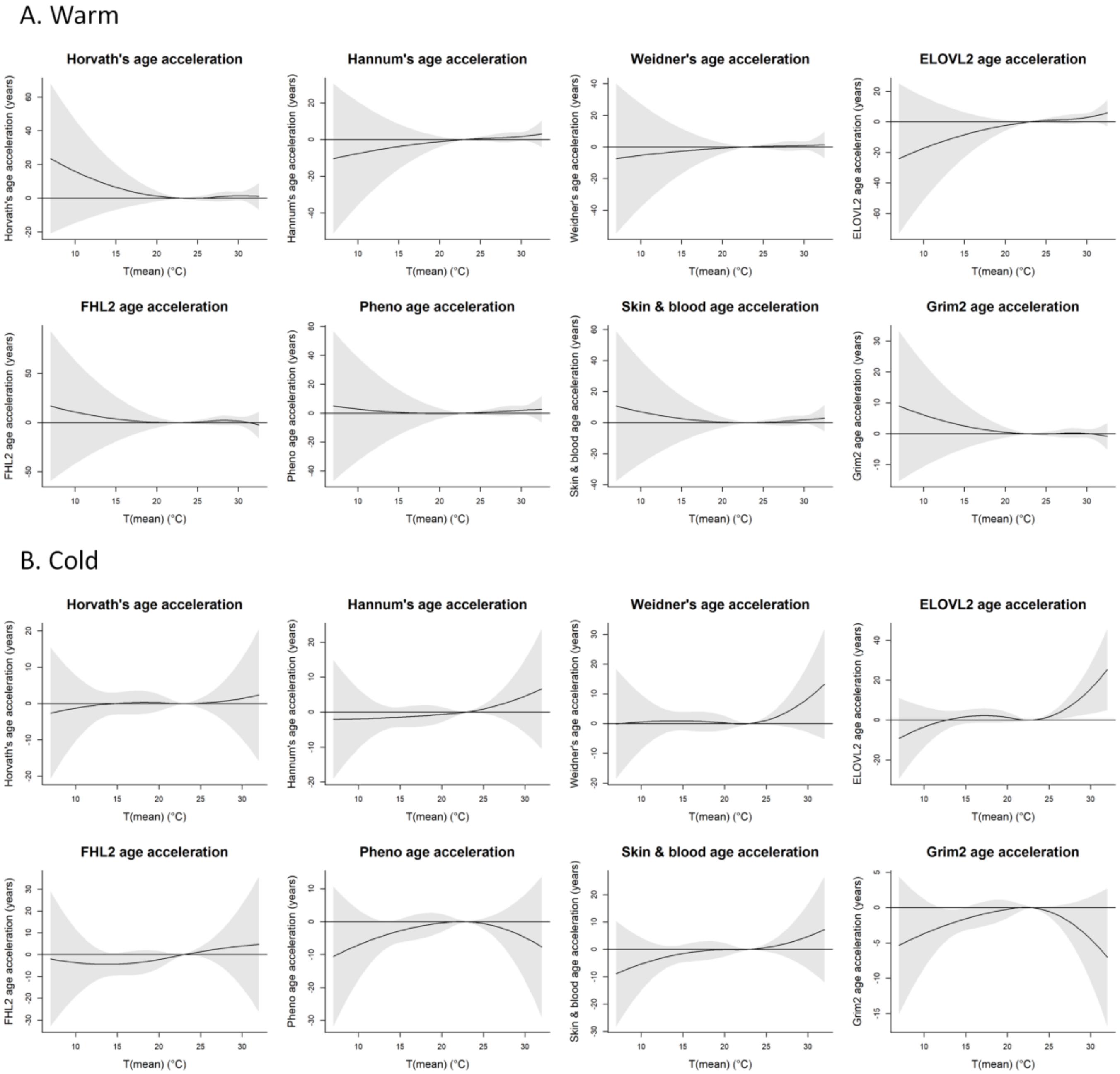

Figure 2- 11. Overall cumulative associations between T(mean) and DNA methylation age acceleration within 90 days exposure window in distributed lag non-linear models among participants enrolled in the A. warm and B. cold seasons.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, year of enrollment, and RH. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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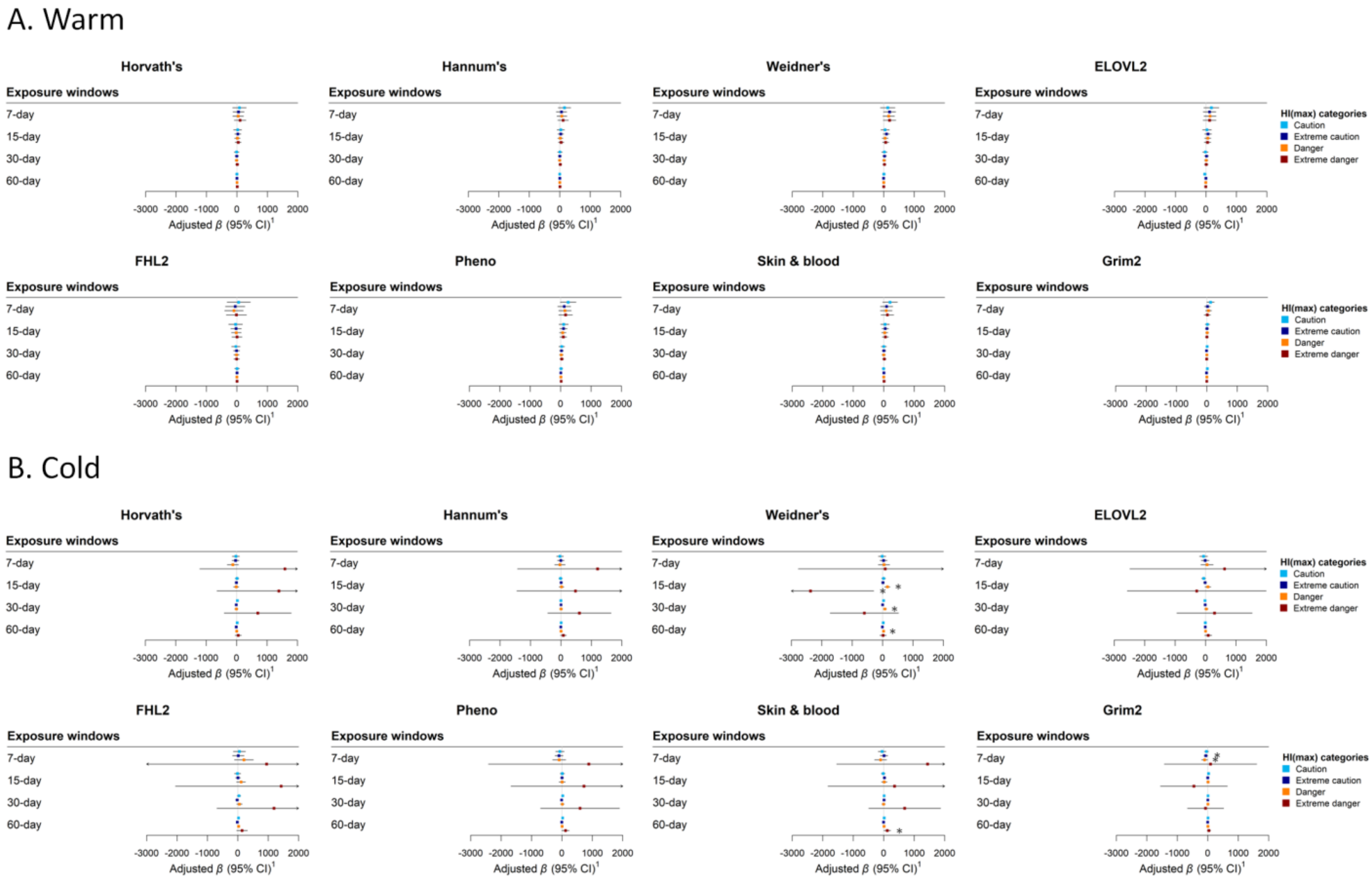

Figure 2- 12. The associations between number of heat stress days in a given exposure window and DNA methylation age acceleration among participants enrolled in the A. warm and B. cold season in multivariable linear regression models.

[1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 7-day exposure windows. Year of enrollment was additionally adjusted in models of 15- to 60-day exposure windows.

The colored boxes represented the point estimates, and the black lines represented the 95% confidence intervals.

HI(max), heat index of maximum temperature.

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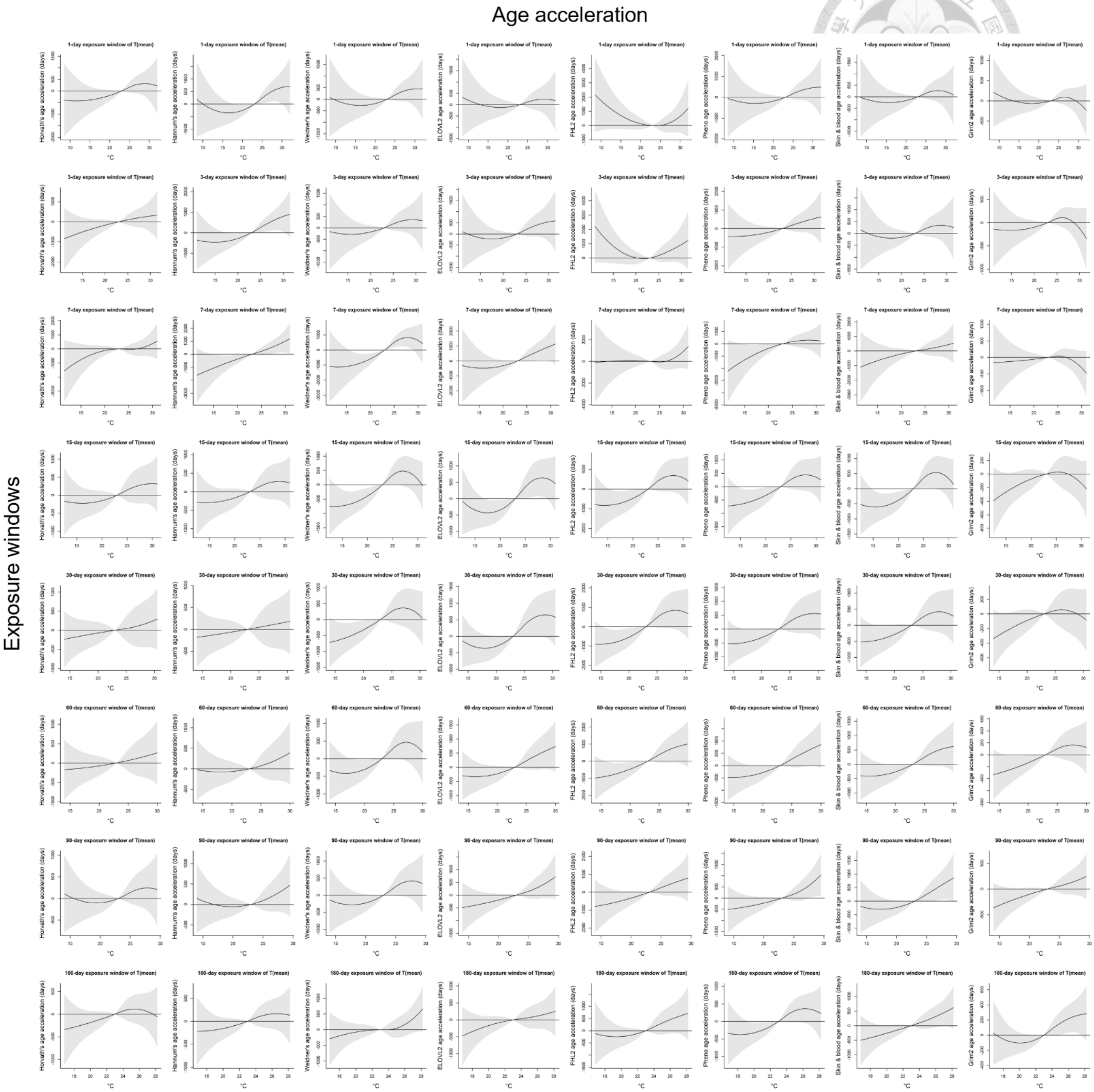

Figure 2- 13. The associations between T(mean) and DNA methylation age acceleration in generalized additive models among participants enrolled in the northern area.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season (warm or cold season) of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. Results of the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin

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& blood, and Grim2 age accelerations were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, 90-, and 180-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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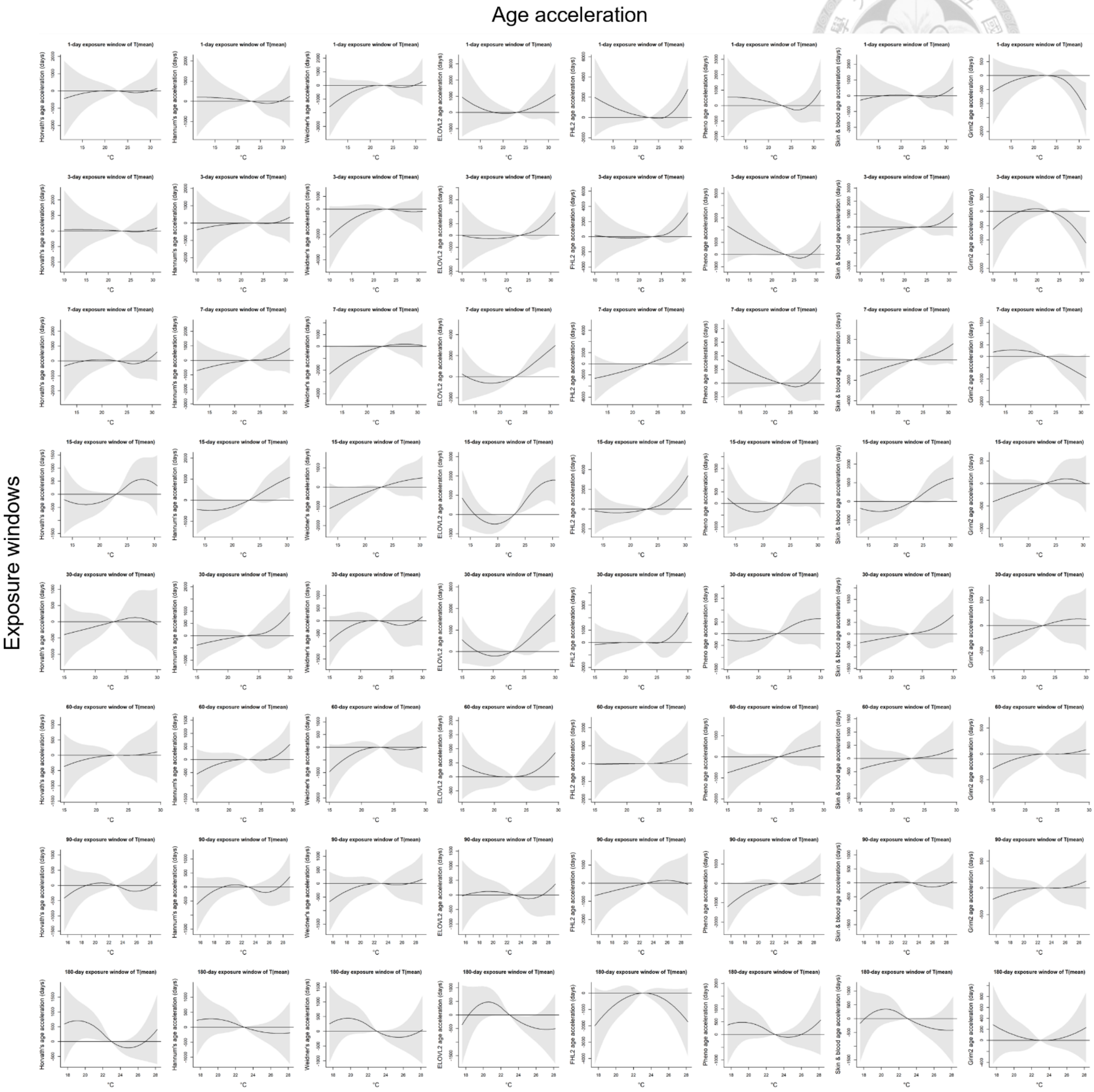

Figure 2- 14. The associations between T(mean) and DNA methylation age acceleration in generalized additive models among participants enrolled in the central area.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season (warm or cold season) of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. Results of the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin

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& blood, and Grim2 age accelerations were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, 90-, and 180-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23 ̊C.

T(mean), mean temperature; RH, relative humidity.

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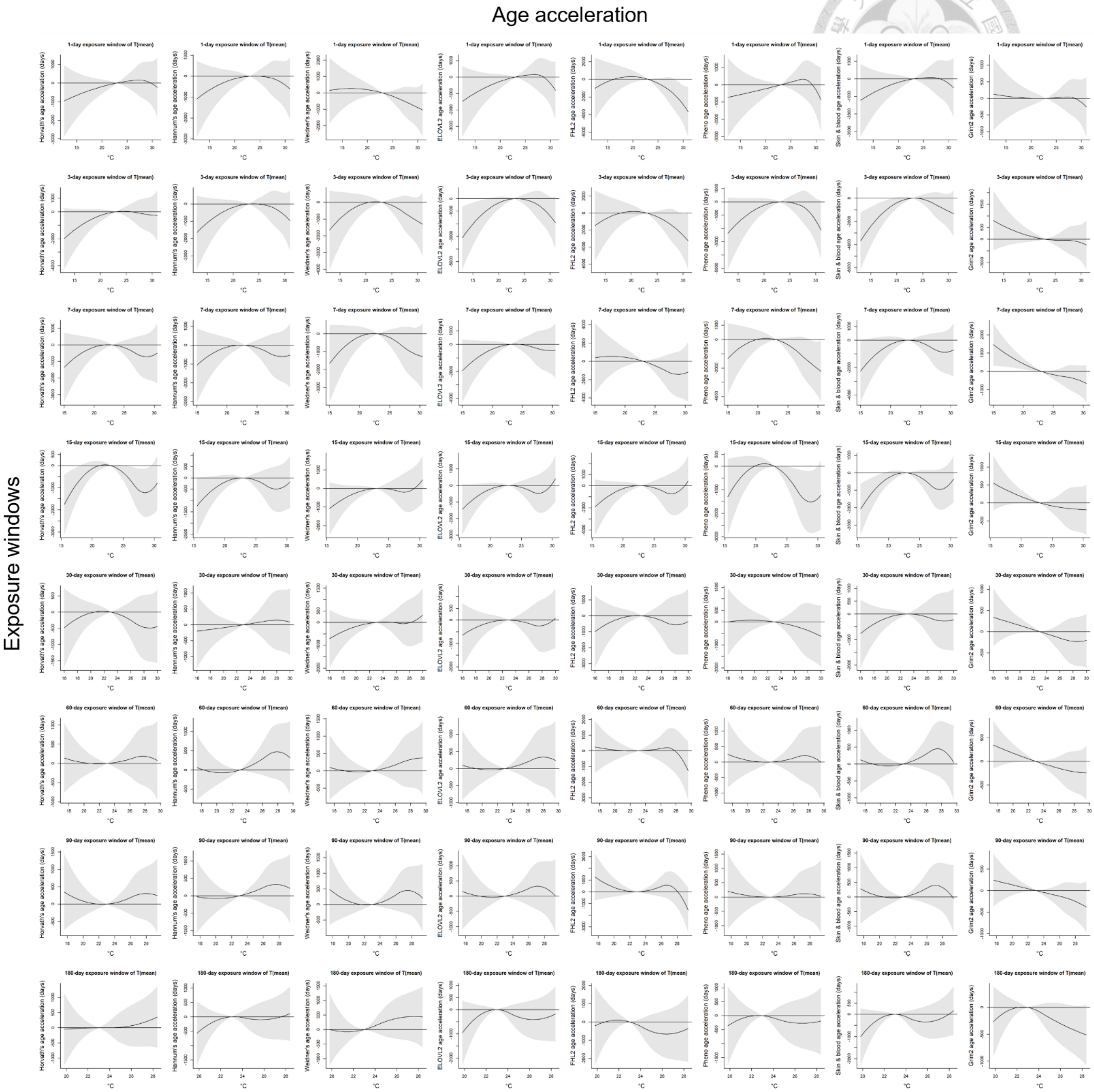

Figure 2- 15. The associations between T(mean) and DNA methylation age acceleration in generalized additive models among participants enrolled in the southern area.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season (warm or cold season) of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. Results of the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin

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& blood, and Grim2 age accelerations were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, 90-, and 180-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23 °C.

T(mean), mean temperature; RH, relative humidity.

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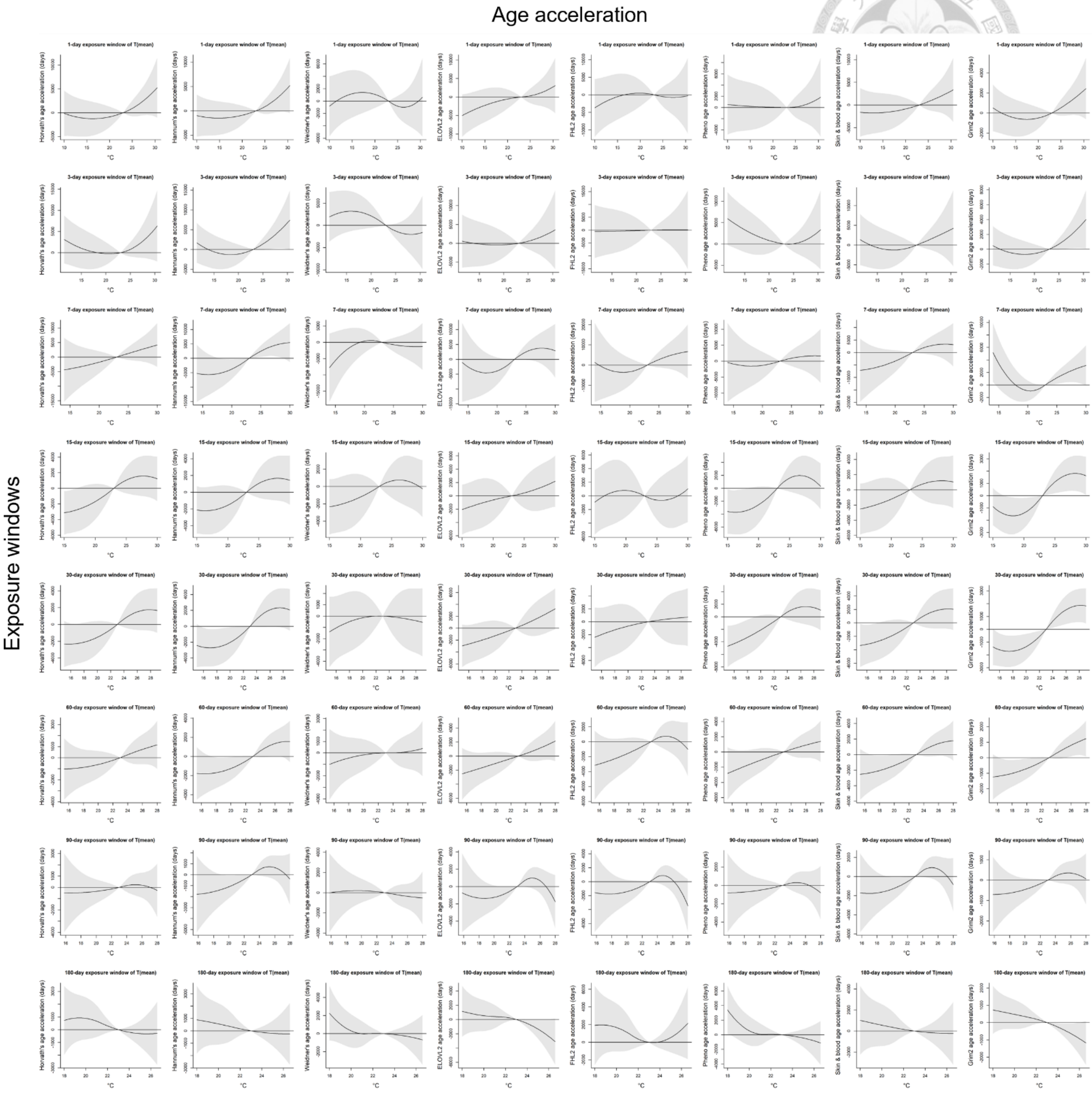

Figure 2- 16. The associations between T(mean) and DNA methylation age acceleration in generalized additive models among participants enrolled in the eastern area.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, RH, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season (warm or cold season) of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. Results of the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin

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& blood, and Grim2 age accelerations were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, 90-, and 180-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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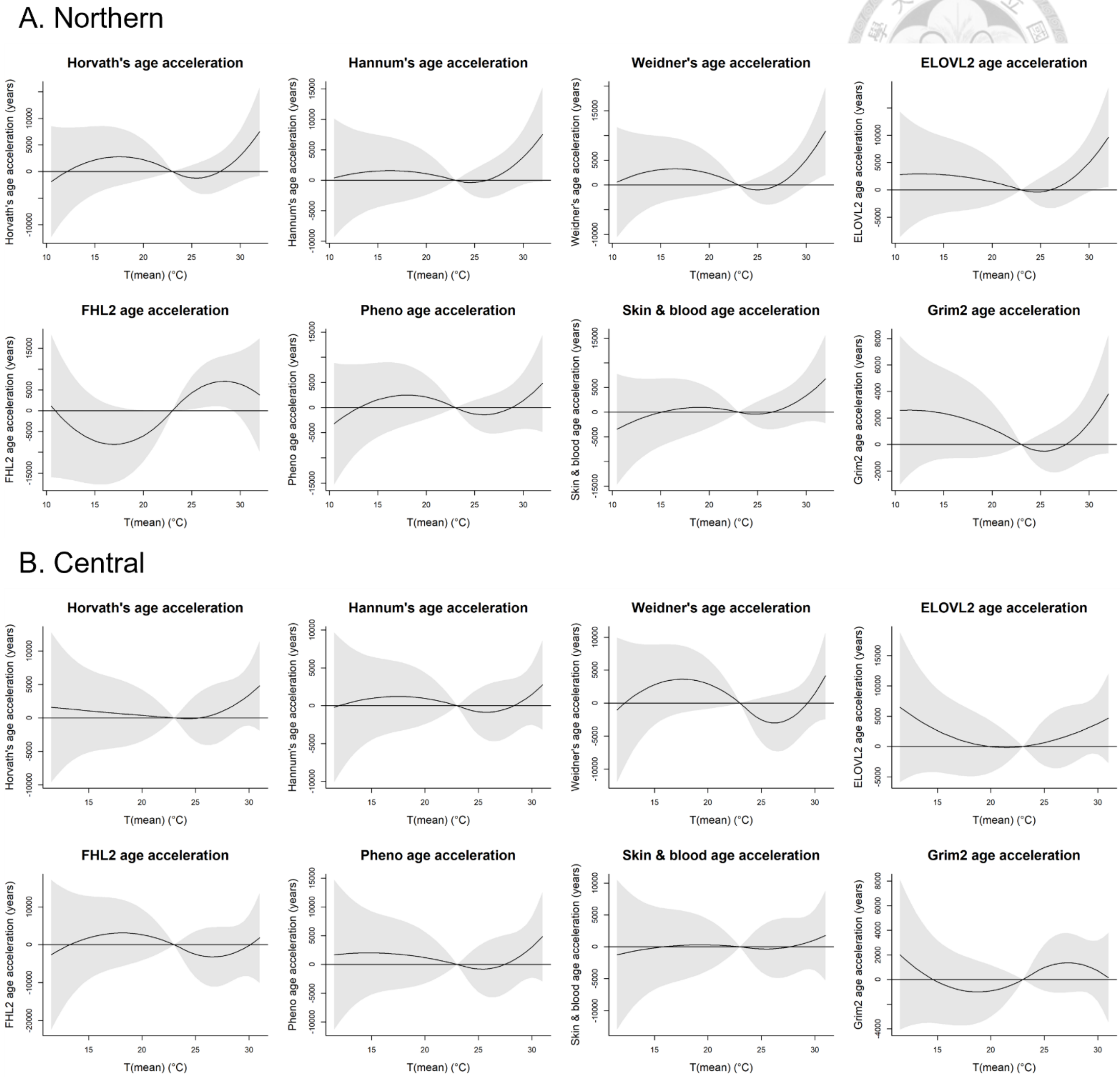

Figure 2- 17. Overall cumulative associations between T(mean) and DNA methylation age acceleration within 52 weeks exposure window in distributed lag non-linear models among participants enrolled in the A. northern, B. central, C. southern, and D. eastern areas.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, year and season (warm or cold season) of enrollment, and RH. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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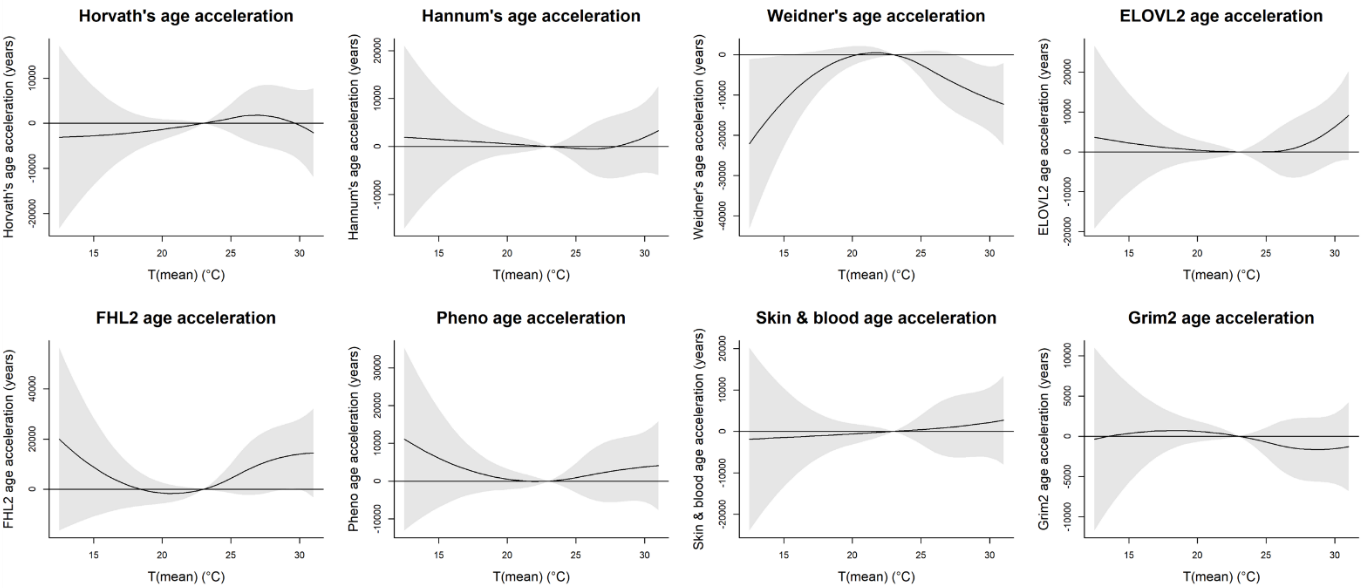
C. Southern



D. Eastern

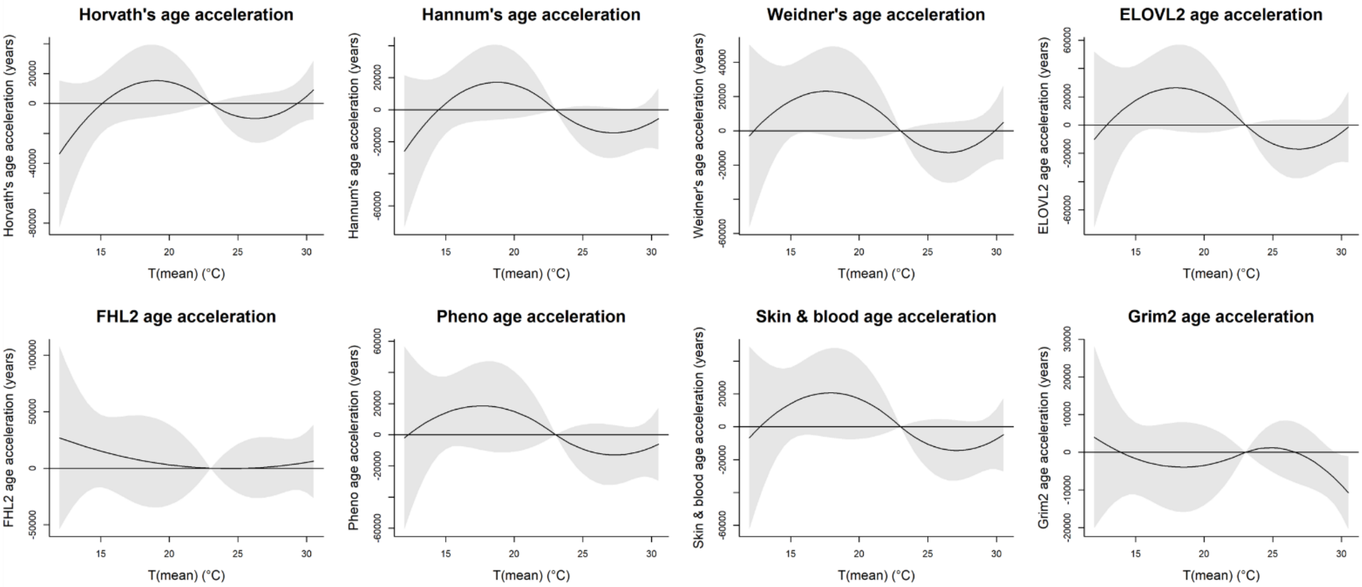


Figure 2- 17 (cont.). Overall cumulative associations between T(mean) and DNA methylation age acceleration within 52 weeks exposure window in distributed lag non-linear models among participants enrolled in the A. northern, B. central, C. southern, and D. eastern areas.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, year and season (warm or cold season) of enrollment, and RH. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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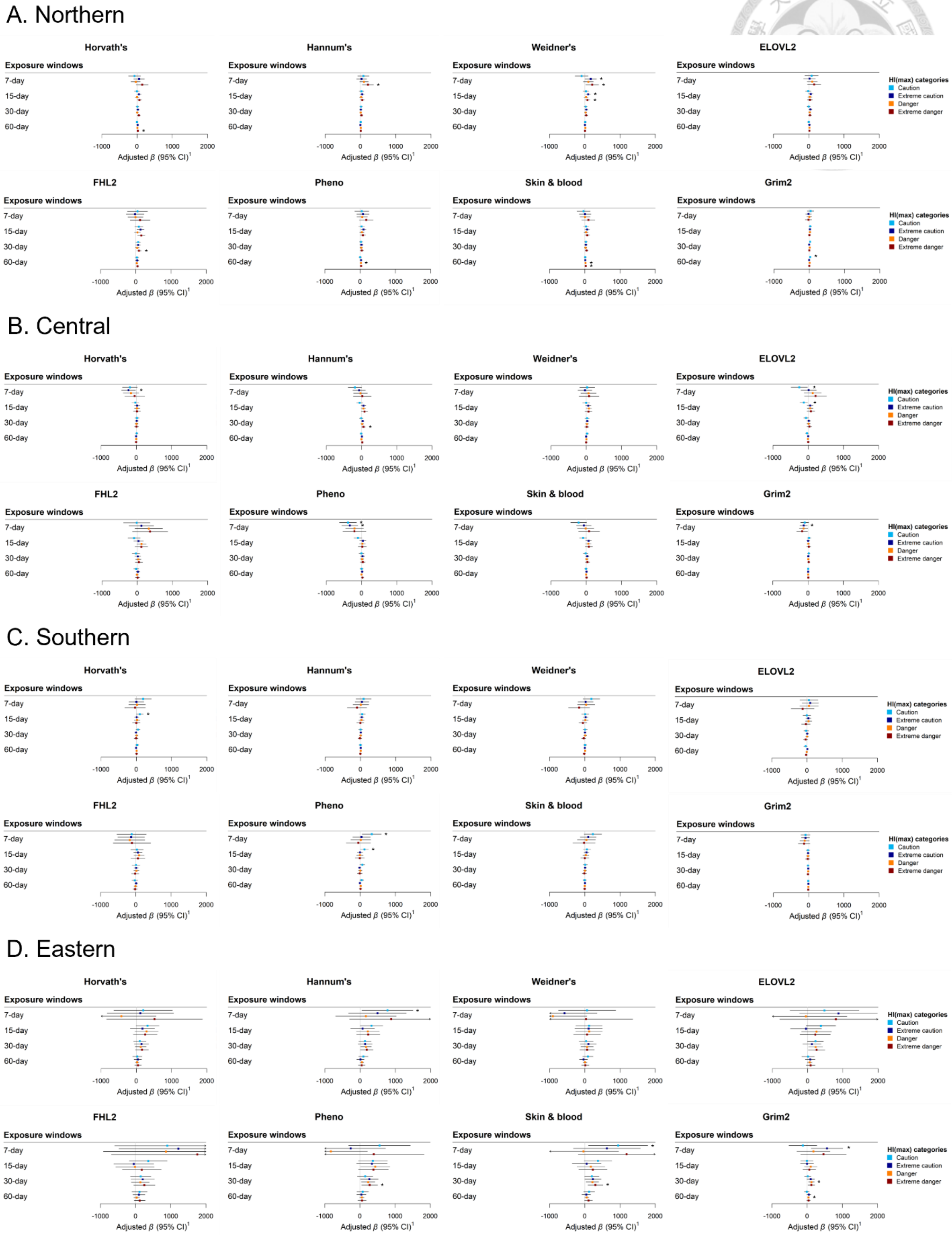

Figure 2- 18. The associations between number of heat stress days in a given exposure window and DNA methylation age acceleration among participants enrolled in the A. northern, B. central, C. southern, and

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D. eastern areas in multivariable linear regression models.

[1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 7-day exposure windows. Year and season (warm and cold season) of enrollment were additionally adjusted in models of 15- to 60-day exposure windows.

The colored boxes represented the point estimates, and the black lines represented the 95% confidence intervals.

HI(max), heat index of maximum temperature.

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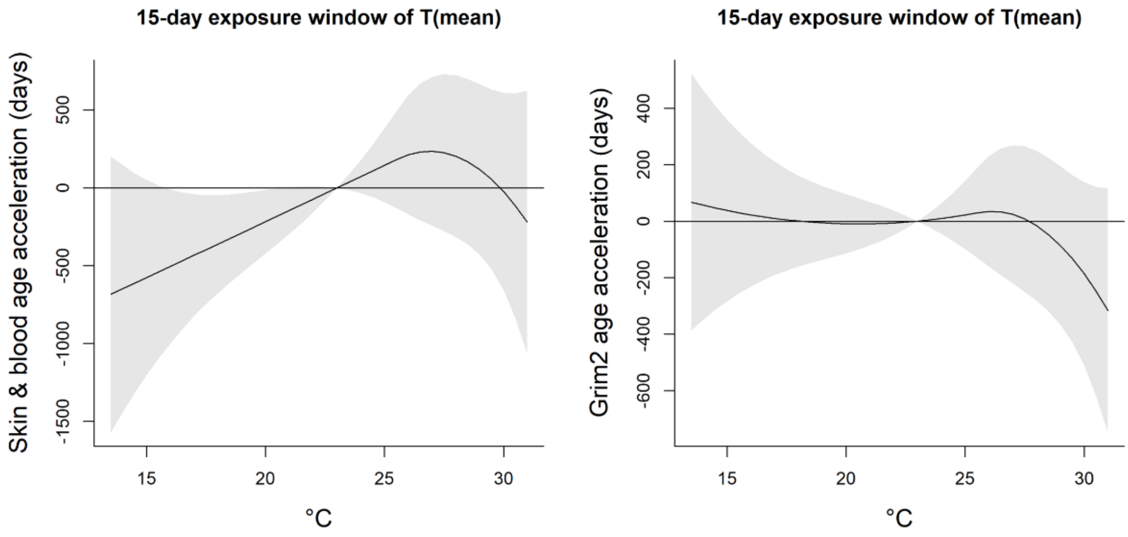
A. Males



B. Females

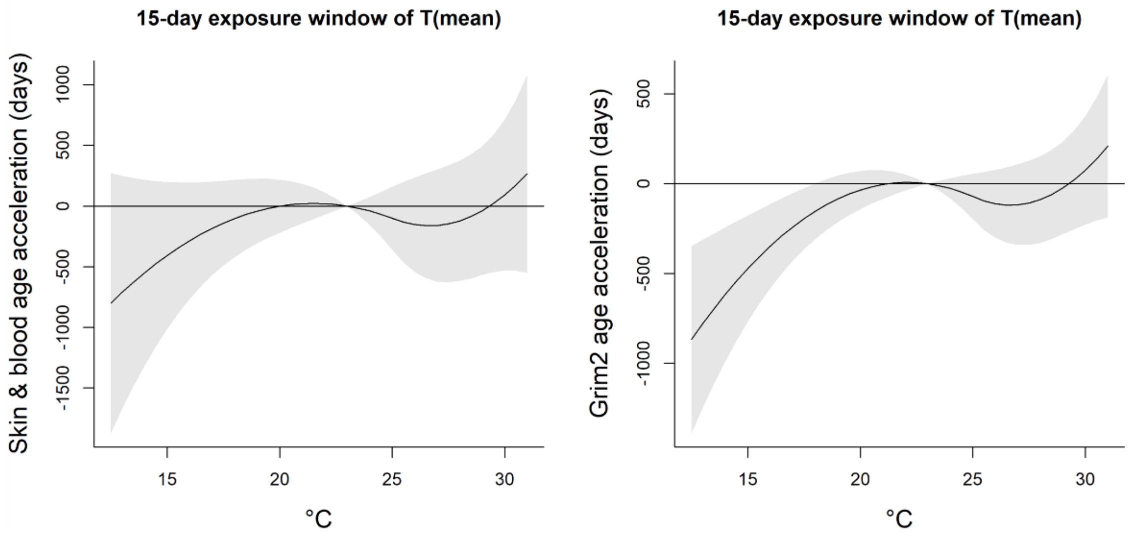


Figure 2- 19. The associations between T(mean) and Skin & blood and Grim2 DNA methylation age acceleration in generalized additive models among A. male and B. female participants.

Models were adjusted for chronological age, BMI, educational level, smoking status, RH, $PM_{2.5}$, and year and season (warm or cold season) of enrollment. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of T(mean) for each model was the annual mean of 23˚C.

T(mean), mean temperature; RH, relative humidity.

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Appendix

Table S1- 1. Sequences of primers and probe sets for *PPARγ* H3K4me3 measurements.

Primer names		Sequences
PPARγ R1	Forward	AATGTCACTGGAAAGAACATCTTGG
	Reverse	GCCCAGAGAGGGTCCCATT
	Probe	FAM-TGAAGGGCAAGCCACTCTGGCC--BBQ
PPARγ R2	Forward	CGCTCCGGGGGAACT
	Reverse	GGGCTCTGGACAGCGAA
	Probe	6FAM-CCCCTGCTGAGGAGGAGGTCC--BBQ
PPARγ R3	Forward	CCTCCTGGGAGCCTAACTG
	Reverse	CACTGACCTTATATAAAAGCCGCA
	Probe	6FAM-AGGCAGCAGAGGTTAACAGAAATCTCAGGT--BBQ

Table S1- 2. Concentration of chlorpyrifos (ng/mL) in cord plasma.

LOD	Detection rate (%)	GM (GSD)	Median	IQR
0.01	82.81	0.13 (5.29)	0.17	0.31

LOD, limit of detection; GM, geometric mean; GSD geometric standard deviation; IQR, interquartile range.

Table S1- 3. Distributions of placental H3K4me3 levels in the *PPARγ* gene.

H3K4me3 levels	Mean (SD) (% Input) [1]
R1	13.5 (20.63)
R2	14.01 (21.37)
R3	10.37 (18.25)

[1] H3K4me3 levels exceed 100 (% Input) were substituted by 100 (% Input).

SD, standard deviation.

Table S1- 4. The correlations of placental H3K4me3 levels of *PPARγ* gene.

	Statistics	R1 H3K4me3 level	R2 H3K4me3 level
R2 H3K4me3 level	r [1]	0.67	
	p	< 0.0001	
R3 H3K4me3 level	r [1]	0.72	0.73
	p	< 0.0001	< 0.0001

[1] Pearson’s correlation coefficient.

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Table S1- 5. The association of dichotomized prenatal chlorpyrifos exposure and health outcomes.

Health outcomes	**Chlorpyrifos** [1]		***p*** [2]
	Low exposure	**High exposure**	
Birth outcomes (mean (SD))			
Gestational age (week)	38.39 (1.6)	38.46 (1.5)	0.67
Birth weight (g)	3162.88 (434.2)	3166.15 (440.9)	0.95
Birth length (cm)	49.14 (2)	49.05 (2)	0.65
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old (mean (SD))			
Whole test	98.84 (12.5)	97.98 (13.3)	0.66
Cognitive	95.14 (12.2)	92.42 (12.4)	0.14
Language	100.52 (12.6)	99.68 (13.3)	0.67
Motor	88.77 (12.4)	85.75 (11.2)	0.09
Gross-motor	86.27 (13.9)	83.14 (13.6)	0.13
Fine-motor	95.62 (12.8)	94.23 (12.4)	0.45
Social	108.56 (14.5)	107.72 (18)	0.73
Self-help	99.88 (16.6)	101.43 (15.5)	0.52

[1] Chlorpyrifos exposure effects were evaluated by dichotomized status (i.e., below or above median).

[2] Student’s t-test.

SD, standard deviation.

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Table S1- 6. Significant level of interaction terms between chlorpyrifos exposure and sex.

Health outcomes	Interaction terms of chlorpyrifos [1] and sex	
	Crude	Adjusted
	p	*p* [2]
Birth outcomes		
Gestational age (week)	0.58	0.86
Birth weight (g)	0.25	0.094
Birth length (cm)	0.59	0.46
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old		
Whole test	0.62	0.65
Cognitive	0.35	0.52
Language	0.22	0.28
Motor	0.71	0.7
Gross-motor	0.96	0.99
Fine-motor	0.45	0.47
Social	0.36	0.46
Self-help	0.89	0.67

[1] Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). [2] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, and gestational age (week) except for the association with gestational age.

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Table S1- 7. Health outcomes in association with prenatal chlorpyrifos exposure in boys.

Health outcomes	Chlorpyrifos [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI) [2]	Adjusted p [2]
Birth outcomes				
Gestational age (week)	-0.04 (-0.18, 0.10)	0.53	-0.02 (-0.16, 0.13)	0.81
Birth weight (g)	22.74 (-18.92, 64.40)	0.28	25.33 (-11.34, 62.01)	0.17
Birth length (cm)	0.008 (-0.17, 0.19)	0.93	0.02 (-0.14, 0.18)	0.81
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old				
Whole test	-0.77 (-2.19, 0.66)	0.29	-0.92 (-2.39, 0.56)	0.22
Cognitive	**-1.54 (-2.87, -0.22)**	**0.023***	**-1.66 (-3.02, -0.31)**	**0.016***
Language	**-1.72 (-3.21, -0.23)**	**0.024***	**-1.79 (-3.33, -0.26)**	**0.023***
Motor	-0.53 (-1.80, 0.74)	0.41	-0.56 (-1.80, 0.69)	0.38
Gross-motor	-0.90 (-2.57, 0.77)	0.29	-0.92 (-2.59, 0.76)	0.28
Fine-motor	0.26 (-0.99, 1.51)	0.68	0.22 (-1.06, 1.50)	0.73
Social	-0.45 (-2.47, 1.58)	0.66	-0.63 (-2.73, 1.48)	0.56
Self-help	0.52 (-1.17, 2.20)	0.55	0.41 (-1.33, 2.15)	0.64

* $p < 0.05$. [1] Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). [2] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, and gestational age (week) except for the association with gestational age.

p values before adjustment for multiple comparisons. p values less than 0.05 shown in bold.

aβ, adjusted β; CI, confidence interval.

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Table S1- 8. Health outcomes in association with prenatal chlorpyrifos exposure in girls.

Health outcomes	**Chlorpyrifos** [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI)[2]	Adjusted p [2]
Birth outcomes				
Gestational age (week)	0.01 (-0.16, 0.15)	0.87	0.002 (-0.13, 0.14)	0.98
Birth weight (g)	-9.45 (-45.68, 26.78)	0.61	-12.83 (-41.26, 15.60)	0.37
Birth length (cm)	-0.06 (-0.24, 0.12)	0.50	-0.05 (-0.21, 0.10)	0.50
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old				
Whole test	-0.21 (-1.95, 1.54)	0.82	-0.14 (-1.90, 1.62)	0.87
Cognitive	-0.50 (-2.31, 1.31)	0.59	-0.84 (-2.61, 0.93)	0.35
Language	-0.32 (-2.02, 1.39)	0.71	-0.48 (-2.14, 1.17)	0.56
Motor	-0.93 (-2.71, 0.86)	0.30	-0.93 (-2.73, 0.88)	0.31
Gross-motor	-0.84 (-2.68, 1.0)	0.37	-0.76 (-2.60, 1.09)	0.42
Fine-motor	-0.58 (-2.48, 1.33)	0.55	-0.67 (-2.64, 1.31)	0.51
Social	0.93 (-1.16, 3.01)	0.38	1.02 (-1.06, 3.09)	0.33
Self-help	0.70 (-1.56, 2.96)	0.54	1.33 (-0.70, 3.35)	0.20

[1] Cord blood chlorpyrifos levels were log-transformed (log-ng/mL). [2] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, and gestational age (week) except for the association with gestational age.

p values before adjustment for multiple comparisons.

aβ, adjusted β; CI, confidence interval.

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Table S1- 9. The associations between H3K4me3 levels in *PPARγ* gene and health outcomes.

Health outcomes	H3K4me3 level in R1 [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI) [2]	Adjusted p [2]
Birth outcomes				
Gestational age (week)	**0.15 (0.03, 0.28)**	**0.016***	**0.16 (0.04, 0.29)**	**0.011***
Birth weight (g)	**46.53 (12.71, 80.34)**	**0.007***	16.90 (-10.69, 44.48)	0.23
Birth length (cm)	**0.24 (0.08, 0.40)**	**0.004***	0.12 (-0.02, 0.26)	0.10
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old				
Whole test	-0.31 (-1.67, 1.06)	0.66	0.19 (-1.13, 1.50)	0.78
Cognitive	-0.84 (-2.15, 0.46)	0.21	-0.57 (-1.84, 0.70)	0.38
Language	-1.17 (-2.52, 0.17)	0.09	-0.93 (-2.25, 0.39)	0.16
Motor	0.35 (-0.95, 1.64)	0.6	0.45 (-0.85, 1.76)	0.50
Gross-motor	0.82 (-0.67, 2.31)	0.28	0.79 (-0.73, 2.30)	0.31
Fine-motor	-0.55 (-1.86, 0.77)	0.41	-0.28 (-1.63, 1.07)	0.68
Social	-0.45 (-2.20, 1.31)	0.62	-0.14 (-1.93, 1.64)	0.88
Self-help	0.16 (-1.53, 1.85)	0.85	0.90 (-0.69, 2.49)	0.27

Table S1- 9 (cont.). The associations between H3K4me3 levels in *PPARγ* gene and health outcomes.

Health outcomes	H3K4me3 level in R2 [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI) [2]	Adjusted p [2]
Birth outcomes				
Gestational age (week)	0.09 (-0.03, 0.20)	0.130	0.10 (-0.01, 0.21)	0.071
Birth weight (g)	**49.45 (19.37, 79.53)**	**0.001***	**30.52 (6.36, 54.67)**	**0.013***
Birth length (cm)	**0.26 (0.11, 0.40)**	**< 0.001***	**0.18 (0.06, 0.30)**	**0.003***
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old				
Whole test	-0.07 (-1.30, 1.15)	0.91	0.16 (-1.0, 1.32)	0.78
Cognitive	-1.10 (-2.27, 0.07)	0.06	-0.78 (-1.90, 0.33)	0.17
Language	-0.43 (-1.66, 0.80)	0.49	-0.15 (-1.33, 1.03)	0.80
Motor	-0.01 (-1.17, 1.15)	0.99	0.04 (-1.11, 1.19)	0.95
Gross-motor	0.38 (-0.97, 1.73)	0.58	0.31 (-1.03, 1.66)	0.65
Fine-motor	-0.44 (-1.60, 0.73)	0.46	-0.27 (-1.43, 0.90)	0.66
Social	0.38 (-1.20, 1.95)	0.64	0.53 (-1.04, 2.09)	0.51
Self-help	0.51 (-1.0, 2.01)	0.51	0.63 (-0.77, 2.02)	0.38

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Table S1- 9 (cont.). The associations between H3K4me3 levels in *PPARγ* gene and health outcomes.

Health outcomes	H3K4me3 level in R3 [1]			
	Crude β (95% CI)	Crude p	aβ (95% CI) [2]	Adjusted p [2]
Birth outcomes				
Gestational age (week)	0.09 (-0.04, 0.22)	0.17	0.1 (-0.03, 0.23)	0.14
Birth weight (g)	**43.56 (8.63, 78.49)**	**0.015***	25.60 (-3.04, 54.24)	0.08
Birth length (cm)	**0.22 (0.06, 0.39)**	**0.009***	**0.15 (0.01, 0.29)**	**0.042***
Comprehensive Developmental Inventory for Infants and Toddlers at 2 years old				
Whole test	0.02 (-1.40, 1.44)	0.98	0.38 (-0.98, 1.74)	0.59
Cognitive	-1.32 (-2.67, 0.04)	0.06	-0.78 (-2.08, 0.54)	0.25
Language	-0.96 (-2.37, 0.46)	0.18	-0.63 (-2.01, 0.75)	0.37
Motor	0.75 (-0.60, 2.09)	0.28	0.98 (-0.36, 2.33)	0.15
Gross-motor	1.51 (-0.04, 3.06)	0.06	**1.67 (0.11, 3.23)**	**0.036***
Fine-motor	-0.60 (-1.96, 0.76)	0.39	-0.40 (-1.78, 0.98)	0.57
Social	-0.05 (-1.88, 1.78)	0.96	0.11 (-1.73, 1.96)	0.91
Self-help	1.41 (-0.31, 3.12)	0.11	1.48 (-0.13, 3.10)	0.07

* $p < 0.05$. [1] *PPARγ* H3K4me3 levels were log-transformed (log-% Input). [2] All the health outcomes were adjusted for maternal age, maternal BMI, maternal educational level, type of delivery (vaginal delivery or cesarean section), parity, infant sex, and gestational age (week) except for the association with gestational age.

p values before adjustment for multiple comparisons. *p* values less than 0.05 shown in bold.

aβ, adjusted β; CI, confidence interval.

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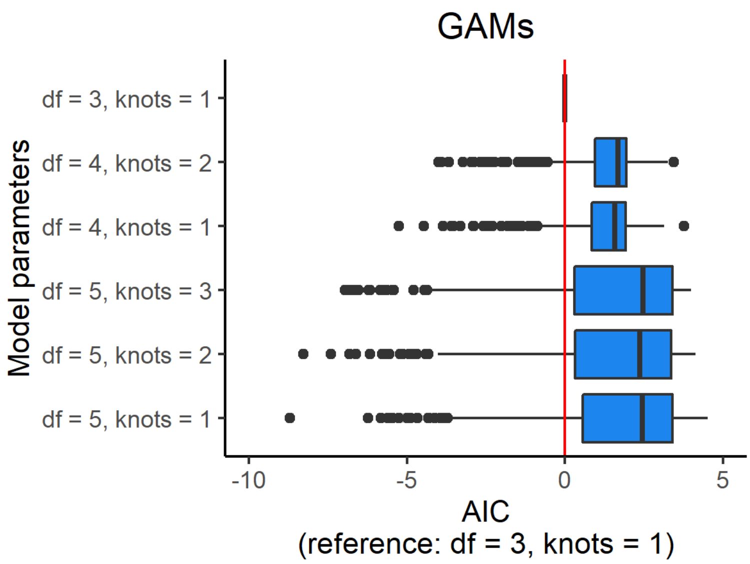

Figure S2- 1. AIC Comparisons of GAMs with three to five degrees of freedom and one to three internal knots.

Quadratic B-splines with one internal knot (df = 3, knots =1) was used as reference.

AIC, Akaike's Information Criterion; GAM, generalized additive model.

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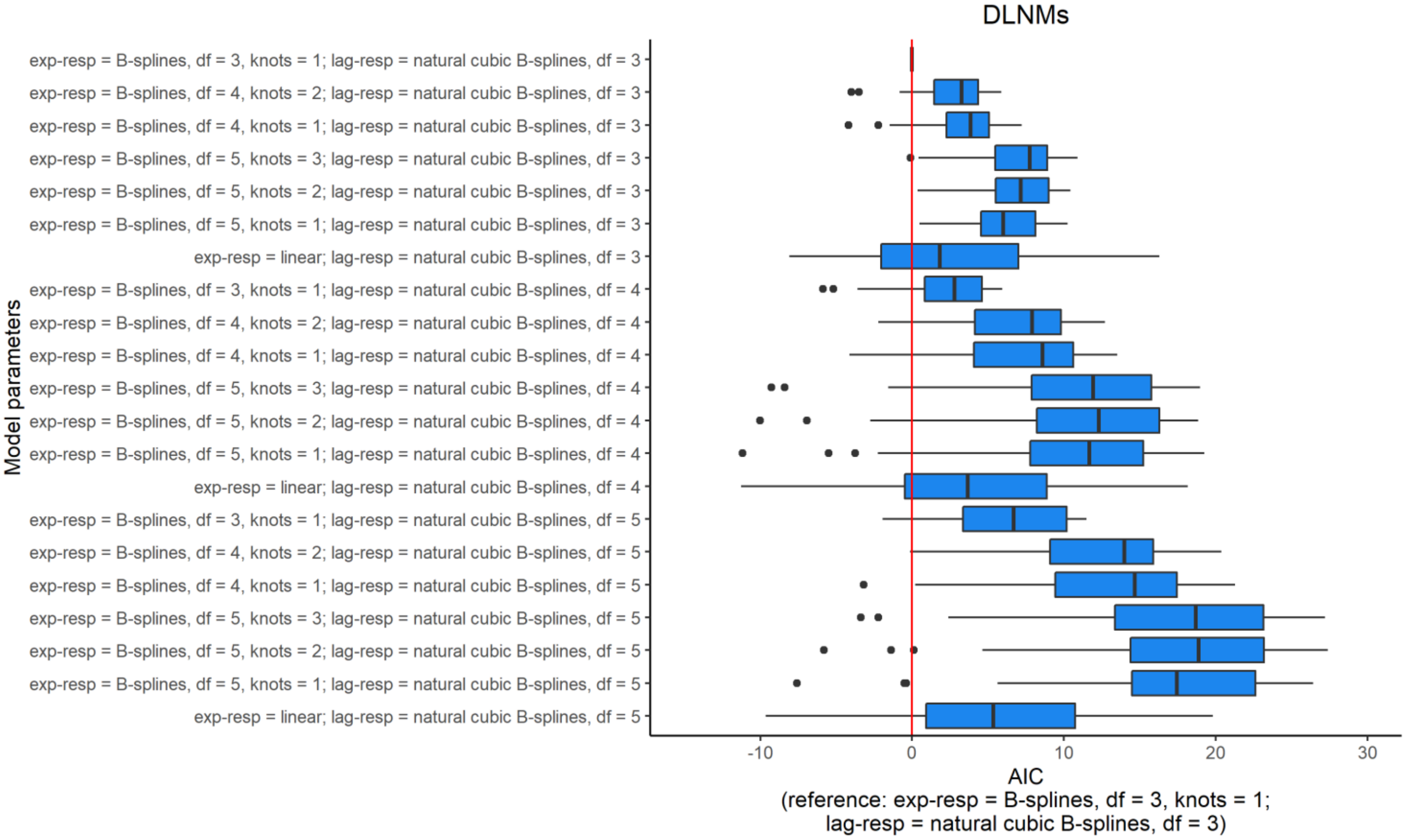

Figure S2- 2. AIC Comparisons of B-splines with three to five degrees of freedom and one to three internal knots and linear model for the exposure-response functions and natural cubic B-splines with three to five degrees of freedom for the lag-response functions in DLNMs.

Quadratic B-splines with one internal knot for the exposure-response function (df = 3, knots =1) and natural cubic B-splines with three degrees of freedom (df = 3) for the lag-response function was used as reference.

AIC, Akaike's Information Criterion; DLNM, distributed lag non-linear model; exp-resp, exposure-response function; lag-resp, lag-response function.

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Table S2- 1. Distributions of moving averages of temperature (°C), RH (%), and HI (°C) from 1 day to 365 days prior to participant enrollment.

Exposure windows	Statistics	T(min) (°C)	T(mean) (°C)	T(max) (°C)	RH (%)	HI(min) (°C)	HI(mean) (°C)	HI(max) (°C)
1-day	Mean (SD)	21.04 (4.71)	24.11 (4.82)	28.21 (5.36)	77.72 (8.53)	21.43 (5.45)	26.1 (6.85)	35.4 (11.48)
	Range	7.29-29.45	8.31-32.2	10.61-37.9	34.83-98.74	6.42-32.72	7.48-40.81	9.92-65.35
3-day	Mean (SD)	21.12 (4.57)	24.2 (4.6)	28.3 (4.97)	77.84 (7.25)	21.53 (5.3)	26.23 (6.63)	35.61 (10.95)
	Range	7.78-28.78	9.63-31.9	12.5-36.8	50.68-96.91	6.53-32.58	8.94-39.34	12.01-60.51
7-day	Mean (SD)	21.2 (4.45)	24.27 (4.46)	28.38 (4.72)	77.82 (6.14)	21.62 (5.16)	26.32 (6.47)	35.73 (10.47)
	Range	7.8-28.61	11.47-31.45	13.86-36.21	57.72-96.38	6.4-32.6	11.02-38.82	13.65-59.22
15-day	Mean (SD)	21.2 (4.33)	24.29 (4.33)	28.41 (4.51)	77.8 (5.23)	21.61 (5.01)	26.34 (6.28)	35.77 (10.05)
	Range	9.36-28.32	12.34-31.13	15.81-36.04	61.51-95	8.54-32.1	11.88-38.89	15.69-58.06
30-day	Mean (SD)	21.22 (4.19)	24.32 (4.19)	28.45 (4.32)	77.64 (4.47)	21.63 (4.85)	26.36 (6.1)	35.76 (9.68)
	Range	11.06-27.89	13.79-30.76	17.21-35.42	64.83-94.69	10.33-31.25	13.17-37.13	16.93-56.51
60-day	Mean (SD)	21.08 (4.06)	24.19 (4.06)	28.33 (4.15)	77.65 (3.96)	21.47 (4.69)	26.16 (5.84)	35.47 (9.2)
	Range	10.93-27.33	13.76-30.19	17.54-34.94	66.87-92.58	10.03-30.28	13.29-36.11	17.45-54.49
90-day	Mean (SD)	20.84 (3.94)	23.98 (3.93)	28.14 (4)	77.66 (3.71)	21.2 (4.53)	25.88 (5.56)	35.14 (8.62)
	Range	11.24-26.95	13.98-29.83	17.68-34.6	67.74-90.54	10.53-29.42	13.55-35.99	17.63-54.19
180-day	Mean (SD)	20.13 (3.07)	23.29 (3.1)	27.49 (3.2)	77.67 (3.37)	20.4 (3.53)	24.98 (4.34)	33.95 (6.73)
	Range	13.42-26.2	16.65-28.59	20.14-33.4	68.32-88.15	12.95-28.18	16.51-33.38	20.74-50.79
365-day	Mean (SD)	20.05 (0.93)	23.16 (0.97)	27.31 (1.04)	77.74 (2.92)	20.31 (1.09)	24.81 (1.35)	33.56 (1.84)
	Range	17.59-22.73	20.63-25.41	24.61-30.43	71.33-86.86	17.62-23.58	21.47-28.1	28.71-41.43

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature; SD, standard deviation.

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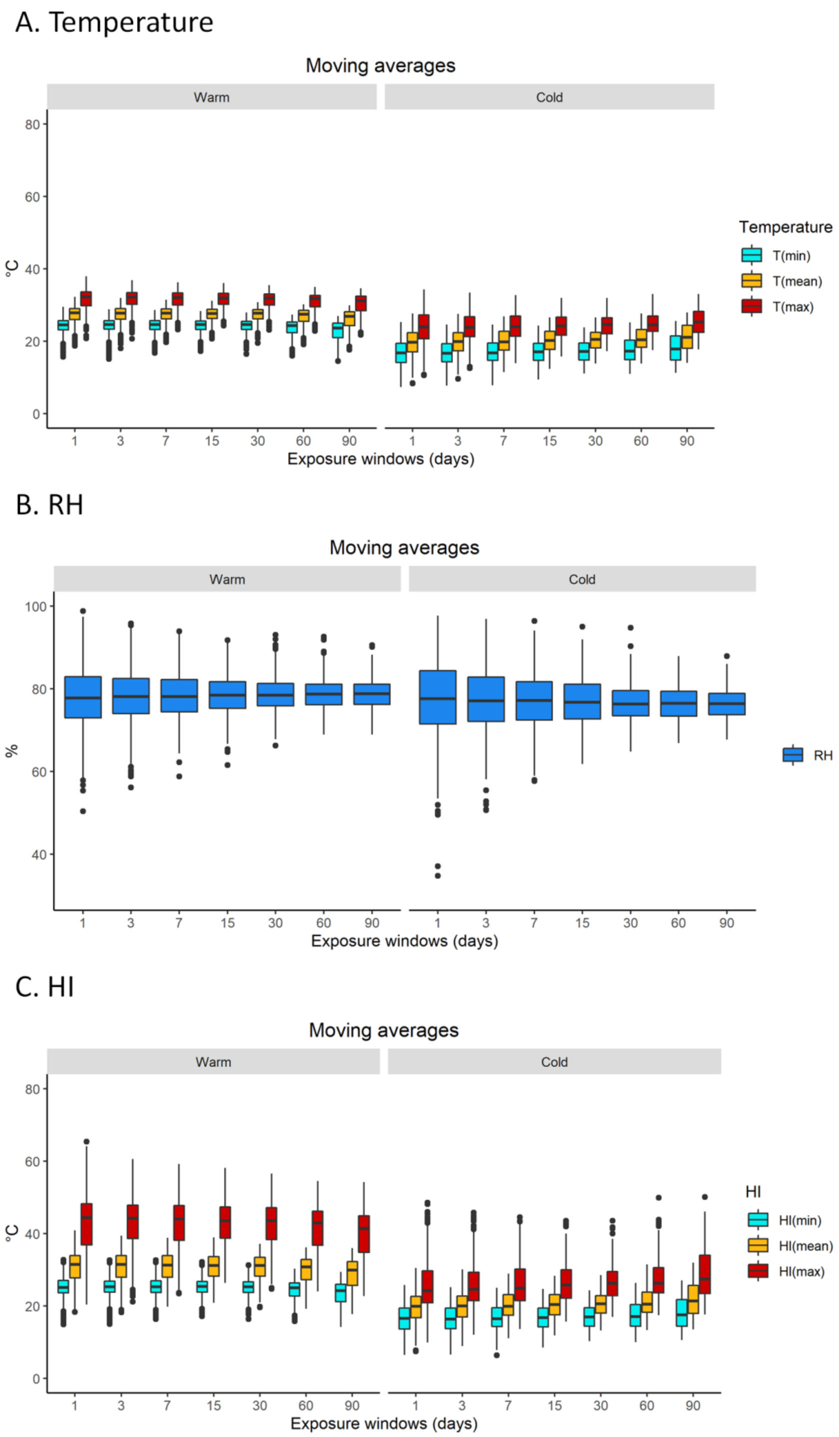

Figure S2- 3. Distributions of moving averages stratified by season of A. temperature (˚C), B. RH (%), and C. HI (˚C) from 1 day to 90 days prior to participant enrollment.

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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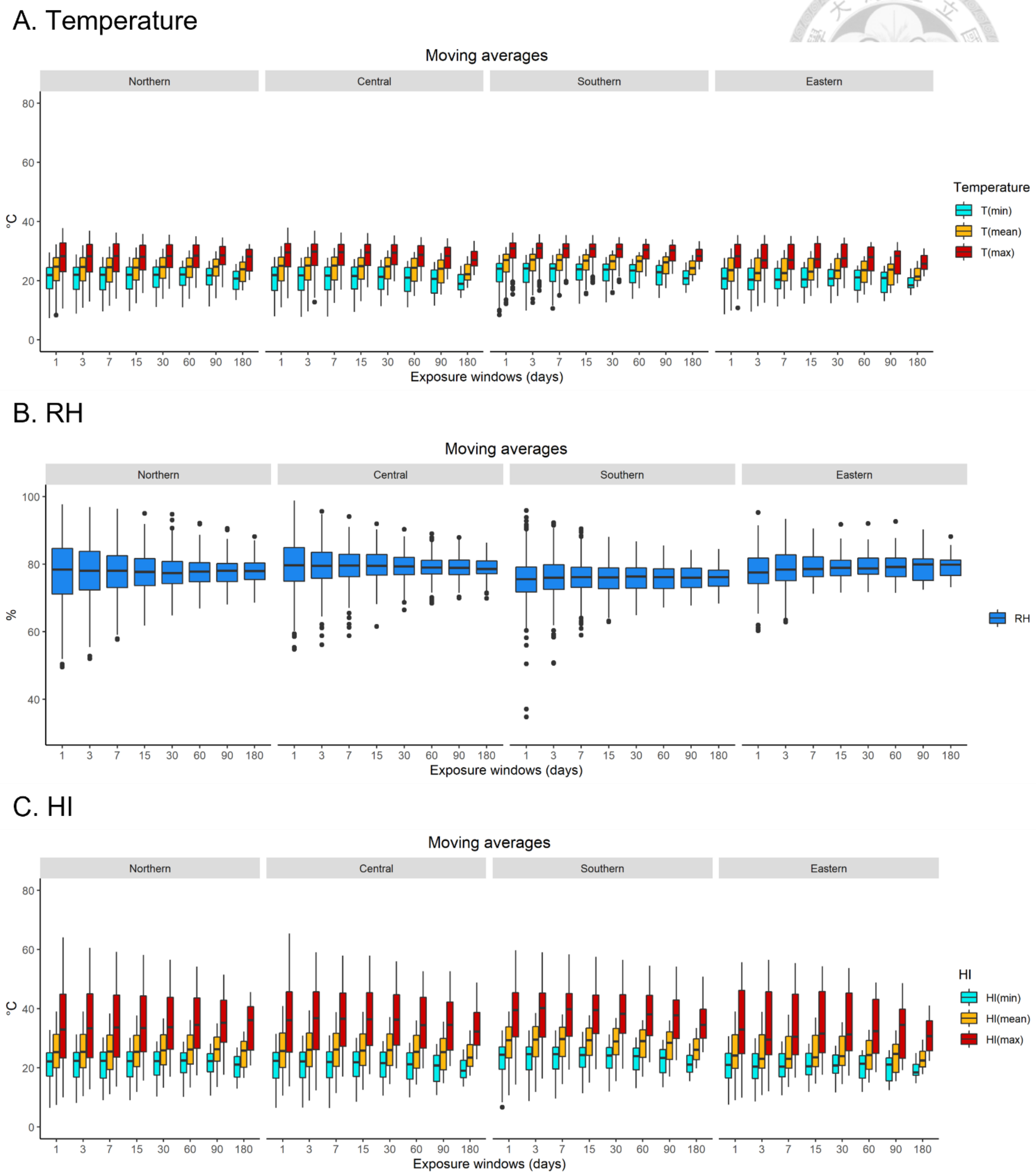

Figure S2- 4. Distributions of moving averages stratified by area of A. temperature (˚C), B. RH (%), and C. HI (˚C) from 1 day to 90 days prior to participant enrollment.

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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Table S2- 2. Number of heat stress days in HI(max) in multiple exposure windows.

Exposure windows	Statistics	No warning (days)	Caution (days)	Extreme caution (days)	Danger (days)	Extreme danger (days)
1-day	Mean (SD)	0.3 (0.46)	0.12 (0.33)	0.17 (0.37)	0.34 (0.47)	0.07 (0.26)
	Range	0-1	0-1	0-1	0-1	0-1
3-day	Mean (SD)	0.87 (1.22)	0.38 (0.72)	0.49 (0.84)	1.03 (1.23)	0.23 (0.67)
	Range	0-3	0-3	0-3	0-3	0-3
7-day	Mean (SD)	1.94 (2.58)	0.88 (1.34)	1.22 (1.67)	2.43 (2.66)	0.52 (1.39)
	Range	0-7	0-7	0-7	0-7	0-7
15-day	Mean (SD)	4.09 (5.18)	1.94 (2.44)	2.65 (2.97)	5.2 (5.26)	1.11 (2.68)
	Range	0-15	0-14	0-15	0-15	0-15
30-day	Mean (SD)	8.03 (9.77)	4.12 (4.35)	5.29 (5.16)	10.39 (10.01)	2.12 (4.69)
	Range	0-30	0-24	0-24	0-30	0-28
60-day	Mean (SD)	16.55 (18.45)	8.35 (7.27)	10.63 (8.25)	20.24 (18.32)	4.12 (8.51)
	Range	0-60	0-34	0-41	0-59	0-48
90-day	Mean (SD)	26.11 (26.48)	12.04 (8.62)	15.72 (9.62)	29.84 (24.49)	6.09 (11.24)
	Range	0-90	0-40	0-53	0-86	0-72
180-day	Mean (SD)	61.94 (41.01)	23.76 (10.97)	28.56 (9.38)	52.85 (34.4)	12.38 (17.65)
	Range	0-156	1-66	5-66	0-141	0-107
365-day	Mean (SD)	129.53 (29.59)	49.28 (11.39)	56.14 (15.49)	107.42 (21.29)	21.54 (21.75)
	Range	57-191	19-87	24-106	63-158	0-108

HI(max), heat index of maximum temperature; SD, standard deviation.

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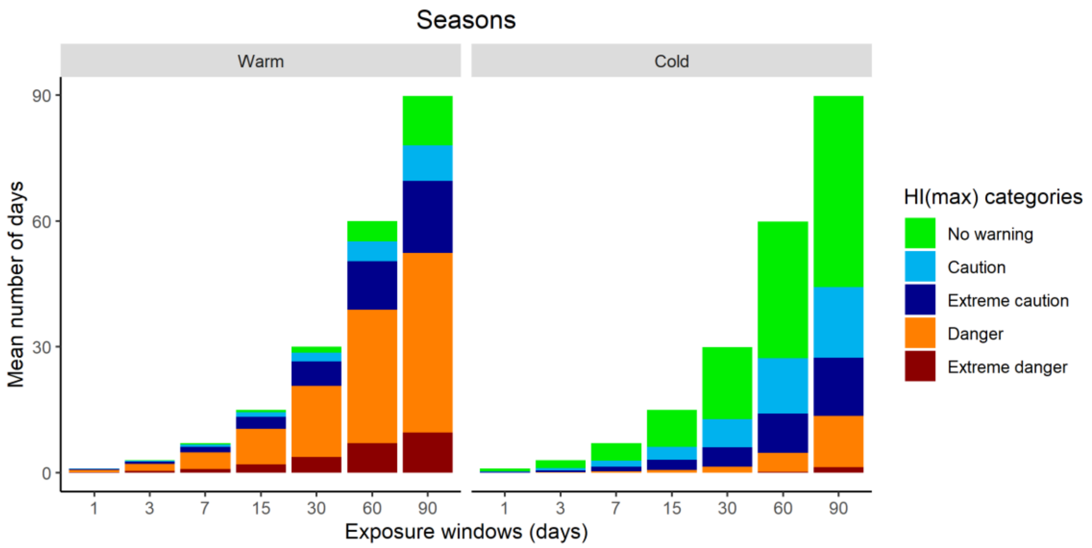

Figure S2- 5. Number of days of HI(max) in HI categories stratified by season in multiple exposure windows.

HI(max), heat index of maximum temperature.

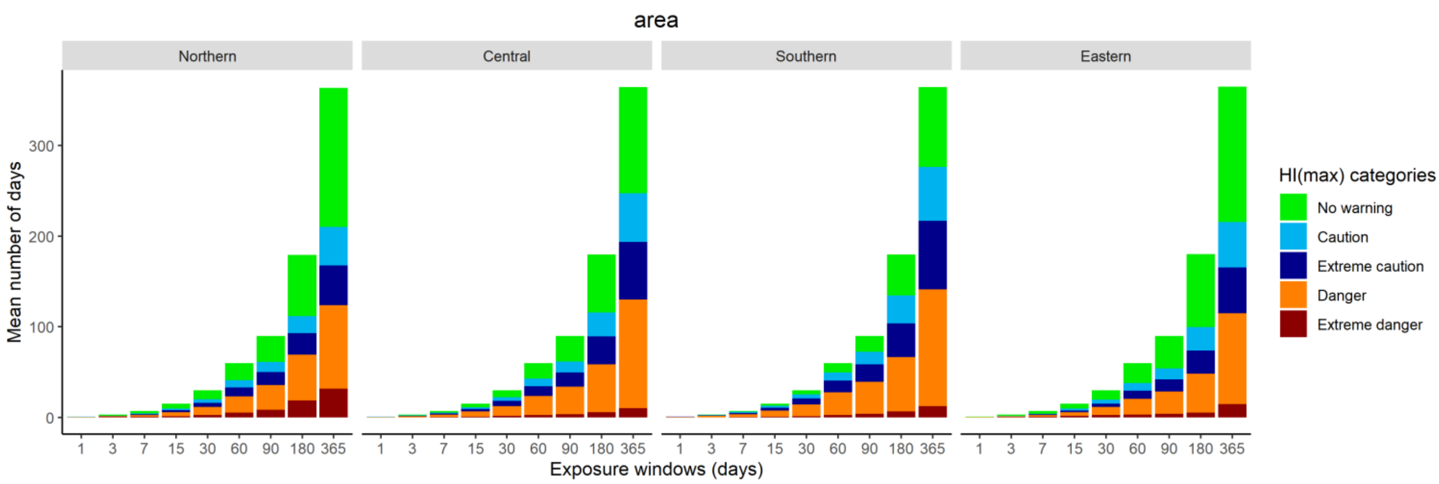

Figure S2- 6. Number of days of HI(max) in HI categories stratified by area in multiple exposure windows.

HI(max), heat index of maximum temperature.

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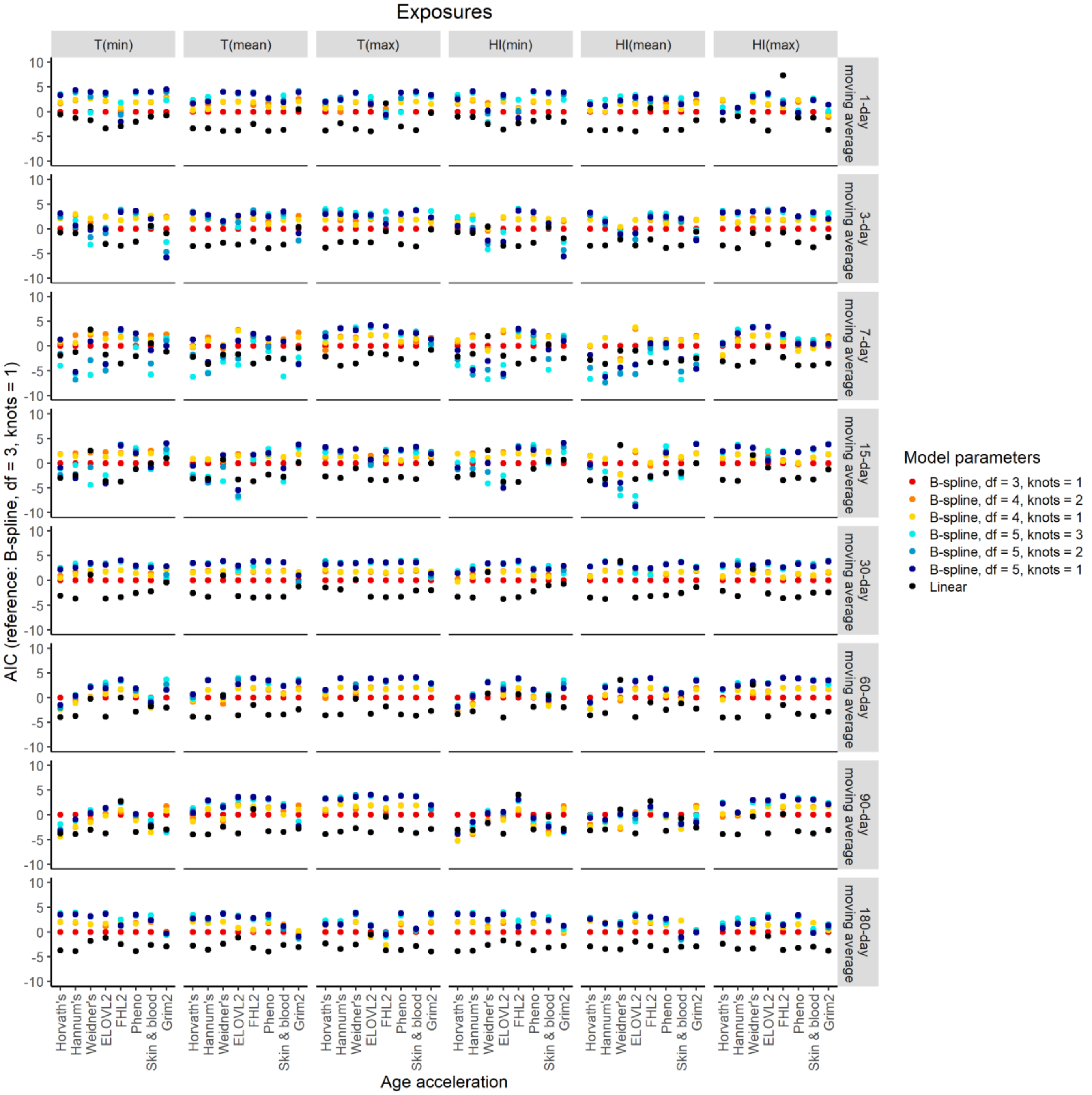

Figure S2- 7. AIC Comparisons of GAMs with different B-spline parameters and linear models. AIC, Akaike's Information Criterion; GAM, generalized additive model. T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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Table S2- 3. The Horvath's, Hannum's, ELOVL2, Pheno, Skin & blood, and Grim2 age accelerations in relation to temperature (°C) and HI (°C) exposures in linear regression models.

Exposures	Exposure windows (days)	Age acceleration (days)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
T(min)	1	Horvath's	21.33 (-2.59, 45.25)	0.081	18.12 (-23.22, 59.45)	0.39
T(min)	3	Horvath's	17.19 (-7.42, 41.8)	0.17	5.94 (-40.32, 52.2)	0.8
T(min)	7	Horvath's	16.55 (-8.72, 41.82)	0.2	-11.19 (-65.27, 42.9)	0.69
T(min)	15	Horvath's	22.07 (-3.93, 48.07)	0.096	7.05 (-28.84, 42.95)	0.7
T(min)	30	Horvath's	24.68 (-2.17, 51.54)	0.072	3.5 (-34.11, 41.11)	0.86
T(min)	60	Horvath's	36.98 (9.3, 64.67)	**0.009**	18.61 (-16.95, 54.16)	0.3
T(min)	90	Horvath's	47.09 (18.56, 75.62)	**0.001**	20.54 (-12.46, 53.54)	0.22
T(min)	180	Horvath's	72.06 (35.57, 108.55)	< **0.001**	22.43 (-10.7, 55.56)	0.18
T(min)	1	Hannum's	31.08 (8.7, 53.46)	**0.007**	13.63 (-24.81, 52.08)	0.49
T(min)	3	Hannum's	29.95 (6.93, 52.98)	**0.011**	13.76 (-29.25, 56.77)	0.53
T(min)	7	Hannum's	30.79 (7.15, 54.44)	**0.011**	2.81 (-47.52, 53.13)	0.91
T(min)	15	Hannum's	34.34 (10.02, 58.66)	**0.006**	14.48 (-18.94, 47.9)	0.4
T(min)	30	Hannum's	37.2 (12.08, 62.32)	**0.004**	11.06 (-23.96, 46.08)	0.54
T(min)	60	Hannum's	50.11 (24.23, 75.99)	< **0.001**	30.96 (-2.11, 64.03)	0.066
T(min)	90	Hannum's	57.61 (30.94, 84.28)	< **0.001**	26 (-4.69, 56.68)	0.097
T(min)	180	Hannum's	68.16 (33.99, 102.33)	< **0.001**	18.06 (-12.73, 48.85)	0.25
T(min)	1	ELOVL2	24.96 (0.34, 49.59)	**0.047**	15.86 (-30.25, 61.97)	0.5
T(min)	3	ELOVL2	24.65 (-0.68, 49.99)	0.056	25.14 (-26.38, 76.66)	0.34
T(min)	7	ELOVL2	25.56 (-0.45, 51.58)	0.054	27.95 (-32.31, 88.21)	0.36
T(min)	15	ELOVL2	27.24 (0.47, 54.01)	**0.046**	22.96 (-17.09, 63.01)	0.26
T(min)	30	ELOVL2	28.73 (1.08, 56.38)	**0.042**	19.07 (-22.94, 61.08)	0.37
T(min)	60	ELOVL2	34.73 (6.21, 63.24)	**0.017**	23.16 (-16.53, 62.85)	0.25
T(min)	90	ELOVL2	38.5 (9.09, 67.9)	**0.01**	17.9 (-18.95, 54.75)	0.34
T(min)	180	ELOVL2	43.87 (6.2, 81.53)	**0.022**	2.73 (-34.28, 39.73)	0.89
T(min)	1	Pheno	19.53 (-4.77, 43.83)	0.12	-10.23 (-58.67, 38.2)	0.68
T(min)	3	Pheno	17.15 (-7.85, 42.14)	0.18	-25.72 (-79.8, 28.36)	0.35
T(min)	7	Pheno	19.52 (-6.14, 45.18)	0.14	-39.02 (-102.2, 24.17)	0.23
T(min)	15	Pheno	25.56 (-0.84, 51.96)	0.058	15.1 (-26.89, 57.09)	0.48
T(min)	30	Pheno	28.22 (0.96, 55.49)	**0.042**	14.05 (-29.99, 58.09)	0.53
T(min)	60	Pheno	41.14 (13.04, 69.24)	**0.004**	40.81 (-0.79, 82.41)	0.055
T(min)	90	Pheno	47.7 (18.73, 76.67)	**0.001**	41.14 (2.52, 79.75)	**0.037**
T(min)	180	Pheno	57.57 (20.46, 94.67)	**0.002**	27.74 (-11.04, 66.52)	0.16

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude β (95% CI)	Crude p	aβ (95% CI) [1]	Adjusted p [1]
T(min)	1	Skin & blood	23.97 (2.46, 45.49)	**0.029**	10.08 (-34.49, 54.65)	0.66
T(min)	3	Skin & blood	23.71 (1.58, 45.84)	**0.036**	9.85 (-40.1, 59.79)	0.7
T(min)	7	Skin & blood	25.69 (2.97, 48.41)	**0.027**	5.33 (-53.08, 63.74)	0.86
T(min)	15	Skin & blood	29.89 (6.51, 53.26)	**0.012**	32.3 (-6.49, 71.08)	0.1
T(min)	30	Skin & blood	32.26 (8.12, 56.4)	**0.009**	26.78 (-13.87, 67.42)	0.2
T(min)	60	Skin & blood	43.07 (18.2, 67.95)	< **0.001**	41.66 (3.26, 80.05)	**0.033**
T(min)	90	Skin & blood	49.28 (23.64, 74.93)	< **0.001**	36.49 (0.84, 72.13)	**0.045**
T(min)	180	Skin & blood	57.12 (24.26, 89.97)	< **0.001**	26.38 (-9.41, 62.18)	0.15
T(min)	1	Grim2	17.09 (1.61, 32.57)	**0.03**	-4.49 (-27.09, 18.11)	0.7
T(min)	3	Grim2	15.95 (0.02, 31.89)	**0.05**	-5.1 (-30.37, 20.17)	0.69
T(min)	7	Grim2	16.1 (-0.26, 32.46)	0.054	-19.53 (-49.03, 9.97)	0.19
T(min)	15	Grim2	19.97 (3.14, 36.8)	**0.02**	10.74 (-8.74, 30.23)	0.28
T(min)	30	Grim2	20.25 (2.86, 37.64)	**0.022**	10.07 (-10.38, 30.52)	0.33
T(min)	60	Grim2	24.74 (6.81, 42.67)	**0.007**	14.62 (-4.69, 33.93)	0.14
T(min)	90	Grim2	28.19 (9.7, 46.68)	**0.003**	14.15 (-3.78, 32.07)	0.12
T(min)	180	Grim2	32.5 (8.82, 56.19)	**0.007**	11.25 (-6.74, 29.25)	0.22
T(mean)	1	Horvath's	23.1 (-0.24, 46.44)	0.052	26.7 (-14.13, 67.53)	0.2
T(mean)	3	Horvath's	18.95 (-5.5, 43.41)	0.13	23.02 (-23.92, 69.96)	0.34
T(mean)	7	Horvath's	18.54 (-6.66, 43.75)	0.15	2.61 (-54.03, 59.25)	0.93
T(mean)	15	Horvath's	23.5 (-2.46, 49.46)	0.076	12.65 (-23.04, 48.34)	0.49
T(mean)	30	Horvath's	25.42 (-1.41, 52.25)	0.063	8.62 (-29.03, 46.28)	0.65
T(mean)	60	Horvath's	38.17 (10.51, 65.83)	**0.007**	21.51 (-13.98, 57)	0.23
T(mean)	90	Horvath's	49.18 (20.6, 77.76)	< **0.001**	21.92 (-10.56, 54.41)	0.19
T(mean)	180	Horvath's	76.37 (40.18, 112.57)	< **0.001**	22.69 (-9.01, 54.39)	0.16
T(mean)	1	Hannum's	28.7 (6.86, 50.55)	**0.01**	10.52 (-27.47, 48.52)	0.59
T(mean)	3	Hannum's	28.22 (5.34, 51.1)	**0.016**	20.84 (-22.81, 64.49)	0.35
T(mean)	7	Hannum's	30.43 (6.85, 54.01)	**0.011**	13.29 (-39.41, 65.98)	0.62
T(mean)	15	Hannum's	33.83 (9.54, 58.12)	**0.006**	14.67 (-18.56, 47.9)	0.39
T(mean)	30	Hannum's	36 (10.9, 61.1)	**0.005**	10.32 (-24.75, 45.38)	0.56
T(mean)	60	Hannum's	49.04 (23.18, 74.9)	< **0.001**	28.32 (-4.69, 61.34)	0.093
T(mean)	90	Hannum's	57.73 (31.01, 84.46)	< **0.001**	23.44 (-6.77, 53.65)	0.13
T(mean)	180	Hannum's	69.67 (35.76, 103.58)	< **0.001**	15.56 (-13.9, 45.03)	0.3
T(mean)	1	ELOVL2	24.26 (0.22, 48.29)	**0.048**	11.92 (-33.64, 57.47)	0.61
T(mean)	3	ELOVL2	23.32 (-1.86, 48.5)	0.069	28.33 (-23.95, 80.62)	0.29

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
T(mean)	7	ELOVL2	24.85 (-1.1, 50.8)	0.061	29.59 (-33.51, 92.69)	0.36
T(mean)	15	ELOVL2	26.66 (-0.07, 53.39)	0.051	22.49 (-17.34, 62.32)	0.27
T(mean)	30	ELOVL2	27.23 (-0.39, 54.86)	0.053	16.73 (-25.33, 58.8)	0.44
T(mean)	60	ELOVL2	33.28 (4.78, 61.77)	**0.022**	18.17 (-21.45, 57.8)	0.37
T(mean)	90	ELOVL2	37.95 (8.49, 67.42)	**0.012**	12.69 (-23.59, 48.98)	0.49
T(mean)	180	ELOVL2	45.25 (7.87, 82.63)	**0.018**	-0.04 (-35.46, 35.37)	1
T(mean)	1	Pheno	19.84 (-3.87, 43.55)	0.1	-7.37 (-55.25, 40.51)	0.76
T(mean)	3	Pheno	17.34 (-7.49, 42.18)	0.17	-20.61 (-75.5, 34.27)	0.46
T(mean)	7	Pheno	21.4 (-4.19, 47)	0.1	-31.35 (-97.52, 34.83)	0.35
T(mean)	15	Pheno	27.58 (1.23, 53.94)	**0.04**	19.21 (-22.55, 60.97)	0.37
T(mean)	30	Pheno	30.08 (2.85, 57.32)	**0.03**	19.51 (-24.58, 63.61)	0.39
T(mean)	60	Pheno	43.32 (15.24, 71.39)	**0.003**	44.34 (2.81, 85.86)	**0.036**
T(mean)	90	Pheno	50.66 (21.64, 79.68)	< **0.001**	42.71 (4.7, 80.72)	**0.028**
T(mean)	180	Pheno	62.13 (25.32, 98.94)	< **0.001**	28.07 (-9.03, 65.18)	0.14
T(mean)	1	Skin & blood	22.09 (1.09, 43.08)	**0.039**	9.03 (-35.03, 53.09)	0.69
T(mean)	3	Skin & blood	22 (0.01, 44)	**0.05**	14.59 (-36.1, 65.27)	0.57
T(mean)	7	Skin & blood	25.57 (2.9, 48.23)	**0.027**	13.95 (-47.22, 75.12)	0.65
T(mean)	15	Skin & blood	29.8 (6.46, 53.14)	**0.012**	33.05 (-5.51, 71.62)	0.093
T(mean)	30	Skin & blood	31.58 (7.46, 55.7)	**0.01**	27.76 (-12.93, 68.46)	0.18
T(mean)	60	Skin & blood	42.47 (17.61, 67.33)	< **0.001**	41.68 (3.35, 80)	**0.033**
T(mean)	90	Skin & blood	49.82 (24.12, 75.51)	< **0.001**	36.52 (1.43, 71.6)	**0.041**
T(mean)	180	Skin & blood	58.51 (25.9, 91.11)	< **0.001**	25.25 (-9.01, 59.5)	0.15
T(mean)	1	Grim2	18.47 (3.36, 33.59)	**0.017**	0.8 (-21.54, 23.14)	0.94
T(mean)	3	Grim2	16.77 (0.94, 32.61)	**0.038**	2.07 (-23.58, 27.71)	0.87
T(mean)	7	Grim2	16.18 (-0.14, 32.51)	0.052	-16.59 (-47.49, 14.31)	0.29
T(mean)	15	Grim2	19.87 (3.06, 36.68)	**0.021**	12.72 (-6.65, 32.1)	0.2
T(mean)	30	Grim2	20.71 (3.34, 38.09)	**0.019**	12.44 (-8.03, 32.91)	0.23
T(mean)	60	Grim2	26.14 (8.23, 44.06)	**0.004**	15.44 (-3.83, 34.72)	0.12
T(mean)	90	Grim2	30.6 (12.09, 49.12)	**0.001**	14.66 (-2.99, 32.3)	0.1
T(mean)	180	Grim2	36.84 (13.35, 60.33)	**0.002**	11.08 (-6.14, 28.3)	0.21
T(max)	1	Horvath's	23.58 (2.58, 44.58)	**0.028**	22.36 (-9.59, 54.32)	0.17
T(max)	3	Horvath's	17.87 (-4.78, 40.51)	0.12	27.16 (-12.01, 66.33)	0.17
T(max)	7	Horvath's	15.32 (-8.54, 39.19)	0.21	-4.88 (-55.29, 45.54)	0.85
T(max)	15	Horvath's	21.66 (-3.3, 46.61)	0.089	11.03 (-21.5, 43.56)	0.51

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
T(max)	30	Horvath's	23.44 (-2.6, 49.49)	0.078	8.57 (-26.48, 43.61)	0.63
T(max)	60	Horvath's	36.85 (9.8, 63.91)	**0.008**	20.78 (-12.8, 54.36)	0.23
T(max)	90	Horvath's	49.5 (21.4, 77.59)	< **0.001**	21.34 (-9.27, 51.96)	0.17
T(max)	180	Horvath's	78.75 (43.72, 113.79)	< **0.001**	21.4 (-8.18, 50.97)	0.16
T(max)	1	Hannum's	25.03 (5.36, 44.69)	**0.013**	6.36 (-23.37, 36.09)	0.67
T(max)	3	Hannum's	23.06 (1.86, 44.26)	**0.033**	18.02 (-18.41, 54.45)	0.33
T(max)	7	Hannum's	24.53 (2.2, 46.87)	**0.031**	3.61 (-43.29, 50.51)	0.88
T(max)	15	Hannum's	29.61 (6.25, 52.96)	**0.013**	7.48 (-22.81, 37.77)	0.63
T(max)	30	Hannum's	31.68 (7.31, 56.06)	**0.011**	4.02 (-28.62, 36.66)	0.81
T(max)	60	Hannum's	44.89 (19.59, 70.2)	< **0.001**	20.36 (-10.89, 51.61)	0.2
T(max)	90	Hannum's	55.27 (28.99, 81.55)	< **0.001**	17.49 (-10.99, 45.97)	0.23
T(max)	180	Hannum's	68.63 (35.8, 101.46)	< **0.001**	10.85 (-16.64, 38.35)	0.44
T(max)	1	ELOVL2	20 (-1.63, 41.64)	0.07	-3.08 (-38.74, 32.58)	0.87
T(max)	3	ELOVL2	17.37 (-5.96, 40.69)	0.14	11.21 (-32.44, 54.87)	0.61
T(max)	7	ELOVL2	18.4 (-6.18, 42.97)	0.14	2.46 (-53.71, 58.64)	0.93
T(max)	15	ELOVL2	21 (-4.7, 46.7)	0.11	8.3 (-28.01, 44.61)	0.65
T(max)	30	ELOVL2	21.2 (-5.63, 48.03)	0.12	2.19 (-36.96, 41.35)	0.91
T(max)	60	ELOVL2	27.48 (-0.4, 55.37)	0.053	4 (-33.51, 41.5)	0.83
T(max)	90	ELOVL2	32.98 (4, 61.96)	**0.026**	0.03 (-34.17, 34.23)	1
T(max)	180	ELOVL2	41.98 (5.78, 78.18)	**0.023**	-7.71 (-40.75, 25.33)	0.65
T(max)	1	Pheno	20.05 (-1.29, 41.39)	0.065	-2.09 (-39.54, 35.37)	0.91
T(max)	3	Pheno	16.07 (-6.93, 39.07)	0.17	-8.94 (-54.76, 36.88)	0.7
T(max)	7	Pheno	19.25 (-4.99, 43.48)	0.12	-28.9 (-87.8, 30)	0.34
T(max)	15	Pheno	27.11 (1.78, 52.44)	**0.036**	17.45 (-20.61, 55.51)	0.37
T(max)	30	Pheno	29.13 (2.68, 55.57)	**0.031**	17.85 (-23.18, 58.89)	0.39
T(max)	60	Pheno	42.63 (15.17, 70.09)	**0.002**	40.34 (1.05, 79.64)	**0.044**
T(max)	90	Pheno	51.28 (22.75, 79.81)	< **0.001**	38.91 (3.09, 74.74)	**0.033**
T(max)	180	Pheno	64.18 (28.55, 99.82)	< **0.001**	25.38 (-9.24, 60)	0.15
T(max)	1	Skin & blood	18.61 (-0.3, 37.51)	0.054	3 (-31.47, 37.47)	0.86
T(max)	3	Skin & blood	17.35 (-3.02, 37.73)	0.095	8.47 (-33.84, 50.78)	0.69
T(max)	7	Skin & blood	20.14 (-1.32, 41.61)	0.066	-3.94 (-58.39, 50.5)	0.89
T(max)	15	Skin & blood	26.43 (3.99, 48.87)	**0.021**	24.56 (-10.6, 59.71)	0.17
T(max)	30	Skin & blood	27.85 (4.42, 51.27)	**0.02**	21.13 (-16.75, 59.01)	0.27
T(max)	60	Skin & blood	38.79 (14.46, 63.11)	**0.002**	34.3 (-1.98, 70.58)	0.064

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
T(max)	90	Skin & blood	47.73 (22.47, 73)	**< 0.001**	31.44 (-1.64, 64.51)	0.062
T(max)	180	Skin & blood	57.09 (25.52, 88.66)	**< 0.001**	21.03 (-10.93, 52.99)	0.2
T(max)	1	Grim2	19.71 (6.12, 33.29)	**0.004**	5.61 (-11.87, 23.09)	0.53
T(max)	3	Grim2	16.2 (1.53, 30.86)	**0.03**	9.44 (-11.96, 30.84)	0.39
T(max)	7	Grim2	14.6 (-0.85, 30.06)	0.064	-14.21 (-41.71, 13.29)	0.31
T(max)	15	Grim2	19.32 (3.16, 35.47)	**0.019**	11.77 (-5.89, 29.43)	0.19
T(max)	30	Grim2	20.62 (3.76, 37.49)	**0.017**	10.96 (-8.09, 30.02)	0.26
T(max)	60	Grim2	26.82 (9.3, 44.34)	**0.003**	13.28 (-4.95, 31.52)	0.15
T(max)	90	Grim2	33.01 (14.82, 51.21)	**< 0.001**	13.51 (-3.12, 30.14)	0.11
T(max)	180	Grim2	41.29 (18.56, 64.02)	**< 0.001**	9.04 (-7.03, 25.11)	0.27
HI(min)	1	Horvath's	17.55 (-3.12, 38.23)	0.096	11.01 (-24.05, 46.06)	0.54
HI(min)	3	Horvath's	13.99 (-7.25, 35.24)	0.2	-0.09 (-39.34, 39.17)	1
HI(min)	7	Horvath's	13.48 (-8.3, 35.27)	0.23	-14.38 (-59.39, 30.63)	0.53
HI(min)	15	Horvath's	18.35 (-4.11, 40.8)	0.11	6.86 (-23.63, 37.34)	0.66
HI(min)	30	Horvath's	20.77 (-2.41, 43.96)	0.079	11.37 (-20.1, 42.85)	0.48
HI(min)	60	Horvath's	31.24 (7.27, 55.21)	**0.011**	20.66 (-8.51, 49.84)	0.16
HI(min)	90	Horvath's	39.95 (15.16, 64.74)	**0.002**	21.38 (-5.91, 48.66)	0.12
HI(min)	180	Horvath's	62.18 (30.44, 93.93)	**< 0.001**	20.59 (-7.17, 48.35)	0.15
HI(min)	1	Hannum's	26.42 (7.07, 45.76)	**0.007**	8.24 (-24.37, 40.84)	0.62
HI(min)	3	Hannum's	25.43 (5.56, 45.31)	**0.012**	6.52 (-30, 43.03)	0.73
HI(min)	7	Hannum's	26.03 (5.65, 46.41)	**0.012**	-6.16 (-48.05, 35.74)	0.77
HI(min)	15	Hannum's	29.24 (8.23, 50.24)	**0.006**	11.74 (-16.63, 40.11)	0.42
HI(min)	30	Hannum's	31.87 (10.18, 53.55)	**0.004**	14.25 (-15.03, 43.53)	0.34
HI(min)	60	Hannum's	43.03 (20.62, 65.44)	**< 0.001**	24.06 (-3.06, 51.19)	0.082
HI(min)	90	Hannum's	49.53 (26.36, 72.71)	**< 0.001**	20.49 (-4.88, 45.86)	0.11
HI(min)	180	Hannum's	59.42 (29.69, 89.15)	**< 0.001**	12.71 (-13.1, 38.52)	0.33
HI(min)	1	ELOVL2	21.31 (0.02, 42.59)	**0.05**	11.72 (-27.38, 50.81)	0.56
HI(min)	3	ELOVL2	21.32 (-0.55, 43.19)	0.056	18.66 (-25.06, 62.38)	0.4
HI(min)	7	ELOVL2	22.01 (-0.42, 44.43)	0.054	16.28 (-33.89, 66.44)	0.52
HI(min)	15	ELOVL2	23.67 (0.55, 46.79)	**0.045**	19.09 (-14.91, 53.09)	0.27
HI(min)	30	ELOVL2	25.3 (1.43, 49.16)	**0.038**	19.38 (-15.72, 54.48)	0.28
HI(min)	60	ELOVL2	30.13 (5.44, 54.82)	**0.017**	16.5 (-16.05, 49.06)	0.32
HI(min)	90	ELOVL2	33.3 (7.75, 58.85)	**0.011**	12.71 (-17.76, 43.17)	0.41
HI(min)	180	ELOVL2	38.88 (6.11, 71.65)	**0.02**	1.39 (-29.62, 32.41)	0.93

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Exposures	**Exposure windows (days)**	**Age acceleration (days)**	**Crude *β* (95% CI)**	**Crude *p***	**a*β* (95% CI)** [1]	**Adjusted *p*** [1]
HI(min)	1	Pheno	16.06 (-4.94, 37.07)	0.13	-11.8 (-52.89, 29.28)	0.57
HI(min)	3	Pheno	14.08 (-7.5, 35.65)	0.2	-25.86 (-71.76, 20.04)	0.27
HI(min)	7	Pheno	15.9 (-6.22, 38.03)	0.16	-39.42 (-92.01, 13.17)	0.14
HI(min)	15	Pheno	20.99 (-1.81, 43.79)	0.071	11.84 (-23.82, 47.49)	0.52
HI(min)	30	Pheno	23.48 (-0.06, 47.02)	0.051	16 (-20.82, 52.81)	0.39
HI(min)	60	Pheno	34.71 (10.37, 59.04)	**0.005**	32.44 (-1.68, 66.57)	0.062
HI(min)	90	Pheno	40.66 (15.49, 65.83)	**0.002**	31.65 (-0.27, 63.58)	0.052
HI(min)	180	Pheno	50.28 (18, 82.56)	**0.002**	19.68 (-12.83, 52.18)	0.24
HI(min)	1	Skin & blood	19.66 (1.06, 38.26)	**0.038**	3.36 (-34.43, 41.15)	0.86
HI(min)	3	Skin & blood	19.48 (0.37, 38.58)	**0.046**	1.94 (-40.45, 44.33)	0.93
HI(min)	7	Skin & blood	20.85 (1.26, 40.44)	**0.037**	-5.61 (-54.23, 43.01)	0.82
HI(min)	15	Skin & blood	24.62 (4.43, 44.81)	**0.017**	25.36 (-7.57, 58.3)	0.13
HI(min)	30	Skin & blood	26.83 (5.98, 47.67)	**0.012**	26.58 (-7.41, 60.57)	0.13
HI(min)	60	Skin & blood	36.23 (14.68, 57.77)	< **0.001**	33.62 (2.12, 65.12)	**0.036**
HI(min)	90	Skin & blood	41.9 (19.62, 64.18)	< **0.001**	29.07 (-0.4, 58.53)	0.053
HI(min)	180	Skin & blood	50.06 (21.47, 78.64)	< **0.001**	19.09 (-10.92, 49.09)	0.21
HI(min)	1	Grim2	14.52 (1.14, 27.9)	**0.033**	-5.07 (-24.25, 14.1)	0.6
HI(min)	3	Grim2	13.81 (0.06, 27.57)	**0.049**	-6.47 (-27.92, 14.98)	0.55
HI(min)	7	Grim2	14.11 (0, 28.22)	**0.05**	-21.25 (-45.83, 3.33)	0.09
HI(min)	15	Grim2	17.19 (2.65, 31.73)	**0.021**	5.36 (-11.21, 21.92)	0.53
HI(min)	30	Grim2	17.3 (2.29, 32.31)	**0.024**	4.4 (-12.69, 21.5)	0.61
HI(min)	60	Grim2	21.2 (5.67, 36.73)	**0.007**	5.44 (-10.41, 21.3)	0.5
HI(min)	90	Grim2	24.19 (8.12, 40.25)	**0.003**	6.07 (-8.77, 20.9)	0.42
HI(min)	180	Grim2	28.22 (7.61, 48.82)	**0.007**	4.05 (-11.06, 19.16)	0.6
HI(mean)	1	Horvath's	15.16 (-1.26, 31.58)	0.07	17.04 (-12.24, 46.31)	0.25
HI(mean)	3	Horvath's	12.15 (-4.83, 29.13)	0.16	14.36 (-18.37, 47.09)	0.39
HI(mean)	7	Horvath's	11.54 (-5.85, 28.94)	0.19	-1.43 (-39.36, 36.5)	0.94
HI(mean)	15	Horvath's	14.47 (-3.44, 32.39)	0.11	9.6 (-14.79, 33.99)	0.44
HI(mean)	30	Horvath's	16.23 (-2.23, 34.68)	0.085	12.5 (-12.98, 37.98)	0.34
HI(mean)	60	Horvath's	25.41 (6.17, 44.64)	**0.01**	18.96 (-4.86, 42.78)	0.12
HI(mean)	90	Horvath's	33.68 (13.49, 53.86)	**0.001**	19 (-3.26, 41.27)	0.094
HI(mean)	180	Horvath's	53.42 (27.58, 79.25)	< **0.001**	17.35 (-4.81, 39.5)	0.12
HI(mean)	1	Hannum's	19.7 (4.34, 35.07)	**0.012**	6.81 (-20.43, 34.05)	0.62
HI(mean)	3	Hannum's	18.85 (2.96, 34.74)	**0.02**	9.64 (-20.81, 40.09)	0.53

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude β (95% CI)	Crude p	aβ (95% CI) [1]	Adjusted p [1]
HI(mean)	7	Hannum's	20.04 (3.77, 36.32)	**0.016**	2.14 (-33.16, 37.44)	0.91
HI(mean)	15	Hannum's	22.01 (5.26, 38.77)	**0.01**	9.48 (-13.22, 32.18)	0.41
HI(mean)	30	Hannum's	23.94 (6.67, 41.2)	**0.007**	10.76 (-12.94, 34.47)	0.37
HI(mean)	60	Hannum's	33.37 (15.38, 51.35)	< **0.001**	17.66 (-4.49, 39.82)	0.12
HI(mean)	90	Hannum's	40.17 (21.3, 59.04)	< **0.001**	15.45 (-5.25, 36.16)	0.14
HI(mean)	180	Hannum's	49.76 (25.56, 73.95)	< **0.001**	9.56 (-11.04, 30.15)	0.36
HI(mean)	1	ELOVL2	17.07 (0.16, 33.98)	**0.048**	10.39 (-22.26, 43.05)	0.53
HI(mean)	3	ELOVL2	16.15 (-1.33, 33.64)	0.07	17.42 (-19.03, 53.88)	0.35
HI(mean)	7	ELOVL2	17.97 (0.07, 35.87)	**0.049**	20.01 (-22.25, 62.26)	0.35
HI(mean)	15	ELOVL2	18.77 (0.34, 37.21)	**0.046**	18.92 (-8.28, 46.12)	0.17
HI(mean)	30	ELOVL2	19.26 (0.26, 38.26)	**0.047**	16.61 (-11.81, 45.03)	0.25
HI(mean)	60	ELOVL2	23.4 (3.59, 43.22)	**0.021**	12.03 (-14.55, 38.62)	0.37
HI(mean)	90	ELOVL2	26.45 (5.64, 47.26)	**0.013**	7.49 (-17.38, 32.36)	0.55
HI(mean)	180	ELOVL2	32.68 (6, 59.35)	**0.016**	-0.11 (-24.86, 24.63)	0.99
HI(mean)	1	Pheno	12.96 (-3.72, 29.64)	0.13	-6.95 (-41.29, 27.39)	0.69
HI(mean)	3	Pheno	10.75 (-6.5, 27.99)	0.22	-18.66 (-56.94, 19.62)	0.34
HI(mean)	7	Pheno	12.69 (-4.97, 30.35)	0.16	-29.42 (-73.73, 14.89)	0.19
HI(mean)	15	Pheno	16.42 (-1.76, 34.61)	0.077	10.36 (-18.17, 38.89)	0.48
HI(mean)	30	Pheno	18.78 (0.04, 37.51)	**0.049**	15.08 (-14.73, 44.89)	0.32
HI(mean)	60	Pheno	28.31 (8.78, 47.83)	**0.005**	27.28 (-0.58, 55.15)	0.055
HI(mean)	90	Pheno	34.58 (14.08, 55.08)	< **0.001**	27.06 (1.01, 53.12)	**0.042**
HI(mean)	180	Pheno	44.45 (18.18, 70.72)	< **0.001**	17.6 (-8.33, 43.54)	0.18
HI(mean)	1	Skin & blood	15.07 (0.29, 29.84)	**0.046**	7.13 (-24.45, 38.71)	0.66
HI(mean)	3	Skin & blood	14.13 (-1.15, 29.4)	0.07	5.3 (-30.05, 40.65)	0.77
HI(mean)	7	Skin & blood	16.18 (0.54, 31.82)	**0.043**	3.58 (-37.38, 44.55)	0.86
HI(mean)	15	Skin & blood	18.77 (2.66, 34.87)	**0.022**	20.45 (-5.9, 46.81)	0.13
HI(mean)	30	Skin & blood	20.21 (3.62, 36.8)	**0.017**	20.93 (-6.59, 48.45)	0.14
HI(mean)	60	Skin & blood	28.18 (10.89, 45.47)	**0.001**	26.7 (0.98, 52.43)	**0.042**
HI(mean)	90	Skin & blood	34.12 (15.97, 52.27)	< **0.001**	23.76 (-0.29, 47.81)	0.053
HI(mean)	180	Skin & blood	42.17 (18.9, 65.44)	< **0.001**	15.78 (-8.17, 39.72)	0.2
HI(mean)	1	Grim2	11.63 (1, 22.27)	**0.032**	-2.97 (-18.99, 13.04)	0.72
HI(mean)	3	Grim2	10.59 (-0.41, 21.59)	0.059	-5.38 (-23.27, 12.51)	0.56
HI(mean)	7	Grim2	10.34 (-0.93, 21.6)	0.072	-19.85 (-40.56, 0.85)	0.06
HI(mean)	15	Grim2	12.41 (0.81, 24.01)	**0.036**	3.1 (-10.16, 16.35)	0.65

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
HI(mean)	30	Grim2	13.11 (1.16, 25.06)	**0.032**	3.71 (-10.13, 17.56)	0.6
HI(mean)	60	Grim2	17.21 (4.76, 29.67)	**0.007**	4.16 (-8.79, 17.11)	0.53
HI(mean)	90	Grim2	20.75 (7.67, 33.83)	**0.002**	5.01 (-7.1, 17.12)	0.42
HI(mean)	180	Grim2	25.23 (8.46, 41.99)	**0.003**	3.66 (-8.4, 15.71)	0.55
HI(max)	1	Horvath's	10.03 (0.22, 19.83)	**0.045**	11.83 (-3.52, 27.19)	0.13
HI(max)	3	Horvath's	6.46 (-3.82, 16.73)	0.22	13.29 (-4.87, 31.44)	0.15
HI(max)	7	Horvath's	3.71 (-7.04, 14.47)	0.5	-2.95 (-25.7, 19.8)	0.8
HI(max)	15	Horvath's	6.09 (-5.1, 17.29)	0.29	6.07 (-8.73, 20.88)	0.42
HI(max)	30	Horvath's	7.59 (-4.03, 19.21)	0.2	7.65 (-8.34, 23.65)	0.35
HI(max)	60	Horvath's	13.85 (1.63, 26.08)	**0.026**	12.48 (-2.89, 27.86)	0.11
HI(max)	90	Horvath's	20.08 (7.05, 33.11)	**0.003**	12.3 (-2.18, 26.79)	0.096
HI(max)	180	Horvath's	33.68 (17.01, 50.35)	< **0.001**	10.13 (-4.29, 24.54)	0.17
HI(max)	1	Hannum's	12.03 (2.85, 21.21)	**0.01**	7.49 (-6.79, 21.78)	0.3
HI(max)	3	Hannum's	9.91 (0.3, 19.53)	**0.043**	9.68 (-7.21, 26.57)	0.26
HI(max)	7	Hannum's	9 (-1.06, 19.07)	0.08	2.34 (-18.83, 23.51)	0.83
HI(max)	15	Hannum's	10.74 (0.26, 21.21)	**0.045**	4.76 (-9.01, 18.54)	0.5
HI(max)	30	Hannum's	12.3 (1.43, 23.17)	**0.027**	5.12 (-9.76, 20.01)	0.5
HI(max)	60	Hannum's	18.78 (7.35, 30.22)	**0.001**	10.33 (-3.96, 24.63)	0.16
HI(max)	90	Hannum's	24.25 (12.06, 36.44)	< **0.001**	9.05 (-4.43, 22.52)	0.19
HI(max)	180	Hannum's	31.94 (16.33, 47.55)	< **0.001**	5.26 (-8.14, 18.66)	0.44
HI(max)	1	ELOVL2	9.01 (-1.09, 19.11)	0.08	-1.16 (-18.3, 15.98)	0.89
HI(max)	3	ELOVL2	7.23 (-3.35, 17.81)	0.18	3.82 (-16.41, 24.05)	0.71
HI(max)	7	ELOVL2	7.65 (-3.42, 18.73)	0.18	6.73 (-18.62, 32.08)	0.6
HI(max)	15	ELOVL2	8 (-3.53, 19.53)	0.17	7.56 (-8.96, 24.07)	0.37
HI(max)	30	ELOVL2	8.22 (-3.74, 20.19)	0.18	4.61 (-13.24, 22.45)	0.61
HI(max)	60	ELOVL2	11.24 (-1.36, 23.84)	0.08	2.76 (-14.4, 19.92)	0.75
HI(max)	90	ELOVL2	13.41 (-0.03, 26.85)	0.051	-0.9 (-17.08, 15.28)	0.91
HI(max)	180	ELOVL2	17.93 (0.72, 35.14)	**0.041**	-4.75 (-20.85, 11.35)	0.56
HI(max)	1	Pheno	9.2 (-0.76, 19.16)	0.07	1.83 (-16.18, 19.83)	0.84
HI(max)	3	Pheno	6.69 (-3.75, 17.12)	0.21	-1.33 (-22.57, 19.92)	0.9
HI(max)	7	Pheno	5.98 (-4.94, 16.9)	0.28	-13.97 (-40.55, 12.62)	0.3
HI(max)	15	Pheno	8.85 (-2.51, 20.22)	0.13	7.71 (-9.61, 25.02)	0.38
HI(max)	30	Pheno	10.4 (-1.39, 22.2)	0.084	9.93 (-8.78, 28.64)	0.3
HI(max)	60	Pheno	16.87 (4.46, 29.28)	**0.008**	18.29 (0.31, 36.27)	**0.046**

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Exposures	Exposure windows (days)	Age acceleration (days)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
HI(max)	90	Pheno	21.76 (8.52, 34.99)	**0.001**	18.08 (1.13, 35.03)	**0.037**
HI(max)	180	Pheno	29.51 (12.57, 46.46)	< **0.001**	11.97 (-4.9, 28.84)	0.16
HI(max)	1	Skin & blood	9.51 (0.68, 18.33)	**0.035**	5.84 (-10.72, 22.4)	0.49
HI(max)	3	Skin & blood	7.69 (-1.55, 16.94)	0.1	5.41 (-14.2, 25.02)	0.59
HI(max)	7	Skin & blood	7.38 (-2.29, 17.05)	0.13	-1.49 (-26.06, 23.07)	0.91
HI(max)	15	Skin & blood	9.75 (-0.32, 19.82)	0.058	11.27 (-4.72, 27.27)	0.17
HI(max)	30	Skin & blood	10.68 (0.23, 21.13)	**0.045**	11.4 (-5.88, 28.68)	0.2
HI(max)	60	Skin & blood	16.16 (5.17, 27.15)	**0.004**	16.41 (-0.19, 33.01)	0.053
HI(max)	90	Skin & blood	20.89 (9.17, 32.61)	< **0.001**	14.88 (-0.77, 30.53)	0.062
HI(max)	180	Skin & blood	26.96 (11.95, 41.97)	< **0.001**	9.32 (-6.26, 24.9)	0.24
HI(max)	1	Grim2	7.93 (1.58, 14.28)	**0.014**	2.01 (-6.39, 10.41)	0.64
HI(max)	3	Grim2	5.95 (-0.71, 12.6)	0.08	1.28 (-8.64, 11.21)	0.8
HI(max)	7	Grim2	4.72 (-2.25, 11.69)	0.18	-10.58 (-23, 1.84)	0.095
HI(max)	15	Grim2	6.43 (-0.82, 13.68)	0.082	2.27 (-5.77, 10.31)	0.58
HI(max)	30	Grim2	7.5 (-0.03, 15.02)	0.051	3.04 (-5.65, 11.73)	0.49
HI(max)	60	Grim2	10.53 (2.61, 18.44)	**0.009**	3.09 (-5.26, 11.45)	0.47
HI(max)	90	Grim2	13.75 (5.31, 22.2)	**0.001**	3.93 (-3.95, 11.8)	0.33
HI(max)	180	Grim2	17.49 (6.68, 28.31)	**0.002**	2.73 (-5.11, 10.57)	0.49

$p < 0.05$ were shown in bold. [1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year of enrollment and season were additionally adjusted in models of 15- to 180-day exposure windows. RH was further adjusted in the temperature models.

a*β*, adjusted *β*; CI, confidence interval; T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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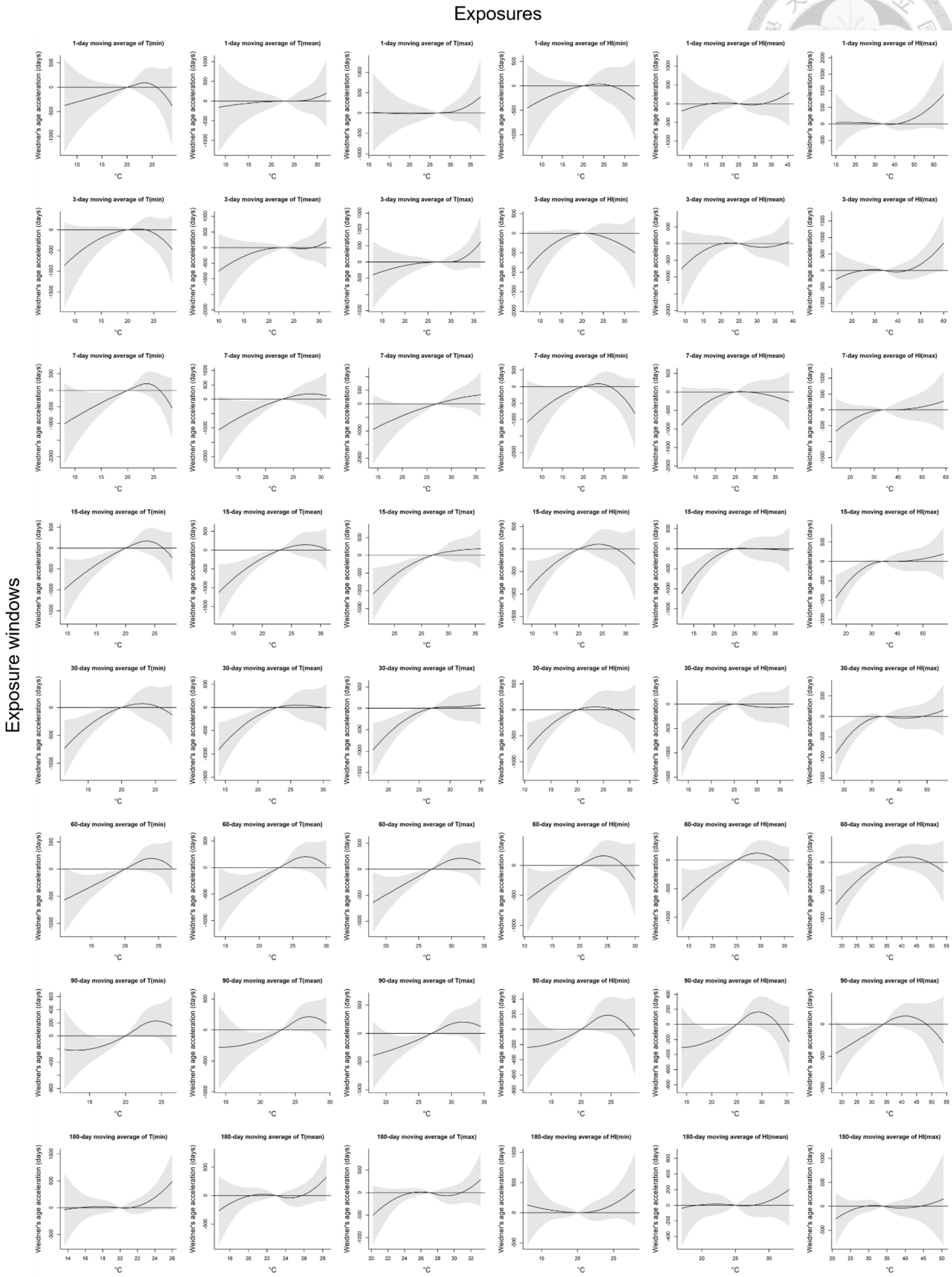

Figure S2- 8. The exposure-response curves between ambient temperature and the Weidner's DNA methylation age acceleration in generalized additive models.

doi:10.6342/NTU202403280

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. RH was further adjusted in the temperature models. Results of T(min), T(mean), T(max), HI(min), HI(mean), and HI(max) exposures were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, 90-, and 180-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The references for each model were the corresponding annual mean of exposures.

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

doi:10.6342/NTU202403280

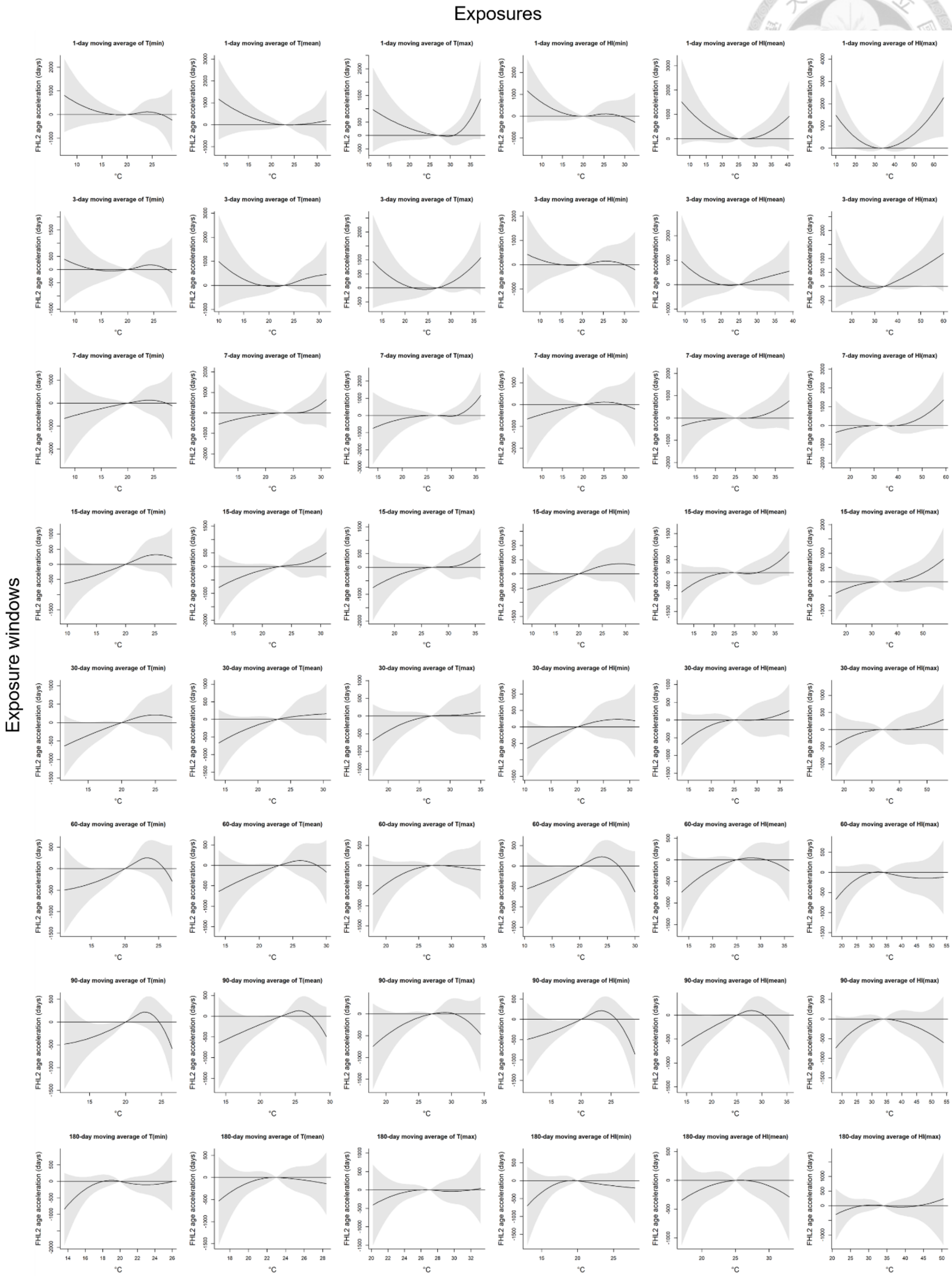

Figure S2- 9. The exposure-response curves between ambient temperature and the *FHL2* DNA methylation age accelerations in generalized additive models.

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Models were adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season of enrollment were additionally adjusted in models of 15- to 180-day exposure windows. RH was further adjusted in the temperature models. Results of T(min), T(mean), T(max), HI(min), HI(mean), and HI(max) exposures were arranged in columns, and results of the 1-, 3-, 7-, 15-, 30-, 60-, 90-, and 180-day exposure windows were arranged in rows. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The references for each model were the corresponding annual mean of exposures.

T(min), minimum temperature; T(mean), mean temperature; T(max), maximum temperature; RH, relative humidity; HI(min), heat index of minimum temperature; HI(mean), heat index of mean temperature; HI(max), heat index of maximum temperature.

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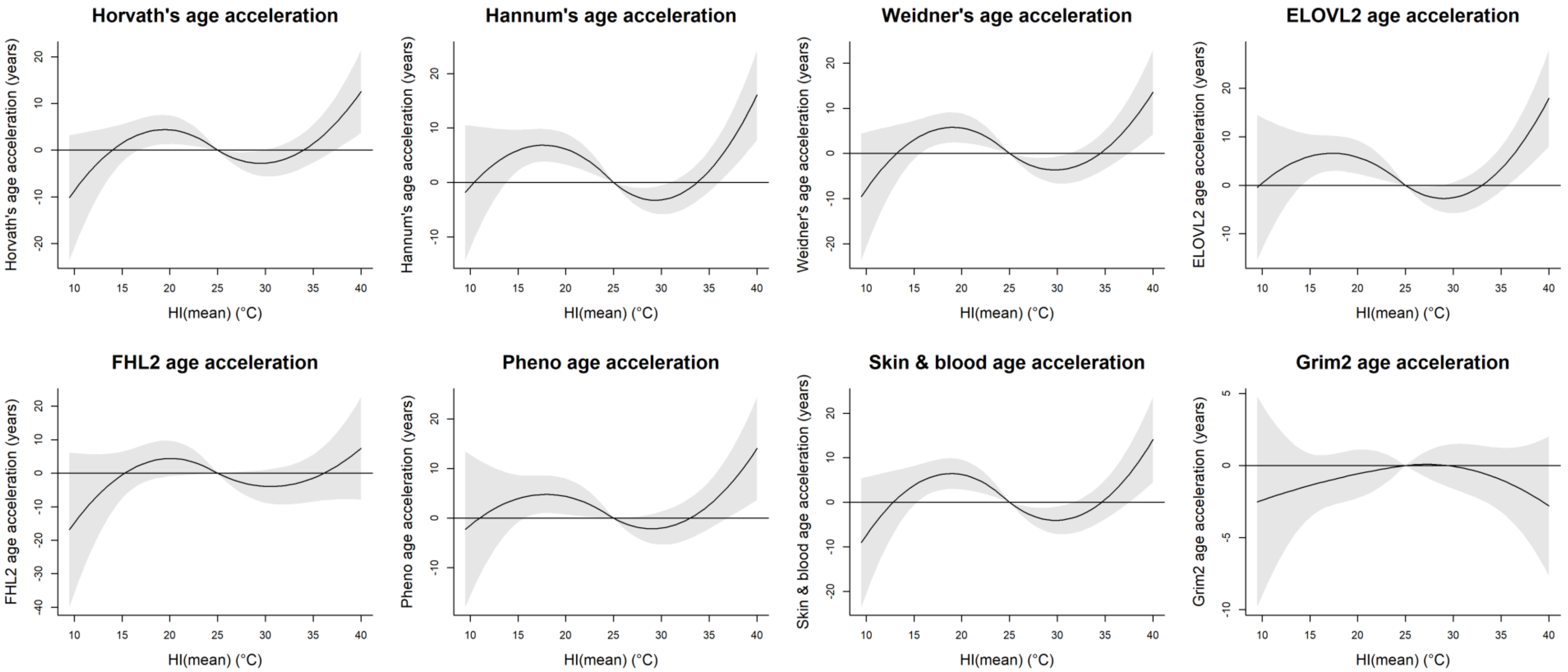

Figure S2- 10. Overall cumulative associations between HI(mean) and DNA methylation age acceleration within 52 weeks exposure window in distributed lag non-linear models.

Models were adjusted for sex, chronological age, BMI, educational level, smoking status, and year of enrollment. The black curves represented the point estimates, and the gray areas represented the 95% confidence intervals. The reference of HI(mean) for each model was the annual mean of 25˚C.

HI(mean), heat index of mean temperature.

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Table S2- 4. Number of days of HI(max) categories associated with the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin & blood, and Grim2 age accelerations in linear regression models.

Age acceleration (days)	**Exposure windows (days)**	**Categories of HI(max)**	**Crude *β* (95% CI)**	**Crude *p***	**a*β* (95% CI) [1]**	**Adjusted *p* [1]**
Horvath's	1	Caution	229.13 (-150.7, 608.95)	0.24	189.5 (-127.68, 506.68)	0.24
Horvath's	1	Extreme caution	268.73 (-76.29, 613.75)	0.13	183.88 (-153.72, 521.47)	0.29
Horvath's	1	Danger	215.1 (-67.82, 498.02)	0.14	92.26 (-290.2, 474.72)	0.64
Horvath's	1	Extreme danger	430.24 (-36.16, 896.64)	0.071	571.38 (42.63, 1100.13)	**0.034**
Horvath's	3	Caution	193.78 (17.5, 370.06)	**0.031**	35.49 (-118.98, 189.96)	0.65
Horvath's	3	Extreme caution	58.09 (-85.07, 201.25)	0.43	51.65 (-94.8, 198.1)	0.49
Horvath's	3	Danger	83.77 (-21.5, 189.05)	0.12	42.4 (-118.24, 203.04)	0.6
Horvath's	3	Extreme danger	100.86 (-76.73, 278.44)	0.27	136.75 (-79.05, 352.56)	0.21
Horvath's	7	Caution	113.74 (14.33, 213.15)	**0.025**	-22.49 (-113.5, 68.53)	0.63
Horvath's	7	Extreme caution	12.48 (-58.65, 83.61)	0.73	-20.04 (-100.39, 60.31)	0.62
Horvath's	7	Danger	35.17 (-14.88, 85.22)	0.17	-58.65 (-147.52, 30.23)	0.2
Horvath's	7	Extreme danger	21.73 (-64.59, 108.06)	0.62	-22.57 (-138.07, 92.94)	0.7
Horvath's	15	Caution	88.34 (29.8, 146.89)	**0.003**	7.07 (-37.69, 51.84)	0.76
Horvath's	15	Extreme caution	8.21 (-31.48, 47.9)	0.68	7.67 (-26.21, 41.56)	0.66
Horvath's	15	Danger	29.83 (3.73, 55.93)	**0.025**	-1.54 (-33.35, 30.26)	0.92
Horvath's	15	Extreme danger	20.56 (-24.87, 65.98)	0.37	24.09 (-17.46, 65.65)	0.26
Horvath's	30	Caution	56.44 (20.31, 92.57)	**0.002**	15.9 (-11.02, 42.81)	0.25
Horvath's	30	Extreme caution	-0.61 (-23.77, 22.56)	0.96	-0.46 (-21.23, 20.31)	0.97
Horvath's	30	Danger	19.1 (4.48, 33.71)	**0.01**	-0.12 (-17.2, 16.97)	0.99
Horvath's	30	Extreme danger	14.51 (-12.11, 41.14)	0.29	18.94 (-4.57, 42.44)	0.11
Horvath's	60	Caution	32.92 (8.6, 57.23)	**0.008**	14.52 (-4.24, 33.28)	0.13
Horvath's	60	Extreme caution	0.24 (-14.98, 15.47)	0.97	-1.96 (-15.01, 11.09)	0.77
Horvath's	60	Danger	13.73 (5.25, 22.22)	**0.002**	4.21 (-4.18, 12.6)	0.33
Horvath's	60	Extreme danger	8.36 (-6.6, 23.32)	0.27	11.41 (-0.96, 23.78)	0.071
Hannum's	1	Caution	302.79 (-52.6, 658.17)	0.095	191.47 (-103.58, 486.51)	0.2
Hannum's	1	Extreme caution	307.56 (-15.26, 630.38)	0.062	134.39 (-179.65, 448.42)	0.4
Hannum's	1	Danger	311.44 (46.72, 576.15)	**0.021**	104.67 (-251.1, 460.44)	0.56
Hannum's	1	Extreme danger	524.37 (87.97, 960.76)	**0.019**	528.02 (36.16, 1019.87)	**0.035**
Hannum's	3	Caution	232.82 (67.94, 397.7)	**0.006**	71.48 (-72.22, 215.18)	0.33
Hannum's	3	Extreme caution	85.84 (-48.06, 219.74)	0.21	79.17 (-57.06, 215.41)	0.25
Hannum's	3	Danger	134.74 (36.27, 233.2)	**0.007**	93.92 (-55.52, 243.36)	0.22
Hannum's	3	Extreme danger	133.85 (-32.25, 299.94)	0.11	125.88 (-74.89, 326.64)	0.22

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Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Crude β (95% CI)	Crude p	aβ (95% CI) [1]	Adjusted p [1]
Hannum's	7	Caution	126.95 (33.94, 219.97)	**0.007**	-2.08 (-86.82, 82.67)	0.96
Hannum's	7	Extreme caution	24.99 (-41.57, 91.54)	0.46	0.31 (-74.51, 75.12)	0.99
Hannum's	7	Danger	59.82 (12.99, 106.64)	**0.012**	-10.46 (-93.22, 72.3)	0.8
Hannum's	7	Extreme danger	44.54 (-36.23, 125.31)	0.28	5.52 (-102.04, 113.07)	0.92
Hannum's	15	Caution	75.79 (20.97, 130.61)	**0.007**	-1.79 (-43.45, 39.87)	0.93
Hannum's	15	Extreme caution	16.83 (-20.34, 53.99)	0.37	11.96 (-19.57, 43.49)	0.46
Hannum's	15	Danger	34.27 (9.83, 58.71)	**0.006**	-4.23 (-33.83, 25.37)	0.78
Hannum's	15	Extreme danger	30.56 (-11.97, 73.1)	0.16	21.5 (-17.17, 60.17)	0.28
Hannum's	30	Caution	41.49 (7.65, 75.33)	**0.016**	3.5 (-21.55, 28.54)	0.78
Hannum's	30	Extreme caution	5.56 (-16.14, 27.26)	0.62	4.86 (-14.47, 24.19)	0.62
Hannum's	30	Danger	19.08 (5.39, 32.77)	**0.006**	-3.54 (-19.43, 12.36)	0.66
Hannum's	30	Extreme danger	18.78 (-6.16, 43.72)	0.14	16.84 (-5.04, 38.71)	0.13
Hannum's	60	Caution	21.81 (-0.95, 44.58)	0.06	5.55 (-11.9, 23)	0.53
Hannum's	60	Extreme caution	5.09 (-9.16, 19.34)	0.48	2.96 (-9.18, 15.1)	0.63
Hannum's	60	Danger	12.85 (4.9, 20.79)	**0.002**	2.05 (-5.75, 9.85)	0.61
Hannum's	60	Extreme danger	10.83 (-3.17, 24.84)	0.13	10.87 (-0.63, 22.38)	0.064
Weidner's	1	Caution	366.3 (-98.05, 830.66)	0.12	27.26 (-307.56, 362.09)	0.87
Weidner's	1	Extreme caution	338.28 (-83.53, 760.08)	0.12	-133.67 (-490.04, 222.71)	0.46
Weidner's	1	Danger	564.44 (218.56, 910.32)	**0.001**	49.47 (-354.27, 453.2)	0.81
Weidner's	1	Extreme danger	443.46 (-126.74, 1013.67)	0.13	271.41 (-286.76, 829.58)	0.34
Weidner's	3	Caution	356.23 (140.93, 571.53)	**0.001**	38.26 (-124.14, 200.67)	0.64
Weidner's	3	Extreme caution	107.35 (-67.5, 282.2)	0.23	-18.06 (-172.03, 135.9)	0.82
Weidner's	3	Danger	227.58 (99.01, 356.16)	< **0.001**	43.31 (-125.58, 212.2)	0.62
Weidner's	3	Extreme danger	156.06 (-60.83, 372.95)	0.16	100.48 (-126.41, 327.37)	0.39
Weidner's	7	Caution	187.81 (66.44, 309.19)	**0.002**	-5.89 (-101.6, 89.82)	0.9
Weidner's	7	Extreme caution	83.59 (-3.26, 170.43)	0.059	43.77 (-40.72, 128.26)	0.31
Weidner's	7	Danger	116.27 (55.16, 177.38)	< **0.001**	27.48 (-65.99, 120.94)	0.56
Weidner's	7	Extreme danger	43.02 (-62.38, 148.42)	0.42	38.25 (-83.22, 159.72)	0.54
Weidner's	15	Caution	127.82 (56.34, 199.29)	< **0.001**	19.64 (-27.34, 66.62)	0.41
Weidner's	15	Extreme caution	46.53 (-1.93, 94.98)	0.06	50.79 (15.22, 86.35)	**0.005**
Weidner's	15	Danger	66.34 (34.48, 98.2)	< **0.001**	26.6 (-6.78, 59.98)	0.12
Weidner's	15	Extreme danger	30.53 (-24.93, 85.99)	0.28	43.9 (0.28, 87.52)	**0.049**
Weidner's	30	Caution	78.67 (34.56, 122.78)	< **0.001**	23.45 (-4.81, 51.71)	0.1

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Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
Weidner's	30	Extreme caution	19.48 (-8.8, 47.76)	0.18	22.86 (1.04, 44.67)	**0.04**
Weidner's	30	Danger	39.25 (21.41, 57.09)	**< 0.001**	13.71 (-4.23, 31.65)	0.13
Weidner's	30	Extreme danger	14.86 (-17.64, 47.37)	0.37	24.78 (0.09, 49.46)	**0.049**
Weidner's	60	Caution	43.42 (13.74, 73.09)	**0.004**	19.91 (0.2, 39.62)	**0.048**
Weidner's	60	Extreme caution	10.67 (-7.91, 29.25)	0.26	5.16 (-8.55, 18.87)	0.46
Weidner's	60	Danger	24.26 (13.91, 34.62)	**< 0.001**	9.29 (0.47, 18.1)	**0.039**
Weidner's	60	Extreme danger	6.32 (-11.93, 24.58)	0.5	9.76 (-3.23, 22.76)	0.14
ELOVL2	1	Caution	149.95 (-241.33, 541.23)	0.45	86.22 (-268.12, 440.55)	0.63
ELOVL2	1	Extreme caution	201.44 (-153.98, 556.87)	0.27	-8.33 (-385.47, 368.81)	0.97
ELOVL2	1	Danger	227 (-64.45, 518.45)	0.13	-93.1 (-520.36, 334.17)	0.67
ELOVL2	1	Extreme danger	312.67 (-167.8, 793.13)	0.2	41.57 (-549.13, 632.26)	0.89
ELOVL2	3	Caution	148.36 (-33.2, 329.92)	0.11	37.65 (-134.43, 209.73)	0.67
ELOVL2	3	Extreme caution	57.4 (-90.05, 204.85)	0.45	65.49 (-97.65, 228.63)	0.43
ELOVL2	3	Danger	112.6 (4.18, 221.03)	**0.042**	71.07 (-107.88, 250.02)	0.44
ELOVL2	3	Extreme danger	42.2 (-140.71, 225.1)	0.65	-11.71 (-252.12, 228.69)	0.92
ELOVL2	7	Caution	62.28 (-40.11, 164.68)	0.23	-30.14 (-131.59, 71.31)	0.56
ELOVL2	7	Extreme caution	-1.61 (-74.87, 71.66)	0.97	9.43 (-80.13, 98.99)	0.84
ELOVL2	7	Danger	52.42 (0.87, 103.97)	**0.046**	27.75 (-71.32, 126.81)	0.58
ELOVL2	7	Extreme danger	0.97 (-87.95, 89.89)	0.98	-3.25 (-132, 125.5)	0.96
ELOVL2	15	Caution	21.23 (-39.13, 81.6)	0.49	-48.77 (-98.66, 1.12)	0.055
ELOVL2	15	Extreme caution	4.01 (-36.91, 44.93)	0.85	8.09 (-29.67, 45.85)	0.67
ELOVL2	15	Danger	27.33 (0.43, 54.24)	**0.046**	7.75 (-27.7, 43.19)	0.67
ELOVL2	15	Extreme danger	-10.68 (-57.52, 36.16)	0.65	-5.23 (-51.54, 41.09)	0.82
ELOVL2	30	Caution	13.9 (-23.36, 51.16)	0.46	-21.08 (-51.11, 8.95)	0.17
ELOVL2	30	Extreme caution	0.93 (-22.96, 24.82)	0.94	5.36 (-17.82, 28.53)	0.65
ELOVL2	30	Danger	14.54 (-0.53, 29.62)	0.059	1.61 (-17.45, 20.68)	0.87
ELOVL2	30	Extreme danger	-5.54 (-33, 21.92)	0.69	-0.45 (-26.68, 25.79)	0.97
ELOVL2	60	Caution	4.74 (-20.35, 29.82)	0.71	-10.65 (-31.59, 10.3)	0.32
ELOVL2	60	Extreme caution	3.13 (-12.58, 18.83)	0.7	1.44 (-13.13, 16.01)	0.85
ELOVL2	60	Danger	7.97 (-0.79, 16.72)	0.074	-0.44 (-9.81, 8.93)	0.93
ELOVL2	60	Extreme danger	-1.73 (-17.16, 13.7)	0.83	-0.19 (-14, 13.62)	0.98
FHL2	1	Caution	-233.35 (-773.05, 306.35)	0.4	-609.07 (-1154.05, -64.09)	**0.029**
FHL2	1	Extreme caution	-44.29 (-534.54, 445.95)	0.86	-556.25 (-1136.31, 23.81)	0.06

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Age acceleration (days)	**Exposure windows (days)**	**Categories of HI(max)**	**Crude *β* (95% CI)**	**Crude *p***	**a*β* (95% CI)** [1]	**Adjusted *p*** [1]
FHL2	1	Danger	181.7 (-220.31, 583.7)	0.38	-339.8 (-996.95, 317.35)	0.31
FHL2	1	Extreme danger	229.92 (-432.8, 892.64)	0.5	-127.57 (-1036.08, 780.94)	0.78
FHL2	3	Caution	120.23 (-130.29, 370.75)	0.35	-58.61 (-322.86, 205.64)	0.66
FHL2	3	Extreme caution	52.53 (-150.92, 255.99)	0.61	18.33 (-232.2, 268.85)	0.89
FHL2	3	Danger	126.58 (-23.03, 276.19)	0.097	70.84 (-203.97, 345.64)	0.61
FHL2	3	Extreme danger	120.8 (-131.58, 373.17)	0.35	148.86 (-220.31, 518.04)	0.43
FHL2	7	Caution	123.51 (-17.71, 264.74)	0.086	28.56 (-127.17, 184.29)	0.72
FHL2	7	Extreme caution	25.51 (-75.54, 126.56)	0.62	15.03 (-122.45, 152.51)	0.83
FHL2	7	Danger	69.2 (-1.89, 140.3)	0.056	20.84 (-131.23, 172.92)	0.79
FHL2	7	Extreme danger	52.2 (-70.44, 174.84)	0.4	67.69 (-129.95, 265.33)	0.5
FHL2	15	Caution	59.6 (-23.66, 142.86)	0.16	-0.43 (-77.35, 76.49)	0.99
FHL2	15	Extreme caution	5.87 (-50.57, 62.31)	0.84	17.43 (-40.79, 75.65)	0.56
FHL2	15	Danger	39 (1.88, 76.11)	**0.039**	20.64 (-34.01, 75.29)	0.46
FHL2	15	Extreme danger	17.65 (-46.96, 82.25)	0.59	37.13 (-34.27, 108.54)	0.31
FHL2	30	Caution	50.98 (-0.38, 102.33)	0.052	18.08 (-28.19, 64.34)	0.44
FHL2	30	Extreme caution	-2.98 (-35.91, 29.95)	0.86	3.5 (-32.21, 39.21)	0.85
FHL2	30	Danger	27.35 (6.58, 48.12)	**0.01**	9.63 (-19.75, 39)	0.52
FHL2	30	Extreme danger	0.72 (-37.12, 38.57)	0.97	9.94 (-30.48, 50.35)	0.63
FHL2	60	Caution	35.02 (0.46, 69.58)	**0.047**	20.01 (-12.24, 52.27)	0.22
FHL2	60	Extreme caution	7.61 (-14.03, 29.25)	0.49	5.29 (-17.14, 27.73)	0.64
FHL2	60	Danger	16.29 (4.23, 28.35)	**0.008**	3.46 (-10.97, 17.88)	0.64
FHL2	60	Extreme danger	3.8 (-17.46, 25.07)	0.73	5.14 (-16.12, 26.4)	0.64
Pheno	1	Caution	326.42 (-59.23, 712.07)	0.097	164.36 (-207.54, 536.25)	0.39
Pheno	1	Extreme caution	293.66 (-56.65, 643.98)	0.1	49.52 (-346.31, 445.35)	0.81
Pheno	1	Danger	184.46 (-102.79, 471.72)	0.21	-91.86 (-540.29, 356.58)	0.69
Pheno	1	Extreme danger	509.15 (35.59, 982.71)	**0.035**	398.28 (-221.69, 1018.25)	0.21
Pheno	3	Caution	191.75 (12.74, 370.77)	**0.036**	1.82 (-178.91, 182.55)	0.98
Pheno	3	Extreme caution	76.98 (-68.41, 222.36)	0.3	-13.31 (-184.65, 158.03)	0.88
Pheno	3	Danger	82.07 (-24.84, 188.97)	0.13	-45.65 (-233.6, 142.3)	0.63
Pheno	3	Extreme danger	110.35 (-69.99, 290.69)	0.23	-0.84 (-253.33, 251.65)	0.99
Pheno	7	Caution	125.03 (24.11, 225.96)	**0.015**	-25.27 (-131.67, 81.12)	0.64
Pheno	7	Extreme caution	22.41 (-49.8, 94.63)	0.54	-51 (-144.92, 42.92)	0.29

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Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Crude *β* (95% CI)	Crude *p*	a*β* (95% CI) [1]	Adjusted *p* [1]
Pheno	7	Danger	45.32 (-5.49, 96.13)	0.08	-69.62 (-173.52, 34.27)	0.19
Pheno	7	Extreme danger	31.9 (-55.74, 119.54)	0.48	-71.89 (-206.91, 63.13)	0.3
Pheno	15	Caution	76.86 (17.39, 136.33)	**0.011**	10.17 (-42.19, 62.53)	0.7
Pheno	15	Extreme caution	23.34 (-16.97, 63.66)	0.26	19.05 (-20.58, 58.68)	0.35
Pheno	15	Danger	30.31 (3.8, 56.82)	**0.025**	4.34 (-32.86, 41.54)	0.82
Pheno	15	Extreme danger	26.27 (-19.87, 72.41)	0.26	24.46 (-24.15, 73.06)	0.32
Pheno	30	Caution	52.11 (15.42, 88.8)	**0.005**	20.36 (-11.13, 51.85)	0.2
Pheno	30	Extreme caution	5.43 (-18.1, 28.96)	0.65	3.79 (-20.52, 28.09)	0.76
Pheno	30	Danger	20.3 (5.46, 35.14)	**0.007**	5.04 (-14.96, 25.03)	0.62
Pheno	30	Extreme danger	17.04 (-10, 44.08)	0.22	19.83 (-7.67, 47.34)	0.16
Pheno	60	Caution	35.14 (10.47, 59.82)	**0.005**	20.64 (-1.3, 42.57)	0.065
Pheno	60	Extreme caution	4.6 (-10.85, 20.05)	0.56	3.22 (-12.04, 18.47)	0.68
Pheno	60	Danger	13.92 (5.31, 22.53)	**0.002**	6.94 (-2.87, 16.75)	0.17
Pheno	60	Extreme danger	14.81 (-0.37, 29.99)	0.056	16.82 (2.36, 31.28)	**0.023**
Skin & blood	1	Caution	179.1 (-162.62, 520.82)	0.3	60.33 (-281.88, 402.53)	0.73
Skin & blood	1	Extreme caution	179.52 (-130.89, 489.93)	0.26	-30.78 (-395.01, 333.45)	0.87
Skin & blood	1	Danger	163.67 (-90.86, 418.21)	0.21	-79.16 (-491.8, 333.48)	0.71
Skin & blood	1	Extreme danger	488.52 (68.91, 908.14)	**0.023**	349.64 (-220.83, 920.11)	0.23
Skin & blood	3	Caution	151.47 (-7.14, 310.08)	0.061	17.33 (-149.54, 184.19)	0.84
Skin & blood	3	Extreme caution	77.29 (-51.52, 206.1)	0.24	27.75 (-130.45, 185.95)	0.73
Skin & blood	3	Danger	77.94 (-16.78, 172.66)	0.11	-0.86 (-174.39, 172.68)	0.99
Skin & blood	3	Extreme danger	111.21 (-48.57, 271)	0.17	28.14 (-204.98, 261.27)	0.81
Skin & blood	7	Caution	79.83 (-9.63, 169.29)	0.08	-28.8 (-127.13, 69.54)	0.57
Skin & blood	7	Extreme caution	31.26 (-32.75, 95.27)	0.34	-9.49 (-96.3, 77.31)	0.83
Skin & blood	7	Danger	37.27 (-7.77, 82.31)	0.1	-42.71 (-138.73, 53.32)	0.38
Skin & blood	7	Extreme danger	35.54 (-42.15, 113.22)	0.37	-42.52 (-167.32, 82.28)	0.5
Skin & blood	15	Caution	42.98 (-9.75, 95.71)	0.11	-2.01 (-50.38, 46.36)	0.94
Skin & blood	15	Extreme caution	20.07 (-15.67, 55.82)	0.27	23.35 (-13.26, 59.96)	0.21
Skin & blood	15	Danger	21.18 (-2.33, 44.68)	0.077	3.16 (-31.21, 37.52)	0.86
Skin & blood	15	Extreme danger	29.26 (-11.65, 70.17)	0.16	29.71 (-15.2, 74.61)	0.19
Skin & blood	30	Caution	35.65 (3.12, 68.18)	**0.032**	11.83 (-17.24, 40.91)	0.42
Skin & blood	30	Extreme caution	5.24 (-15.62, 26.1)	0.62	9.87 (-12.57, 32.31)	0.39
Skin & blood	30	Danger	14.25 (1.09, 27.41)	**0.034**	2.04 (-16.42, 20.5)	0.83
Skin & blood	30	Extreme danger	21.07 (-2.9, 45.04)	0.085	22.92 (-2.47, 48.32)	0.077

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Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Crude β (95% CI)	Crude p	aβ (95% CI) [1]	Adjusted p [1]
Skin & blood	60	Caution	24.15 (2.28, 46.03)	**0.03**	12.66 (-7.59, 32.92)	0.22
Skin & blood	60	Extreme caution	3.25 (-10.45, 16.95)	0.64	4.66 (-9.43, 18.76)	0.52
Skin & blood	60	Danger	10.68 (3.05, 18.31)	**0.006**	4.63 (-4.43, 13.69)	0.32
Skin & blood	60	Extreme danger	14.42 (0.96, 27.88)	**0.036**	15.52 (2.17, 28.88)	**0.023**
Grim2	1	Caution	181.66 (-64.07, 427.38)	0.15	9.65 (-164.14, 183.44)	0.91
Grim2	1	Extreme caution	203.84 (-19.37, 427.04)	0.073	34.09 (-150.89, 219.07)	0.72
Grim2	1	Danger	252.55 (69.52, 435.57)	**0.007**	29.37 (-180.19, 238.94)	0.78
Grim2	1	Extreme danger	79.33 (-222.4, 381.07)	0.61	-21.59 (-311.31, 268.13)	0.88
Grim2	3	Caution	214.71 (100.81, 328.6)	**< 0.001**	59.65 (-24.75, 144.05)	0.17
Grim2	3	Extreme caution	52.08 (-40.42, 144.57)	0.27	21.25 (-58.77, 101.26)	0.6
Grim2	3	Danger	106.87 (38.86, 174.89)	**0.002**	29.6 (-58.18, 117.37)	0.51
Grim2	3	Extreme danger	49.37 (-65.37, 164.11)	0.4	-13.74 (-131.66, 104.17)	0.82
Grim2	7	Caution	118.96 (54.73, 183.19)	**< 0.001**	-6.38 (-56.08, 43.31)	0.8
Grim2	7	Extreme caution	9.12 (-36.84, 55.08)	0.7	-36.39 (-80.26, 7.48)	0.1
Grim2	7	Danger	51.03 (18.69, 83.37)	**0.002**	-27.11 (-75.63, 21.42)	0.27
Grim2	7	Extreme danger	9.44 (-46.34, 65.22)	0.74	-62.29 (-125.35, 0.78)	0.053
Grim2	15	Caution	84.96 (47.14, 122.77)	**< 0.001**	20.58 (-3.73, 44.9)	0.097
Grim2	15	Extreme caution	8.32 (-17.31, 33.96)	0.52	3.66 (-14.74, 22.06)	0.7
Grim2	15	Danger	32.2 (15.34, 49.05)	**< 0.001**	9.55 (-7.72, 26.83)	0.28
Grim2	15	Extreme danger	16.58 (-12.76, 45.92)	0.27	3.01 (-19.56, 25.58)	0.79
Grim2	30	Caution	46.35 (22.99, 69.7)	**< 0.001**	13.06 (-1.56, 27.68)	0.08
Grim2	30	Extreme caution	2.16 (-12.81, 17.14)	0.78	-2.37 (-13.66, 8.91)	0.68
Grim2	30	Danger	18.59 (9.14, 28.03)	**< 0.001**	5.36 (-3.92, 14.65)	0.26
Grim2	30	Extreme danger	8.58 (-8.63, 25.8)	0.33	1.1 (-11.67, 13.87)	0.87
Grim2	60	Caution	21.59 (5.85, 37.33)	**0.007**	10.6 (0.41, 20.79)	**0.042**
Grim2	60	Extreme caution	3.22 (-6.63, 13.07)	0.52	-3.14 (-10.23, 3.94)	0.38
Grim2	60	Danger	10.3 (4.81, 15.79)	**< 0.001**	3.64 (-0.92, 8.2)	0.12
Grim2	60	Extreme danger	4.36 (-5.32, 14.04)	0.38	0.39 (-6.32, 7.11)	0.91

$p < 0.05$ were shown in bold. [1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year of enrollment and season were additionally adjusted in models of 15- to 60-day exposure windows.

aβ, adjusted β; CI, confidence interval; HI(max), heat index of maximum temperature.

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Table S2- 5. Number of days of HI(max) categories associated with the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin & blood, and Grim2 age accelerations in linear regression models stratified by season.

Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	a*β* (95% CI) [1]	Adjusted *p* [1]
Warm	Horvath's	7	Caution	82.26 (-140.81, 305.32)	0.47
Warm	Horvath's	7	Extreme caution	51.97 (-134, 237.95)	0.58
Warm	Horvath's	7	Danger	42.14 (-135.12, 219.41)	0.64
Warm	Horvath's	7	Extreme danger	103.55 (-90.01, 297.1)	0.29
Warm	Horvath's	15	Caution	23.55 (-108.51, 155.6)	0.73
Warm	Horvath's	15	Extreme caution	29.76 (-71.79, 131.31)	0.57
Warm	Horvath's	15	Danger	14.99 (-77.85, 107.83)	0.75
Warm	Horvath's	15	Extreme danger	40.78 (-55.54, 137.1)	0.41
Warm	Horvath's	30	Caution	-11.11 (-92.07, 69.85)	0.79
Warm	Horvath's	30	Extreme caution	-6.78 (-64.94, 51.39)	0.82
Warm	Horvath's	30	Danger	-10.25 (-61.65, 41.16)	0.7
Warm	Horvath's	30	Extreme danger	8.83 (-45.49, 63.15)	0.75
Warm	Horvath's	60	Caution	-0.22 (-45.37, 44.92)	0.99
Warm	Horvath's	60	Extreme caution	1.34 (-24.97, 27.65)	0.92
Warm	Horvath's	60	Danger	3.16 (-16.13, 22.44)	0.75
Warm	Horvath's	60	Extreme danger	10 (-11.38, 31.37)	0.36
Warm	Hannum's	7	Caution	154.25 (-51.86, 360.35)	0.14
Warm	Hannum's	7	Extreme caution	55.55 (-116.29, 227.39)	0.53
Warm	Hannum's	7	Danger	66.6 (-97.19, 230.38)	0.43
Warm	Hannum's	7	Extreme danger	108.34 (-70.5, 287.18)	0.23
Warm	Hannum's	15	Caution	33.2 (-88.57, 154.98)	0.59
Warm	Hannum's	15	Extreme caution	32.28 (-61.37, 125.93)	0.5
Warm	Hannum's	15	Danger	16.7 (-68.92, 102.32)	0.7
Warm	Hannum's	15	Extreme danger	41.37 (-47.46, 130.2)	0.36
Warm	Hannum's	30	Caution	2.61 (-72.04, 77.26)	0.95
Warm	Hannum's	30	Extreme caution	1.96 (-51.67, 55.59)	0.94
Warm	Hannum's	30	Danger	-5.34 (-52.74, 42.05)	0.82
Warm	Hannum's	30	Extreme danger	14.01 (-36.08, 64.09)	0.58
Warm	Hannum's	60	Caution	-2.64 (-44.27, 38.99)	0.9
Warm	Hannum's	60	Extreme caution	0.61 (-23.65, 24.88)	0.96
Warm	Hannum's	60	Danger	-0.42 (-18.21, 17.36)	0.96

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	aβ (95% CI) [1]	Adjusted p [1]
Warm	Hannum's	60	Extreme danger	6.8 (-12.91, 26.51)	0.5
Warm	Weidner's	7	Caution	131.06 (-109.76, 371.89)	0.29
Warm	Weidner's	7	Extreme caution	190.28 (-10.51, 391.06)	0.063
Warm	Weidner's	7	Danger	163.97 (-27.41, 355.35)	0.093
Warm	Weidner's	7	Extreme danger	190.6 (-18.37, 399.57)	0.074
Warm	Weidner's	15	Caution	44.83 (-96.42, 186.08)	0.53
Warm	Weidner's	15	Extreme caution	88.28 (-20.35, 196.9)	0.11
Warm	Weidner's	15	Danger	44.97 (-54.34, 144.28)	0.37
Warm	Weidner's	15	Extreme danger	64.43 (-38.6, 167.47)	0.22
Warm	Weidner's	30	Caution	20.05 (-66.69, 106.79)	0.65
Warm	Weidner's	30	Extreme caution	27.16 (-35.15, 89.48)	0.39
Warm	Weidner's	30	Danger	12.67 (-42.4, 67.74)	0.65
Warm	Weidner's	30	Extreme danger	23.17 (-35.02, 81.37)	0.43
Warm	Weidner's	60	Caution	6.2 (-42.18, 54.59)	0.8
Warm	Weidner's	60	Extreme caution	-6.34 (-34.54, 21.86)	0.66
Warm	Weidner's	60	Danger	-0.67 (-21.34, 20)	0.95
Warm	Weidner's	60	Extreme danger	-1.17 (-24.08, 21.74)	0.92
Warm	*ELOVL2*	7	Caution	181.8 (-67.01, 430.62)	0.15
Warm	*ELOVL2*	7	Extreme caution	118.96 (-88.49, 326.41)	0.26
Warm	*ELOVL2*	7	Danger	135.52 (-62.21, 333.25)	0.18
Warm	*ELOVL2*	7	Extreme danger	120.12 (-95.78, 336.03)	0.28
Warm	*ELOVL2*	15	Caution	34.13 (-112.43, 180.68)	0.65
Warm	*ELOVL2*	15	Extreme caution	70.23 (-42.47, 182.94)	0.22
Warm	*ELOVL2*	15	Danger	61.42 (-41.62, 164.47)	0.24
Warm	*ELOVL2*	15	Extreme danger	52.61 (-54.3, 159.51)	0.33
Warm	*ELOVL2*	30	Caution	-14.81 (-104.74, 75.13)	0.75
Warm	*ELOVL2*	30	Extreme caution	19.67 (-44.94, 84.28)	0.55
Warm	*ELOVL2*	30	Danger	11.46 (-45.64, 68.56)	0.69
Warm	*ELOVL2*	30	Extreme danger	11.17 (-49.16, 71.51)	0.72
Warm	*ELOVL2*	60	Caution	-36.55 (-86.68, 13.57)	0.15
Warm	*ELOVL2*	60	Extreme caution	0.42 (-28.79, 29.64)	0.98
Warm	*ELOVL2*	60	Danger	-4.1 (-25.51, 17.31)	0.71
Warm	*ELOVL2*	60	Extreme danger	-4.81 (-28.55, 18.92)	0.69
Warm	*FHL2*	7	Caution	59.07 (-325.21, 443.35)	0.76

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	aβ (95% CI) [1]	Adjusted p [1]
Warm	*FHL2*	7	Extreme caution	-55.96 (-376.34, 264.43)	0.73
Warm	*FHL2*	7	Danger	-94.49 (-399.87, 210.88)	0.54
Warm	*FHL2*	7	Extreme danger	-17.44 (-350.89, 316)	0.92
Warm	*FHL2*	15	Caution	-43.73 (-271.29, 183.83)	0.71
Warm	*FHL2*	15	Extreme caution	-26 (-201, 149)	0.77
Warm	*FHL2*	15	Danger	-19.66 (-179.65, 140.34)	0.81
Warm	*FHL2*	15	Extreme danger	3.97 (-162.02, 169.96)	0.96
Warm	*FHL2*	30	Caution	-34.64 (-174.23, 104.95)	0.63
Warm	*FHL2*	30	Extreme caution	-10.6 (-110.88, 89.68)	0.84
Warm	*FHL2*	30	Danger	-11.95 (-100.57, 76.68)	0.79
Warm	*FHL2*	30	Extreme danger	-7.75 (-101.4, 85.91)	0.87
Warm	*FHL2*	60	Caution	4.28 (-73.53, 82.1)	0.91
Warm	*FHL2*	60	Extreme caution	4.25 (-41.1, 49.61)	0.85
Warm	*FHL2*	60	Danger	1.99 (-31.26, 35.23)	0.91
Warm	*FHL2*	60	Extreme danger	3.55 (-33.29, 40.4)	0.85
Warm	Pheno	7	Caution	248.87 (-10.82, 508.56)	0.06
Warm	Pheno	7	Extreme caution	119.35 (-97.16, 335.86)	0.28
Warm	Pheno	7	Danger	144.41 (-61.96, 350.77)	0.17
Warm	Pheno	7	Extreme danger	163.67 (-61.66, 389)	0.15
Warm	Pheno	15	Caution	99.14 (-54.65, 252.93)	0.21
Warm	Pheno	15	Extreme caution	96.71 (-21.56, 214.98)	0.11
Warm	Pheno	15	Danger	70.34 (-37.79, 178.47)	0.2
Warm	Pheno	15	Extreme danger	91.42 (-20.76, 203.6)	0.11
Warm	Pheno	30	Caution	38.53 (-55.85, 132.91)	0.42
Warm	Pheno	30	Extreme caution	29.02 (-38.78, 96.82)	0.4
Warm	Pheno	30	Danger	22.7 (-37.22, 82.62)	0.46
Warm	Pheno	30	Extreme danger	38.77 (-24.55, 102.09)	0.23
Warm	Pheno	60	Caution	15.23 (-37.38, 67.83)	0.57
Warm	Pheno	60	Extreme caution	8.24 (-22.42, 38.9)	0.6
Warm	Pheno	60	Danger	9.49 (-12.98, 31.96)	0.41
Warm	Pheno	60	Extreme danger	18.43 (-6.48, 43.34)	0.15
Warm	Skin & blood	7	Caution	206.76 (-35.64, 449.17)	0.094
Warm	Skin & blood	7	Extreme caution	92.68 (-109.42, 294.78)	0.37
Warm	Skin & blood	7	Danger	81.87 (-110.76, 274.51)	0.4

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	a*β* (95% CI) [1]	Adjusted *p* [1]
Warm	Skin & blood	7	Extreme danger	118.5 (-91.84, 328.83)	0.27
Warm	Skin & blood	15	Caution	43.76 (-99.95, 187.47)	0.55
Warm	Skin & blood	15	Extreme caution	50.63 (-59.89, 161.14)	0.37
Warm	Skin & blood	15	Danger	31.87 (-69.17, 132.91)	0.54
Warm	Skin & blood	15	Extreme danger	55.74 (-49.09, 160.56)	0.3
Warm	Skin & blood	30	Caution	2.65 (-85.47, 90.77)	0.95
Warm	Skin & blood	30	Extreme caution	6.69 (-56.62, 69.99)	0.84
Warm	Skin & blood	30	Danger	-0.6 (-56.54, 55.35)	0.98
Warm	Skin & blood	30	Extreme danger	17.98 (-41.15, 77.1)	0.55
Warm	Skin & blood	60	Caution	-6.34 (-55.47, 42.79)	0.8
Warm	Skin & blood	60	Extreme caution	3.91 (-24.72, 32.54)	0.79
Warm	Skin & blood	60	Danger	0.62 (-20.36, 21.61)	0.95
Warm	Skin & blood	60	Extreme danger	9.79 (-13.47, 33.05)	0.41
Warm	Grim2	7	Caution	120.77 (-1.92, 243.46)	0.054
Warm	Grim2	7	Extreme caution	20.37 (-81.92, 122.65)	0.7
Warm	Grim2	7	Danger	53.92 (-43.58, 151.41)	0.28
Warm	Grim2	7	Extreme danger	17.04 (-89.41, 123.5)	0.75
Warm	Grim2	15	Caution	17.94 (-54.25, 90.12)	0.63
Warm	Grim2	15	Extreme caution	5.1 (-50.41, 60.61)	0.86
Warm	Grim2	15	Danger	10.43 (-40.32, 61.17)	0.69
Warm	Grim2	15	Extreme danger	2.04 (-50.61, 54.7)	0.94
Warm	Grim2	30	Caution	10.25 (-33.97, 54.47)	0.65
Warm	Grim2	30	Extreme caution	-11.64 (-43.4, 20.13)	0.47
Warm	Grim2	30	Danger	0.14 (-27.94, 28.21)	0.99
Warm	Grim2	30	Extreme danger	-5.49 (-35.16, 24.18)	0.72
Warm	Grim2	60	Caution	15.63 (-9.01, 40.27)	0.21
Warm	Grim2	60	Extreme caution	-9.95 (-24.31, 4.41)	0.17
Warm	Grim2	60	Danger	1.27 (-9.26, 11.79)	0.81
Warm	Grim2	60	Extreme danger	-2.82 (-14.49, 8.84)	0.63
Cold	Horvath's	7	Caution	-22.02 (-141.16, 97.12)	0.72
Cold	Horvath's	7	Extreme caution	-32.58 (-146.19, 81.02)	0.57
Cold	Horvath's	7	Danger	-122.88 (-306.91, 61.16)	0.19
Cold	Horvath's	7	Extreme danger	1590.79 (-1211.16, 4392.75)	0.27
Cold	Horvath's	15	Caution	14.66 (-45.59, 74.92)	0.63

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	aβ (95% CI) [1]	Adjusted p [1]
Cold	Horvath's	15	Extreme caution	-5.32 (-53.11, 42.47)	0.83
Cold	Horvath's	15	Danger	-12.37 (-98.91, 74.17)	0.78
Cold	Horvath's	15	Extreme danger	1391.87 (-647.62, 3431.36)	0.18
Cold	Horvath's	30	Caution	26.29 (-8.25, 60.83)	0.14
Cold	Horvath's	30	Extreme caution	-8.58 (-39.86, 22.7)	0.59
Cold	Horvath's	30	Danger	-6.56 (-58.52, 45.4)	0.8
Cold	Horvath's	30	Extreme danger	697.42 (-405.02, 1799.86)	0.21
Cold	Horvath's	60	Caution	19.9 (-3.06, 42.86)	0.089
Cold	Horvath's	60	Extreme caution	-8.65 (-31.49, 14.19)	0.46
Cold	Horvath's	60	Danger	6.13 (-20.08, 32.33)	0.65
Cold	Horvath's	60	Extreme danger	56.2 (-47.17, 159.58)	0.29
Cold	Hannum's	7	Caution	-29.93 (-142.03, 82.18)	0.6
Cold	Hannum's	7	Extreme caution	-2.8 (-109.69, 104.1)	0.96
Cold	Hannum's	7	Danger	-32.5 (-205.66, 140.67)	0.71
Cold	Hannum's	7	Extreme danger	1208.03 (-1428.41, 3844.48)	0.37
Cold	Hannum's	15	Caution	-10.3 (-67.22, 46.62)	0.72
Cold	Hannum's	15	Extreme caution	8.08 (-37.06, 53.22)	0.73
Cold	Hannum's	15	Danger	21.02 (-60.73, 102.76)	0.61
Cold	Hannum's	15	Extreme danger	478.58 (-1447.98, 2405.15)	0.63
Cold	Hannum's	30	Caution	1.88 (-30.75, 34.51)	0.91
Cold	Hannum's	30	Extreme caution	2.16 (-27.39, 31.71)	0.89
Cold	Hannum's	30	Danger	4.5 (-44.58, 53.59)	0.86
Cold	Hannum's	30	Extreme danger	608.98 (-432.45, 1650.41)	0.25
Cold	Hannum's	60	Caution	7.39 (-14.26, 29.04)	0.5
Cold	Hannum's	60	Extreme caution	-2.42 (-23.95, 19.12)	0.83
Cold	Hannum's	60	Danger	5.32 (-19.38, 30.03)	0.67
Cold	Hannum's	60	Extreme danger	80.91 (-16.56, 178.38)	0.1
Cold	Weidner's	7	Caution	-13.53 (-134.97, 107.92)	0.83
Cold	Weidner's	7	Extreme caution	31.29 (-84.51, 147.08)	0.6
Cold	Weidner's	7	Danger	45.91 (-141.68, 233.5)	0.63
Cold	Weidner's	7	Extreme danger	83.27 (-2772.82, 2939.36)	0.95
Cold	Weidner's	15	Caution	31.6 (-29.75, 92.94)	0.31
Cold	Weidner's	15	Extreme caution	12.46 (-36.19, 61.11)	0.62
Cold	Weidner's	15	Danger	157.69 (69.59, 245.79)	**< 0.001**

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	a*β* (95% CI) [1]	Adjusted *p* [1]
Cold	Weidner's	15	Extreme danger	-2369.24 (-4445.57, -292.91)	**0.025**
Cold	Weidner's	30	Caution	30.83 (-4.44, 66.1)	0.087
Cold	Weidner's	30	Extreme caution	1.49 (-30.45, 33.43)	0.93
Cold	Weidner's	30	Danger	72.95 (19.89, 126)	**0.007**
Cold	Weidner's	30	Extreme danger	-600.95 (-1726.62, 524.72)	0.3
Cold	Weidner's	60	Caution	21.88 (-1.58, 45.34)	0.068
Cold	Weidner's	60	Extreme caution	-7.51 (-30.85, 15.82)	0.53
Cold	Weidner's	60	Danger	32.3 (5.53, 59.08)	**0.018**
Cold	Weidner's	60	Extreme danger	14.18 (-91.45, 119.81)	0.79
Cold	*ELOVL2*	7	Caution	-63.12 (-195.46, 69.21)	0.35
Cold	*ELOVL2*	7	Extreme caution	-11.68 (-137.86, 114.5)	0.86
Cold	*ELOVL2*	7	Danger	52.1 (-152.31, 256.51)	0.62
Cold	*ELOVL2*	7	Extreme danger	626.86 (-2485.32, 3739.05)	0.69
Cold	*ELOVL2*	15	Caution	-59.86 (-127.3, 7.57)	0.082
Cold	*ELOVL2*	15	Extreme caution	-13.43 (-66.91, 40.05)	0.62
Cold	*ELOVL2*	15	Danger	79.56 (-17.28, 176.41)	0.11
Cold	*ELOVL2*	15	Extreme danger	-288.04 (-2570.48, 1994.4)	0.8
Cold	*ELOVL2*	30	Caution	-16.63 (-55.41, 22.14)	0.4
Cold	*ELOVL2*	30	Extreme caution	-10.02 (-45.13, 25.09)	0.58
Cold	*ELOVL2*	30	Danger	26.82 (-31.5, 85.14)	0.37
Cold	*ELOVL2*	30	Extreme danger	298.12 (-939.32, 1535.55)	0.64
Cold	*ELOVL2*	60	Caution	-4.49 (-30.26, 21.27)	0.73
Cold	*ELOVL2*	60	Extreme caution	-7.43 (-33.06, 18.2)	0.57
Cold	*ELOVL2*	60	Danger	2.63 (-26.78, 32.04)	0.86
Cold	*ELOVL2*	60	Extreme danger	88.16 (-27.87, 204.19)	0.14
Cold	*FHL2*	7	Caution	51.7 (-150.44, 253.84)	0.62
Cold	*FHL2*	7	Extreme caution	16.01 (-176.72, 208.75)	0.87
Cold	*FHL2*	7	Danger	201.14 (-111.09, 513.38)	0.21
Cold	*FHL2*	7	Extreme danger	945.57 (-3808.28, 5699.43)	0.7
Cold	*FHL2*	15	Caution	-8.73 (-111.59, 94.13)	0.87
Cold	*FHL2*	15	Extreme caution	6.75 (-74.82, 88.32)	0.87
Cold	*FHL2*	15	Danger	107.98 (-39.75, 255.7)	0.15
Cold	*FHL2*	15	Extreme danger	1426.04 (-2055.39, 4907.48)	0.42
Cold	*FHL2*	30	Caution	35.62 (-23.33, 94.56)	0.24

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	aβ (95% CI) [1]	Adjusted p [1]
Cold	*FHL2*	30	Extreme caution	-22.73 (-76.11, 30.64)	0.4
Cold	*FHL2*	30	Danger	52.66 (-36, 141.33)	0.24
Cold	*FHL2*	30	Extreme danger	1191.53 (-689.7, 3072.75)	0.21
Cold	*FHL2*	60	Caution	24.25 (-14.9, 63.41)	0.22
Cold	*FHL2*	60	Extreme caution	-15.69 (-54.64, 23.26)	0.43
Cold	*FHL2*	60	Danger	26.27 (-18.42, 70.95)	0.25
Cold	*FHL2*	60	Extreme danger	139.64 (-36.67, 315.94)	0.12
Cold	Pheno	7	Caution	-67.05 (-207.36, 73.25)	0.35
Cold	Pheno	7	Extreme caution	-96.02 (-229.8, 37.76)	0.16
Cold	Pheno	7	Danger	-91.4 (-308.12, 125.33)	0.41
Cold	Pheno	7	Extreme danger	883.53 (-2416.2, 4183.25)	0.6
Cold	Pheno	15	Caution	11.64 (-59.46, 82.73)	0.75
Cold	Pheno	15	Extreme caution	2.15 (-54.23, 58.53)	0.94
Cold	Pheno	15	Danger	6.75 (-95.35, 108.85)	0.9
Cold	Pheno	15	Extreme danger	726.24 (-1680.02, 3132.49)	0.55
Cold	Pheno	30	Caution	27.05 (-13.7, 67.8)	0.19
Cold	Pheno	30	Extreme caution	-9.71 (-46.62, 27.19)	0.61
Cold	Pheno	30	Danger	12.7 (-48.61, 74)	0.68
Cold	Pheno	30	Extreme danger	595.58 (-705.11, 1896.27)	0.37
Cold	Pheno	60	Caution	24.53 (-2.49, 51.56)	0.075
Cold	Pheno	60	Extreme caution	-4.17 (-31.05, 22.71)	0.76
Cold	Pheno	60	Danger	6.71 (-24.13, 37.55)	0.67
Cold	Pheno	60	Extreme danger	118.85 (-2.82, 240.52)	0.056
Cold	Skin & blood	7	Caution	-51.05 (-177.98, 75.89)	0.43
Cold	Skin & blood	7	Extreme caution	11.41 (-109.62, 132.44)	0.85
Cold	Skin & blood	7	Danger	-103.26 (-299.34, 92.81)	0.3
Cold	Skin & blood	7	Extreme danger	1440.93 (-1544.34, 4426.2)	0.34
Cold	Skin & blood	15	Caution	-14.82 (-79.36, 49.73)	0.65
Cold	Skin & blood	15	Extreme caution	23.64 (-27.55, 74.83)	0.36
Cold	Skin & blood	15	Danger	17.34 (-75.36, 110.04)	0.71
Cold	Skin & blood	15	Extreme danger	355.15 (-1829.55, 2539.85)	0.75
Cold	Skin & blood	30	Caution	12.98 (-24, 49.96)	0.49
Cold	Skin & blood	30	Extreme caution	9.25 (-24.24, 42.74)	0.59
Cold	Skin & blood	30	Danger	-3.32 (-58.95, 52.32)	0.91

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Seasons	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	aβ (95% CI) [1]	Adjusted p [1]
Cold	Skin & blood	30	Extreme danger	687.95 (-492.43, 1868.33)	0.25
Cold	Skin & blood	60	Caution	17.67 (-6.83, 42.17)	0.16
Cold	Skin & blood	60	Extreme caution	-4.13 (-28.5, 20.24)	0.74
Cold	Skin & blood	60	Danger	8.86 (-19.1, 36.82)	0.53
Cold	Skin & blood	60	Extreme danger	115.13 (4.82, 225.44)	**0.041**
Cold	Grim2	7	Caution	-40.36 (-104.87, 24.14)	0.22
Cold	Grim2	7	Extreme caution	-61.68 (-123.18, -0.18)	**0.049**
Cold	Grim2	7	Danger	-103.53 (-203.16, -3.89)	**0.042**
Cold	Grim2	7	Extreme danger	90.55 (-1426.4, 1607.5)	0.91
Cold	Grim2	15	Caution	24.62 (-7.91, 57.14)	0.14
Cold	Grim2	15	Extreme caution	1.94 (-23.85, 27.73)	0.88
Cold	Grim2	15	Danger	8.9 (-37.81, 55.61)	0.71
Cold	Grim2	15	Extreme danger	-455.59 (-1556.41, 645.23)	0.42
Cold	Grim2	30	Caution	8.4 (-10.27, 27.08)	0.38
Cold	Grim2	30	Extreme caution	2.74 (-14.17, 19.66)	0.75
Cold	Grim2	30	Danger	3.64 (-24.45, 31.74)	0.8
Cold	Grim2	30	Extreme danger	-72.61 (-668.72, 523.51)	0.81
Cold	Grim2	60	Caution	8.24 (-4.17, 20.64)	0.19
Cold	Grim2	60	Extreme caution	-2.81 (-15.15, 9.53)	0.66
Cold	Grim2	60	Danger	4.64 (-9.52, 18.79)	0.52
Cold	Grim2	60	Extreme danger	37.39 (-18.47, 93.25)	0.19

$p < 0.05$ were shown in bold. [1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year of enrollment was additionally adjusted in models of 15- to 60-day exposure windows.

aβ, adjusted β; CI, confidence interval; HI(max), heat index of maximum temperature.

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Table S2- 6. Number of days of HI(max) categories associated with the Horvath's, Hannum's, Weidner's, *ELOVL2*, *FHL2*, Pheno, Skin & blood, and Grim2 age accelerations in linear regression models stratified by area.

Areas	**Age acceleration (days)**	**Exposure windows (days)**	**Categories of HI(max)**	**Adjusted *β* (95% CI)[1]**	**Adjusted *p*[1]**
Northern	Horvath's	7	Caution	-71.19 (-243.83, 101.45)	0.42
Northern	Horvath's	7	Extreme caution	58.04 (-94.92, 211)	0.46
Northern	Horvath's	7	Danger	-39.31 (-170.35, 91.73)	0.56
Northern	Horvath's	7	Extreme danger	145.69 (-25.26, 316.63)	0.095
Northern	Horvath's	15	Caution	-3.77 (-75.05, 67.52)	0.92
Northern	Horvath's	15	Extreme caution	53.77 (-8.82, 116.36)	0.092
Northern	Horvath's	15	Danger	-0.31 (-54.45, 53.83)	0.99
Northern	Horvath's	15	Extreme danger	65.94 (0.96, 130.92)	**0.047**
Northern	Horvath's	30	Caution	8.67 (-32.24, 49.58)	0.68
Northern	Horvath's	30	Extreme caution	22.6 (-19.33, 64.53)	0.29
Northern	Horvath's	30	Danger	5.04 (-26.65, 36.73)	0.76
Northern	Horvath's	30	Extreme danger	49.79 (10.31, 89.28)	**0.014**
Northern	Horvath's	60	Caution	-2.33 (-33.08, 28.42)	0.88
Northern	Horvath's	60	Extreme caution	14.7 (-14.42, 43.82)	0.32
Northern	Horvath's	60	Danger	9.94 (-7.54, 27.43)	0.26
Northern	Horvath's	60	Extreme danger	22.28 (0.88, 43.67)	**0.041**
Northern	Hannum's	7	Caution	81.93 (-80.18, 244.04)	0.32
Northern	Hannum's	7	Extreme caution	32.03 (-111.6, 175.66)	0.66
Northern	Hannum's	7	Danger	99.43 (-23.62, 222.48)	0.11
Northern	Hannum's	7	Extreme danger	212.04 (51.52, 372.55)	**0.01**
Northern	Hannum's	15	Caution	29.37 (-37.26, 96.01)	0.39
Northern	Hannum's	15	Extreme caution	47.15 (-11.35, 105.66)	0.11
Northern	Hannum's	15	Danger	19.64 (-30.97, 70.25)	0.45
Northern	Hannum's	15	Extreme danger	51.12 (-9.63, 111.86)	0.099
Northern	Hannum's	30	Caution	15.54 (-22.72, 53.79)	0.43
Northern	Hannum's	30	Extreme caution	9.03 (-30.19, 48.24)	0.65
Northern	Hannum's	30	Danger	6.18 (-23.45, 35.81)	0.68
Northern	Hannum's	30	Extreme danger	27.93 (-9, 64.86)	0.14
Northern	Hannum's	60	Caution	6.03 (-22.69, 34.75)	0.68
Northern	Hannum's	60	Extreme caution	-2.54 (-29.73, 24.66)	0.85
Northern	Hannum's	60	Danger	8.73 (-7.6, 25.06)	0.29

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Northern	Hannum's	60	Extreme danger	8.23 (-11.74, 28.21)	0.42
Northern	Weidner's	7	Caution	-90.51 (-276.59, 95.57)	0.34
Northern	Weidner's	7	Extreme caution	167.93 (3.06, 332.81)	**0.046**
Northern	Weidner's	7	Danger	99.75 (-41.5, 241)	0.17
Northern	Weidner's	7	Extreme danger	209.7 (25.44, 393.96)	**0.026**
Northern	Weidner's	15	Caution	32.19 (-43.71, 108.09)	0.41
Northern	Weidner's	15	Extreme caution	95.89 (29.25, 162.53)	**0.005**
Northern	Weidner's	15	Danger	35.52 (-22.12, 93.17)	0.23
Northern	Weidner's	15	Extreme danger	74.36 (5.17, 143.55)	**0.035**
Northern	Weidner's	30	Caution	23.6 (-20.01, 67.2)	0.29
Northern	Weidner's	30	Extreme caution	41.52 (-3.18, 86.22)	0.069
Northern	Weidner's	30	Danger	23.62 (-10.15, 57.4)	0.17
Northern	Weidner's	30	Extreme danger	39.88 (-2.21, 81.97)	0.063
Northern	Weidner's	60	Caution	12.19 (-20.57, 44.95)	0.47
Northern	Weidner's	60	Extreme caution	5.09 (-25.92, 36.11)	0.75
Northern	Weidner's	60	Danger	16.61 (-2.01, 35.23)	0.08
Northern	Weidner's	60	Extreme danger	5.57 (-17.21, 28.36)	0.63
Northern	ELOVL2	7	Caution	79.53 (-112.1, 271.16)	0.42
Northern	ELOVL2	7	Extreme caution	21.63 (-148.17, 191.42)	0.8
Northern	ELOVL2	7	Danger	97.96 (-47.5, 243.43)	0.19
Northern	ELOVL2	7	Extreme danger	154.18 (-35.58, 343.93)	0.11
Northern	ELOVL2	15	Caution	-15.27 (-93.2, 62.67)	0.7
Northern	ELOVL2	15	Extreme caution	56.03 (-12.39, 124.46)	0.11
Northern	ELOVL2	15	Danger	31.97 (-27.22, 91.16)	0.29
Northern	ELOVL2	15	Extreme danger	31.42 (-39.62, 102.46)	0.39
Northern	ELOVL2	30	Caution	-3.99 (-48.73, 40.75)	0.86
Northern	ELOVL2	30	Extreme caution	45.81 (-0.05, 91.67)	0.05
Northern	ELOVL2	30	Danger	26.99 (-7.67, 61.64)	0.13
Northern	ELOVL2	30	Extreme danger	32.93 (-10.25, 76.11)	0.13
Northern	ELOVL2	60	Caution	-1.14 (-34.8, 32.52)	0.95
Northern	ELOVL2	60	Extreme caution	17.45 (-14.42, 49.32)	0.28
Northern	ELOVL2	60	Danger	19.51 (0.38, 38.65)	**0.046**
Northern	ELOVL2	60	Extreme danger	17.32 (-6.09, 40.74)	0.15
Northern	FHL2	7	Caution	48.47 (-236.88, 333.81)	0.74

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Northern	FHL2	7	Extreme caution	-21.71 (-274.53, 231.11)	0.87
Northern	FHL2	7	Danger	-8.76 (-225.36, 207.83)	0.94
Northern	FHL2	7	Extreme danger	120.07 (-162.47, 402.62)	0.4
Northern	FHL2	15	Caution	86.01 (-30.17, 202.19)	0.15
Northern	FHL2	15	Extreme caution	135.27 (33.27, 237.28)	**0.009**
Northern	FHL2	15	Danger	45.83 (-42.41, 134.07)	0.31
Northern	FHL2	15	Extreme danger	155.63 (49.72, 261.54)	**0.004**
Northern	FHL2	30	Caution	66.4 (-0.35, 133.14)	0.051
Northern	FHL2	30	Extreme caution	65.05 (-3.36, 133.47)	0.062
Northern	FHL2	30	Danger	42.2 (-9.49, 93.9)	0.11
Northern	FHL2	30	Extreme danger	90.13 (25.71, 154.55)	**0.006**
Northern	FHL2	60	Caution	32.32 (-17.91, 82.54)	0.21
Northern	FHL2	60	Extreme caution	39.51 (-8.04, 87.07)	0.1
Northern	FHL2	60	Danger	28.01 (-0.54, 56.56)	0.055
Northern	FHL2	60	Extreme danger	47.2 (12.27, 82.14)	**0.008**
Northern	Pheno	7	Caution	48.71 (-151.51, 248.93)	0.63
Northern	Pheno	7	Extreme caution	80.95 (-96.46, 258.35)	0.37
Northern	Pheno	7	Danger	58.92 (-93.06, 210.91)	0.45
Northern	Pheno	7	Extreme danger	174.26 (-24, 372.52)	0.085
Northern	Pheno	15	Caution	41.72 (-40.61, 124.05)	0.32
Northern	Pheno	15	Extreme caution	94.54 (22.26, 166.83)	**0.01**
Northern	Pheno	15	Danger	50.03 (-12.49, 112.56)	0.12
Northern	Pheno	15	Extreme danger	80.24 (5.19, 155.29)	**0.036**
Northern	Pheno	30	Caution	25.19 (-22.14, 72.53)	0.3
Northern	Pheno	30	Extreme caution	37.78 (-10.73, 86.3)	0.13
Northern	Pheno	30	Danger	33.35 (-3.31, 70.01)	0.075
Northern	Pheno	30	Extreme danger	48.44 (2.75, 94.12)	**0.038**
Northern	Pheno	60	Caution	1.73 (-33.82, 37.29)	0.92
Northern	Pheno	60	Extreme caution	27.25 (-6.41, 60.92)	0.11
Northern	Pheno	60	Danger	24.81 (4.59, 45.02)	**0.016**
Northern	Pheno	60	Extreme danger	27.99 (3.26, 52.72)	**0.027**
Northern	Skin & blood	7	Caution	-36.96 (-224.9, 150.98)	0.7
Northern	Skin & blood	7	Extreme caution	7.33 (-159.19, 173.84)	0.93
Northern	Skin & blood	7	Danger	6.95 (-135.71, 149.61)	0.92

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Northern	Skin & blood	7	Extreme danger	100.44 (-85.66, 286.53)	0.29
Northern	Skin & blood	15	Caution	35.5 (-41.6, 112.6)	0.37
Northern	Skin & blood	15	Extreme caution	66.37 (-1.33, 134.06)	0.055
Northern	Skin & blood	15	Danger	35.8 (-22.75, 94.36)	0.23
Northern	Skin & blood	15	Extreme danger	70.51 (0.23, 140.8)	**0.049**
Northern	Skin & blood	30	Caution	30.17 (-14.06, 74.39)	0.18
Northern	Skin & blood	30	Extreme caution	28.51 (-16.82, 73.84)	0.22
Northern	Skin & blood	30	Danger	22.84 (-11.41, 57.1)	0.19
Northern	Skin & blood	30	Extreme danger	48.85 (6.16, 91.54)	**0.025**
Northern	Skin & blood	60	Caution	12.7 (-20.47, 45.88)	0.45
Northern	Skin & blood	60	Extreme caution	13.89 (-17.52, 45.3)	0.39
Northern	Skin & blood	60	Danger	20.64 (1.79, 39.5)	**0.032**
Northern	Skin & blood	60	Extreme danger	25.2 (2.12, 48.28)	**0.032**
Northern	Grim2	7	Caution	36.9 (-56.87, 130.67)	0.44
Northern	Grim2	7	Extreme caution	-21.39 (-104.47, 61.69)	0.61
Northern	Grim2	7	Danger	-0.16 (-71.34, 71.01)	1
Northern	Grim2	7	Extreme danger	-22.86 (-115.71, 69.98)	0.63
Northern	Grim2	15	Caution	28.9 (-9.25, 67.04)	0.14
Northern	Grim2	15	Extreme caution	18.02 (-15.47, 51.52)	0.29
Northern	Grim2	15	Danger	18.48 (-10.49, 47.46)	0.21
Northern	Grim2	15	Extreme danger	2.98 (-31.79, 37.76)	0.87
Northern	Grim2	30	Caution	23.4 (1.53, 45.27)	**0.036**
Northern	Grim2	30	Extreme caution	-2.31 (-24.72, 20.11)	0.84
Northern	Grim2	30	Danger	11.51 (-5.43, 28.45)	0.18
Northern	Grim2	30	Extreme danger	0.17 (-20.94, 21.28)	0.99
Northern	Grim2	60	Caution	24.25 (7.84, 40.65)	**0.004**
Northern	Grim2	60	Extreme caution	-4.66 (-20.19, 10.88)	0.56
Northern	Grim2	60	Danger	10.2 (0.87, 19.52)	**0.032**
Northern	Grim2	60	Extreme danger	0.21 (-11.2, 11.62)	0.97
Central	Horvath's	7	Caution	-182.41 (-395.78, 30.97)	0.094
Central	Horvath's	7	Extreme caution	-220.91 (-419.69, -22.14)	**0.029**
Central	Horvath's	7	Danger	-153.16 (-375.32, 69)	0.18
Central	Horvath's	7	Extreme danger	-47.47 (-331.63, 236.69)	0.74
Central	Horvath's	15	Caution	-27.48 (-125.81, 70.86)	0.58

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Central	Horvath's	15	Extreme caution	23.47 (-54.49, 101.43)	0.55
Central	Horvath's	15	Danger	22.25 (-53.09, 97.59)	0.56
Central	Horvath's	15	Extreme danger	19.98 (-81.18, 121.14)	0.7
Central	Horvath's	30	Caution	19.12 (-42.22, 80.47)	0.54
Central	Horvath's	30	Extreme caution	12.46 (-33.64, 58.57)	0.6
Central	Horvath's	30	Danger	7.17 (-35.32, 49.65)	0.74
Central	Horvath's	30	Extreme danger	5.1 (-54.74, 64.94)	0.87
Central	Horvath's	60	Caution	10.74 (-29.41, 50.89)	0.6
Central	Horvath's	60	Extreme caution	-6.57 (-34.89, 21.74)	0.65
Central	Horvath's	60	Danger	-3.88 (-25.68, 17.92)	0.73
Central	Horvath's	60	Extreme danger	-6.03 (-39.4, 27.34)	0.72
Central	Hannum's	7	Caution	-189.26 (-380.93, 2.42)	0.053
Central	Hannum's	7	Extreme caution	-68.64 (-247.2, 109.93)	0.45
Central	Hannum's	7	Danger	-29.95 (-229.51, 169.62)	0.77
Central	Hannum's	7	Extreme danger	21.14 (-234.13, 276.4)	0.87
Central	Hannum's	15	Caution	-52.99 (-140.19, 34.2)	0.23
Central	Hannum's	15	Extreme caution	55.42 (-13.7, 124.54)	0.12
Central	Hannum's	15	Danger	54 (-12.79, 120.8)	0.11
Central	Hannum's	15	Extreme danger	84.23 (-5.46, 173.92)	0.066
Central	Hannum's	30	Caution	-9.19 (-63.78, 45.4)	0.74
Central	Hannum's	30	Extreme caution	31.01 (-10.02, 72.04)	0.14
Central	Hannum's	30	Danger	17.94 (-19.87, 55.74)	0.35
Central	Hannum's	30	Extreme danger	54.48 (1.23, 107.72)	**0.045**
Central	Hannum's	60	Caution	-8.64 (-44.44, 27.17)	0.64
Central	Hannum's	60	Extreme caution	9.14 (-16.11, 34.39)	0.48
Central	Hannum's	60	Danger	-2.71 (-22.15, 16.72)	0.78
Central	Hannum's	60	Extreme danger	21.7 (-8.05, 51.46)	0.15
Central	Weidner's	7	Caution	28.54 (-184.16, 241.24)	0.79
Central	Weidner's	7	Extreme caution	-35.8 (-233.95, 162.35)	0.72
Central	Weidner's	7	Danger	64.29 (-157.17, 285.75)	0.57
Central	Weidner's	7	Extreme danger	78.57 (-204.7, 361.83)	0.59
Central	Weidner's	15	Caution	-2.38 (-101.06, 96.3)	0.96
Central	Weidner's	15	Extreme caution	57.63 (-20.61, 135.86)	0.15
Central	Weidner's	15	Danger	75.58 (-0.03, 151.18)	0.05

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Central	Weidner's	15	Extreme danger	63.18 (-38.33, 164.69)	0.22
Central	Weidner's	30	Caution	24.95 (-36.74, 86.65)	0.43
Central	Weidner's	30	Extreme caution	30.7 (-15.67, 77.07)	0.19
Central	Weidner's	30	Danger	21.66 (-21.06, 64.39)	0.32
Central	Weidner's	30	Extreme danger	15.5 (-44.68, 75.68)	0.61
Central	Weidner's	60	Caution	25.85 (-14.52, 66.21)	0.21
Central	Weidner's	60	Extreme caution	-2.13 (-30.6, 26.34)	0.88
Central	Weidner's	60	Danger	4.9 (-17.01, 26.81)	0.66
Central	Weidner's	60	Extreme danger	-3 (-36.55, 30.55)	0.86
Central	ELOVL2	7	Caution	-254.21 (-489.99, -18.44)	**0.035**
Central	ELOVL2	7	Extreme caution	12.21 (-207.43, 231.86)	0.91
Central	ELOVL2	7	Danger	128.48 (-117, 373.96)	0.3
Central	ELOVL2	7	Extreme danger	205.19 (-108.81, 519.18)	0.2
Central	ELOVL2	15	Caution	-125.44 (-233.89, -17)	**0.023**
Central	ELOVL2	15	Extreme caution	55.09 (-30.88, 141.07)	0.21
Central	ELOVL2	15	Danger	55.18 (-27.91, 138.26)	0.19
Central	ELOVL2	15	Extreme danger	76.33 (-35.22, 187.89)	0.18
Central	ELOVL2	30	Caution	-59.95 (-128.1, 8.2)	0.085
Central	ELOVL2	30	Extreme caution	15.5 (-35.72, 66.72)	0.55
Central	ELOVL2	30	Danger	10.98 (-36.21, 58.17)	0.65
Central	ELOVL2	30	Extreme danger	33.03 (-33.44, 99.51)	0.33
Central	ELOVL2	60	Caution	-35.11 (-79.78, 9.56)	0.12
Central	ELOVL2	60	Extreme caution	-1.48 (-32.98, 30.03)	0.93
Central	ELOVL2	60	Danger	-7.68 (-31.93, 16.57)	0.53
Central	ELOVL2	60	Extreme danger	0.6 (-36.53, 37.73)	0.97
Central	FHL2	7	Caution	-14.37 (-390.14, 361.4)	0.94
Central	FHL2	7	Extreme caution	119.16 (-230.91, 469.22)	0.5
Central	FHL2	7	Danger	328.58 (-62.66, 719.82)	0.1
Central	FHL2	7	Extreme danger	365.18 (-135.26, 865.61)	0.15
Central	FHL2	15	Caution	-88.46 (-263.57, 86.66)	0.32
Central	FHL2	15	Extreme caution	38.77 (-100.05, 177.6)	0.58
Central	FHL2	15	Danger	121.96 (-12.2, 256.12)	0.075
Central	FHL2	15	Extreme danger	118.14 (-61.99, 298.27)	0.2
Central	FHL2	30	Caution	-37.69 (-147.44, 72.06)	0.5

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Central	FHL2	30	Extreme caution	15.58 (-66.91, 98.07)	0.71
Central	FHL2	30	Danger	31.6 (-44.41, 107.6)	0.41
Central	FHL2	30	Extreme danger	48.61 (-58.44, 155.67)	0.37
Central	FHL2	60	Caution	-28.35 (-100.35, 43.64)	0.44
Central	FHL2	60	Extreme caution	20.05 (-30.72, 70.82)	0.44
Central	FHL2	60	Danger	-3.18 (-42.26, 35.9)	0.87
Central	FHL2	60	Extreme danger	9.2 (-50.64, 69.03)	0.76
Central	Pheno	7	Caution	-384.28 (-630.11, -138.45)	**0.002**
Central	Pheno	7	Extreme caution	-333.64 (-562.65, -104.64)	**0.004**
Central	Pheno	7	Danger	-199.31 (-455.26, 56.63)	0.13
Central	Pheno	7	Extreme danger	-201.63 (-529.01, 125.75)	0.23
Central	Pheno	15	Caution	-102.15 (-216.36, 12.06)	0.079
Central	Pheno	15	Extreme caution	37.92 (-52.63, 128.46)	0.41
Central	Pheno	15	Danger	24.77 (-62.73, 112.27)	0.58
Central	Pheno	15	Extreme danger	23.29 (-94.19, 140.78)	0.7
Central	Pheno	30	Caution	-2.59 (-74.12, 68.95)	0.94
Central	Pheno	30	Extreme caution	29.5 (-24.27, 83.27)	0.28
Central	Pheno	30	Danger	14.85 (-34.69, 64.39)	0.56
Central	Pheno	30	Extreme danger	34.05 (-35.73, 103.83)	0.34
Central	Pheno	60	Caution	3.09 (-43.65, 49.83)	0.9
Central	Pheno	60	Extreme caution	17.17 (-15.79, 50.14)	0.31
Central	Pheno	60	Danger	-1.44 (-26.81, 23.94)	0.91
Central	Pheno	60	Extreme danger	26.54 (-12.31, 65.39)	0.18
Central	Skin & blood	7	Caution	-217.09 (-442.33, 8.14)	0.059
Central	Skin & blood	7	Extreme caution	-65.67 (-275.5, 144.15)	0.54
Central	Skin & blood	7	Danger	-16.08 (-250.59, 218.43)	0.89
Central	Skin & blood	7	Extreme danger	80.73 (-219.23, 380.68)	0.6
Central	Skin & blood	15	Caution	-88.69 (-191.54, 14.15)	0.091
Central	Skin & blood	15	Extreme caution	66.9 (-14.63, 148.44)	0.11
Central	Skin & blood	15	Danger	61.01 (-17.78, 139.8)	0.13
Central	Skin & blood	15	Extreme danger	74.54 (-31.25, 180.33)	0.17
Central	Skin & blood	30	Caution	-16.88 (-81.46, 47.69)	0.61
Central	Skin & blood	30	Extreme caution	30.97 (-17.57, 79.51)	0.21
Central	Skin & blood	30	Danger	16.24 (-28.48, 60.96)	0.48

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Central	Skin & blood	30	Extreme danger	35.23 (-27.76, 98.22)	0.27
Central	Skin & blood	60	Caution	-6.41 (-48.76, 35.94)	0.77
Central	Skin & blood	60	Extreme caution	7.46 (-22.41, 37.33)	0.62
Central	Skin & blood	60	Danger	-4.06 (-27.05, 18.93)	0.73
Central	Skin & blood	60	Extreme danger	10.51 (-24.69, 45.71)	0.56
Central	Grim2	7	Caution	-95.86 (-211.98, 20.26)	0.11
Central	Grim2	7	Extreme caution	-122.72 (-230.89, -14.54)	**0.026**
Central	Grim2	7	Danger	-128.28 (-249.18, -7.38)	**0.038**
Central	Grim2	7	Extreme danger	-168.29 (-322.94, -13.65)	**0.033**
Central	Grim2	15	Caution	30.16 (-23.72, 84.03)	0.27
Central	Grim2	15	Extreme caution	3.33 (-39.38, 46.04)	0.88
Central	Grim2	15	Danger	10.87 (-30.4, 52.15)	0.6
Central	Grim2	15	Extreme danger	21.48 (-33.94, 76.9)	0.45
Central	Grim2	30	Caution	20.31 (-13.23, 53.85)	0.23
Central	Grim2	30	Extreme caution	9.28 (-15.93, 34.49)	0.47
Central	Grim2	30	Danger	9.84 (-13.39, 33.07)	0.41
Central	Grim2	30	Extreme danger	19.94 (-12.78, 52.66)	0.23
Central	Grim2	60	Caution	4.4 (-17.61, 26.42)	0.69
Central	Grim2	60	Extreme caution	2.18 (-13.35, 17.7)	0.78
Central	Grim2	60	Danger	2.12 (-9.83, 14.07)	0.73
Central	Grim2	60	Extreme danger	9.02 (-9.28, 27.31)	0.33
Southern	Horvath's	7	Caution	192.69 (-38.83, 424.22)	0.1
Southern	Horvath's	7	Extreme caution	1.98 (-208.5, 212.47)	0.99
Southern	Horvath's	7	Danger	22.34 (-216.51, 261.18)	0.85
Southern	Horvath's	7	Extreme danger	-36.28 (-330.63, 258.07)	0.81
Southern	Horvath's	15	Caution	99.9 (2.34, 197.46)	**0.045**
Southern	Horvath's	15	Extreme caution	11.17 (-54.22, 76.56)	0.74
Southern	Horvath's	15	Danger	21.04 (-59.77, 101.86)	0.61
Southern	Horvath's	15	Extreme danger	-0.78 (-110.73, 109.17)	0.99
Southern	Horvath's	30	Caution	48.14 (-12.63, 108.92)	0.12
Southern	Horvath's	30	Extreme caution	-9.21 (-42.97, 24.54)	0.59
Southern	Horvath's	30	Danger	7.75 (-32.88, 48.39)	0.71
Southern	Horvath's	30	Extreme danger	-6.09 (-63.86, 51.68)	0.84
Southern	Horvath's	60	Caution	23.51 (-22.15, 69.18)	0.31

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Southern	Horvath's	60	Extreme caution	-5.94 (-25.97, 14.09)	0.56
Southern	Horvath's	60	Danger	10.28 (-14.09, 34.65)	0.41
Southern	Horvath's	60	Extreme danger	7.65 (-25.66, 40.96)	0.65
Southern	Hannum's	7	Caution	89.37 (-127.57, 306.31)	0.42
Southern	Hannum's	7	Extreme caution	40.23 (-156.99, 237.45)	0.69
Southern	Hannum's	7	Danger	10.36 (-213.43, 234.16)	0.93
Southern	Hannum's	7	Extreme danger	-98.12 (-373.92, 177.69)	0.48
Southern	Hannum's	15	Caution	48.09 (-42.86, 139.03)	0.3
Southern	Hannum's	15	Extreme caution	38.09 (-22.86, 99.05)	0.22
Southern	Hannum's	15	Danger	29.04 (-46.29, 104.37)	0.45
Southern	Hannum's	15	Extreme danger	-4.36 (-106.85, 98.14)	0.93
Southern	Hannum's	30	Caution	2.38 (-54.29, 59.04)	0.93
Southern	Hannum's	30	Extreme caution	9.93 (-21.54, 41.4)	0.54
Southern	Hannum's	30	Danger	4.55 (-33.34, 42.44)	0.81
Southern	Hannum's	30	Extreme danger	-16.02 (-69.89, 37.84)	0.56
Southern	Hannum's	60	Caution	-0.39 (-42.9, 42.13)	0.99
Southern	Hannum's	60	Extreme caution	7.16 (-11.49, 25.8)	0.45
Southern	Hannum's	60	Danger	5.56 (-17.13, 28.25)	0.63
Southern	Hannum's	60	Extreme danger	-2.6 (-33.61, 28.42)	0.87
Southern	Weidner's	7	Caution	187.41 (-49.85, 424.67)	0.12
Southern	Weidner's	7	Extreme caution	23.43 (-192.26, 239.13)	0.83
Southern	Weidner's	7	Danger	37.63 (-207.13, 282.38)	0.76
Southern	Weidner's	7	Extreme danger	-161.23 (-462.87, 140.4)	0.29
Southern	Weidner's	15	Caution	10.99 (-90.07, 112.05)	0.83
Southern	Weidner's	15	Extreme caution	23.46 (-44.28, 91.2)	0.5
Southern	Weidner's	15	Danger	16.93 (-66.78, 100.64)	0.69
Southern	Weidner's	15	Extreme danger	-53.52 (-167.42, 60.37)	0.36
Southern	Weidner's	30	Caution	8.65 (-54.18, 71.48)	0.79
Southern	Weidner's	30	Extreme caution	5.2 (-29.69, 40.1)	0.77
Southern	Weidner's	30	Danger	12.12 (-29.89, 54.14)	0.57
Southern	Weidner's	30	Extreme danger	-32.48 (-92.2, 27.25)	0.29
Southern	Weidner's	60	Caution	7.55 (-39.56, 54.66)	0.75
Southern	Weidner's	60	Extreme caution	1.84 (-18.83, 22.5)	0.86
Southern	Weidner's	60	Danger	9.08 (-16.06, 34.22)	0.48

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Southern	Weidner's	60	Extreme danger	-15.78 (-50.15, 18.58)	0.37
Southern	ELOVL2	7	Caution	55.69 (-201.03, 312.41)	0.67
Southern	ELOVL2	7	Extreme caution	92.97 (-140.42, 326.35)	0.43
Southern	ELOVL2	7	Danger	57.56 (-207.27, 322.39)	0.67
Southern	ELOVL2	7	Extreme danger	-124.19 (-450.57, 202.19)	0.45
Southern	ELOVL2	15	Caution	-5.78 (-115.26, 103.7)	0.92
Southern	ELOVL2	15	Extreme caution	39.74 (-33.65, 113.12)	0.29
Southern	ELOVL2	15	Danger	45.24 (-45.45, 135.93)	0.33
Southern	ELOVL2	15	Extreme danger	-30.88 (-154.27, 92.51)	0.62
Southern	ELOVL2	30	Caution	-21.24 (-89.4, 46.92)	0.54
Southern	ELOVL2	30	Extreme caution	5.41 (-32.44, 43.26)	0.78
Southern	ELOVL2	30	Danger	3.91 (-41.67, 49.48)	0.87
Southern	ELOVL2	30	Extreme danger	-40.03 (-104.82, 24.75)	0.23
Southern	ELOVL2	60	Caution	-40.1 (-91.18, 10.98)	0.12
Southern	ELOVL2	60	Extreme caution	8.36 (-14.04, 30.77)	0.46
Southern	ELOVL2	60	Danger	-8.24 (-35.5, 19.02)	0.55
Southern	ELOVL2	60	Extreme danger	-23.68 (-60.94, 13.58)	0.21
Southern	FHL2	7	Caution	-118.01 (-535.92, 299.9)	0.58
Southern	FHL2	7	Extreme caution	-132.57 (-512.49, 247.35)	0.49
Southern	FHL2	7	Danger	-173.28 (-604.39, 257.83)	0.43
Southern	FHL2	7	Extreme danger	-109.57 (-640.87, 421.73)	0.69
Southern	FHL2	15	Caution	33.09 (-145.2, 211.38)	0.72
Southern	FHL2	15	Extreme caution	59.97 (-59.53, 179.47)	0.32
Southern	FHL2	15	Danger	92.07 (-55.61, 239.76)	0.22
Southern	FHL2	15	Extreme danger	60.14 (-140.8, 261.07)	0.56
Southern	FHL2	30	Caution	4.58 (-106.43, 115.59)	0.94
Southern	FHL2	30	Extreme caution	10.77 (-50.89, 72.42)	0.73
Southern	FHL2	30	Danger	16.52 (-57.7, 90.75)	0.66
Southern	FHL2	30	Extreme danger	-18.03 (-123.55, 87.49)	0.74
Southern	FHL2	60	Caution	-29.25 (-112.44, 53.95)	0.49
Southern	FHL2	60	Extreme caution	10.61 (-25.88, 47.09)	0.57
Southern	FHL2	60	Danger	-7.92 (-52.31, 36.48)	0.73
Southern	FHL2	60	Extreme danger	-18.01 (-78.7, 42.67)	0.56
Southern	Pheno	7	Caution	329.58 (55.99, 603.17)	**0.018**

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Southern	Pheno	7	Extreme caution	38.58 (-210.15, 287.31)	0.76
Southern	Pheno	7	Danger	18.7 (-263.54, 300.94)	0.9
Southern	Pheno	7	Extreme danger	-50.16 (-397.99, 297.67)	0.78
Southern	Pheno	15	Caution	123 (7.57, 238.43)	**0.037**
Southern	Pheno	15	Extreme caution	-4.89 (-82.26, 72.48)	0.9
Southern	Pheno	15	Danger	-5.57 (-101.19, 90.05)	0.91
Southern	Pheno	15	Extreme danger	-10.64 (-140.73, 119.45)	0.87
Southern	Pheno	30	Caution	63.47 (-8.45, 135.39)	0.084
Southern	Pheno	30	Extreme caution	-16.1 (-56.04, 23.85)	0.43
Southern	Pheno	30	Danger	4.38 (-43.71, 52.47)	0.86
Southern	Pheno	30	Extreme danger	-11.56 (-79.92, 56.8)	0.74
Southern	Pheno	60	Caution	44.75 (-9.26, 98.76)	0.1
Southern	Pheno	60	Extreme caution	-6.99 (-30.68, 16.7)	0.56
Southern	Pheno	60	Danger	15.12 (-13.7, 43.95)	0.3
Southern	Pheno	60	Extreme danger	10.95 (-28.44, 50.35)	0.59
Southern	Skin & blood	7	Caution	230.02 (-20.04, 480.08)	0.071
Southern	Skin & blood	7	Extreme caution	96.43 (-130.9, 323.76)	0.4
Southern	Skin & blood	7	Danger	44.02 (-213.94, 301.98)	0.74
Southern	Skin & blood	7	Extreme danger	-22.53 (-340.44, 295.38)	0.89
Southern	Skin & blood	15	Caution	61.45 (-43.97, 166.87)	0.25
Southern	Skin & blood	15	Extreme caution	47.07 (-23.59, 117.73)	0.19
Southern	Skin & blood	15	Danger	29.21 (-58.11, 116.54)	0.51
Southern	Skin & blood	15	Extreme danger	1.49 (-117.32, 120.3)	0.98
Southern	Skin & blood	30	Caution	13.78 (-51.94, 79.49)	0.68
Southern	Skin & blood	30	Extreme caution	10.23 (-26.26, 46.73)	0.58
Southern	Skin & blood	30	Danger	4.35 (-39.59, 48.29)	0.85
Southern	Skin & blood	30	Extreme danger	-14.12 (-76.58, 48.34)	0.66
Southern	Skin & blood	60	Caution	-4.78 (-54.09, 44.52)	0.85
Southern	Skin & blood	60	Extreme caution	7.43 (-14.19, 29.06)	0.5
Southern	Skin & blood	60	Danger	1 (-25.31, 27.31)	0.94
Southern	Skin & blood	60	Extreme danger	-3.98 (-39.95, 31.98)	0.83
Southern	Grim2	7	Caution	-88.03 (-218.19, 42.13)	0.18
Southern	Grim2	7	Extreme caution	-88.96 (-207.28, 29.37)	0.14
Southern	Grim2	7	Danger	-112.77 (-247.04, 21.49)	0.1

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Southern	Grim2	7	Extreme danger	-128.47 (-293.94, 37.01)	0.13
Southern	Grim2	15	Caution	-18.35 (-72.98, 36.28)	0.51
Southern	Grim2	15	Extreme caution	-15.2 (-51.82, 21.42)	0.42
Southern	Grim2	15	Danger	-20.19 (-65.44, 25.07)	0.38
Southern	Grim2	15	Extreme danger	-26.54 (-88.11, 35.03)	0.4
Southern	Grim2	30	Caution	-17.82 (-51.75, 16.12)	0.3
Southern	Grim2	30	Extreme caution	-9.18 (-28.03, 9.67)	0.34
Southern	Grim2	30	Danger	-11.01 (-33.7, 11.68)	0.34
Southern	Grim2	30	Extreme danger	-19.64 (-51.9, 12.62)	0.23
Southern	Grim2	60	Caution	-10.52 (-35.96, 14.92)	0.42
Southern	Grim2	60	Extreme caution	-5.85 (-17.01, 5.31)	0.3
Southern	Grim2	60	Danger	-8.1 (-21.68, 5.48)	0.24
Southern	Grim2	60	Extreme danger	-8.55 (-27.11, 10.01)	0.37
Eastern	Horvath's	7	Caution	196.44 (-637.07, 1029.95)	0.64
Eastern	Horvath's	7	Extreme caution	114.05 (-827.69, 1055.8)	0.81
Eastern	Horvath's	7	Danger	-424.95 (-1416.44, 566.54)	0.39
Eastern	Horvath's	7	Extreme danger	516.24 (-843.84, 1876.32)	0.45
Eastern	Horvath's	15	Caution	318.34 (-10.41, 647.08)	0.057
Eastern	Horvath's	15	Extreme caution	175.21 (-171.08, 521.5)	0.32
Eastern	Horvath's	15	Danger	290.75 (-42.9, 624.39)	0.087
Eastern	Horvath's	15	Extreme danger	252.3 (-85.08, 589.67)	0.14
Eastern	Horvath's	30	Caution	98.17 (-80.07, 276.41)	0.28
Eastern	Horvath's	30	Extreme caution	147.36 (-56.78, 351.5)	0.15
Eastern	Horvath's	30	Danger	124.99 (-31.29, 281.26)	0.12
Eastern	Horvath's	30	Extreme danger	160.75 (-23.86, 345.36)	0.087
Eastern	Horvath's	60	Caution	27.29 (-106.25, 160.83)	0.68
Eastern	Horvath's	60	Extreme caution	42.92 (-62, 147.83)	0.42
Eastern	Horvath's	60	Danger	24.21 (-27.07, 75.49)	0.35
Eastern	Horvath's	60	Extreme danger	48.47 (-47.81, 144.75)	0.32
Eastern	Hannum's	7	Caution	776.25 (50.93, 1501.58)	**0.037**
Eastern	Hannum's	7	Extreme caution	492.53 (-326.98, 1312.04)	0.23
Eastern	Hannum's	7	Danger	163.13 (-699.67, 1025.93)	0.71
Eastern	Hannum's	7	Extreme danger	881.34 (-302.22, 2064.89)	0.14
Eastern	Hannum's	15	Caution	321.65 (-1.41, 644.7)	0.051

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Eastern	Hannum's	15	Extreme caution	70.47 (-269.83, 410.76)	0.68
Eastern	Hannum's	15	Danger	218.68 (-109.19, 546.55)	0.19
Eastern	Hannum's	15	Extreme danger	229.11 (-102.43, 560.64)	0.17
Eastern	Hannum's	30	Caution	136.44 (-38.5, 311.39)	0.12
Eastern	Hannum's	30	Extreme caution	141.51 (-58.86, 341.87)	0.16
Eastern	Hannum's	30	Danger	168.37 (14.99, 321.76)	**0.032**
Eastern	Hannum's	30	Extreme danger	188.26 (7.06, 369.46)	**0.042**
Eastern	Hannum's	60	Caution	92.52 (-40, 225.04)	0.17
Eastern	Hannum's	60	Extreme caution	10.11 (-94, 114.23)	0.85
Eastern	Hannum's	60	Danger	49.73 (-1.16, 100.62)	0.055
Eastern	Hannum's	60	Extreme danger	45.72 (-49.83, 141.26)	0.34
Eastern	Weidner's	7	Caution	64.05 (-750.4, 878.51)	0.87
Eastern	Weidner's	7	Extreme caution	-573.61 (-1493.82, 346.6)	0.22
Eastern	Weidner's	7	Danger	-907.21 (-1876.03, 61.6)	0.066
Eastern	Weidner's	7	Extreme danger	33.58 (-1295.4, 1362.56)	0.96
Eastern	Weidner's	15	Caution	120.18 (-253.9, 494.26)	0.52
Eastern	Weidner's	15	Extreme caution	107.02 (-287.02, 501.07)	0.59
Eastern	Weidner's	15	Danger	122.73 (-256.93, 502.39)	0.52
Eastern	Weidner's	15	Extreme danger	65.16 (-318.74, 449.06)	0.74
Eastern	Weidner's	30	Caution	36.82 (-163.06, 236.71)	0.71
Eastern	Weidner's	30	Extreme caution	101.73 (-127.2, 330.66)	0.38
Eastern	Weidner's	30	Danger	64.91 (-110.34, 240.16)	0.46
Eastern	Weidner's	30	Extreme danger	66.96 (-140.07, 274)	0.52
Eastern	Weidner's	60	Caution	87.48 (-60.54, 235.5)	0.24
Eastern	Weidner's	60	Extreme caution	-36.24 (-152.54, 80.05)	0.54
Eastern	Weidner's	60	Danger	7.11 (-49.73, 63.96)	0.8
Eastern	Weidner's	60	Extreme danger	14.99 (-91.73, 121.71)	0.78
Eastern	ELOVL2	7	Caution	478.89 (-499.22, 1457)	0.33
Eastern	ELOVL2	7	Extreme caution	875.87 (-229.24, 1980.99)	0.12
Eastern	ELOVL2	7	Danger	-46.85 (-1210.34, 1116.64)	0.94
Eastern	ELOVL2	7	Extreme danger	803.08 (-792.95, 2399.1)	0.32
Eastern	ELOVL2	15	Caution	378.2 (-40.9, 797.3)	0.076
Eastern	ELOVL2	15	Extreme caution	-44.57 (-486.04, 396.9)	0.84
Eastern	ELOVL2	15	Danger	252.54 (-172.81, 677.89)	0.24

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Eastern	ELOVL2	15	Extreme danger	217.31 (-212.79, 647.41)	0.32
Eastern	ELOVL2	30	Caution	223.23 (-3.73, 450.19)	0.054
Eastern	ELOVL2	30	Extreme caution	122.52 (-137.42, 382.45)	0.35
Eastern	ELOVL2	30	Danger	225.2 (26.22, 424.19)	**0.027**
Eastern	ELOVL2	30	Extreme danger	255.63 (20.55, 490.7)	**0.034**
Eastern	ELOVL2	60	Caution	12.94 (-163.69, 189.58)	0.88
Eastern	ELOVL2	60	Extreme caution	75.46 (-63.32, 214.24)	0.28
Eastern	ELOVL2	60	Danger	60.22 (-7.61, 128.05)	0.081
Eastern	ELOVL2	60	Extreme danger	85.78 (-41.57, 213.14)	0.18
Eastern	FHL2	7	Caution	902.72 (-593.99, 2399.43)	0.23
Eastern	FHL2	7	Extreme caution	1216.65 (-474.4, 2907.71)	0.15
Eastern	FHL2	7	Danger	864.24 (-916.14, 2644.62)	0.33
Eastern	FHL2	7	Extreme danger	1753.71 (-688.54, 4195.96)	0.16
Eastern	FHL2	15	Caution	360.32 (-178.61, 899.24)	0.19
Eastern	FHL2	15	Extreme caution	-49.99 (-617.68, 517.7)	0.86
Eastern	FHL2	15	Danger	-17.23 (-564.19, 529.73)	0.95
Eastern	FHL2	15	Extreme danger	176.01 (-377.06, 729.09)	0.53
Eastern	FHL2	30	Caution	146.17 (-145.66, 438.01)	0.32
Eastern	FHL2	30	Extreme caution	203.12 (-131.12, 537.36)	0.23
Eastern	FHL2	30	Danger	135.3 (-120.56, 391.17)	0.3
Eastern	FHL2	30	Extreme danger	248.69 (-53.57, 550.96)	0.11
Eastern	FHL2	60	Caution	111.31 (-106.08, 328.69)	0.31
Eastern	FHL2	60	Extreme caution	94.47 (-76.33, 265.27)	0.27
Eastern	FHL2	60	Danger	31.98 (-51.5, 115.46)	0.45
Eastern	FHL2	60	Extreme danger	117.51 (-39.23, 274.24)	0.14
Eastern	Pheno	7	Caution	557.84 (-319.57, 1435.25)	0.21
Eastern	Pheno	7	Extreme caution	-262.35 (-1253.7, 728.99)	0.6
Eastern	Pheno	7	Danger	-826.47 (-1870.18, 217.23)	0.12
Eastern	Pheno	7	Extreme danger	393.51 (-1038.2, 1825.22)	0.58
Eastern	Pheno	15	Caution	369.19 (-44.49, 782.88)	0.079
Eastern	Pheno	15	Extreme caution	341.59 (-94.17, 777.35)	0.12
Eastern	Pheno	15	Danger	435.6 (15.74, 855.45)	**0.042**
Eastern	Pheno	15	Extreme danger	383.46 (-41.08, 808)	0.076
Eastern	Pheno	30	Caution	148.09 (-72.11, 368.3)	0.18

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted β (95% CI)[1]	Adjusted p[1]
Eastern	Pheno	30	Extreme caution	268.21 (16, 520.41)	**0.037**
Eastern	Pheno	30	Danger	235.47 (42.41, 428.54)	**0.018**
Eastern	Pheno	30	Extreme danger	275.67 (47.59, 503.75)	**0.019**
Eastern	Pheno	60	Caution	78.85 (-87.04, 244.74)	0.35
Eastern	Pheno	60	Extreme caution	42.84 (-87.5, 173.17)	0.51
Eastern	Pheno	60	Danger	55.8 (-7.9, 119.51)	0.085
Eastern	Pheno	60	Extreme danger	60.38 (-59.23, 179.98)	0.32
Eastern	Skin & blood	7	Caution	945.56 (103.65, 1787.46)	**0.029**
Eastern	Skin & blood	7	Extreme caution	626.9 (-324.33, 1578.12)	0.19
Eastern	Skin & blood	7	Danger	-38.02 (-1039.48, 963.45)	0.94
Eastern	Skin & blood	7	Extreme danger	1185.81 (-187.96, 2559.59)	0.089
Eastern	Skin & blood	15	Caution	373.05 (-18.04, 764.15)	0.061
Eastern	Skin & blood	15	Extreme caution	52.67 (-359.3, 464.64)	0.8
Eastern	Skin & blood	15	Danger	171.62 (-225.3, 568.55)	0.39
Eastern	Skin & blood	15	Extreme danger	228.86 (-172.5, 630.23)	0.26
Eastern	Skin & blood	30	Caution	199.52 (-5.47, 404.52)	0.056
Eastern	Skin & blood	30	Extreme caution	230.15 (-4.63, 464.93)	0.055
Eastern	Skin & blood	30	Danger	215.01 (35.28, 394.74)	**0.02**
Eastern	Skin & blood	30	Extreme danger	301.05 (88.73, 513.37)	**0.006**
Eastern	Skin & blood	60	Caution	122.11 (-34.69, 278.9)	0.12
Eastern	Skin & blood	60	Extreme caution	40.31 (-82.88, 163.49)	0.52
Eastern	Skin & blood	60	Danger	57.48 (-2.73, 117.69)	0.061
Eastern	Skin & blood	60	Extreme danger	104.83 (-8.22, 217.88)	0.069
Eastern	Grim2	7	Caution	-121.5 (-518.21, 275.22)	0.54
Eastern	Grim2	7	Extreme caution	563.75 (115.52, 1011.97)	**0.015**
Eastern	Grim2	7	Danger	178.45 (-293.45, 650.35)	0.45
Eastern	Grim2	7	Extreme danger	464.61 (-182.73, 1111.94)	0.16
Eastern	Grim2	15	Caution	-7.52 (-185.77, 170.74)	0.93
Eastern	Grim2	15	Extreme caution	-2.92 (-190.69, 184.85)	0.98
Eastern	Grim2	15	Danger	100.46 (-80.45, 281.38)	0.27
Eastern	Grim2	15	Extreme danger	61.53 (-121.41, 244.46)	0.5
Eastern	Grim2	30	Caution	17.59 (-76.11, 111.3)	0.71
Eastern	Grim2	30	Extreme caution	102.05 (-5.28, 209.37)	0.062
Eastern	Grim2	30	Danger	121.81 (39.65, 203.97)	**0.004**

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Areas	Age acceleration (days)	Exposure windows (days)	Categories of HI(max)	Adjusted *β* (95% CI)[1]	Adjusted *p*[1]
Eastern	Grim2	30	Extreme danger	118.94 (21.88, 216)	**0.017**
Eastern	Grim2	60	Caution	-10.66 (-81.91, 60.59)	0.77
Eastern	Grim2	60	Extreme caution	48.98 (-7, 104.96)	0.085
Eastern	Grim2	60	Danger	38.42 (11.06, 65.79)	**0.007**
Eastern	Grim2	60	Extreme danger	40.13 (-11.24, 91.51)	0.12

$p < 0.05$ were shown in bold. [1] Adjusted for sex, chronological age, BMI, educational level, smoking status, and $PM_{2.5}$. Time trend and weekend/holiday were additionally adjusted in models of 1- to 7-day exposure windows. Year and season (warm or cold season) of enrollment were additionally adjusted in models of 15- to 60-day exposure windows.

a*β*, adjusted *β*; CI, confidence interval; HI(max), heat index of maximum temperature.

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