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Environmental temperature and human epigenetic modifications: A systematic review☆

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ABSTRACT

The knowledge about the effects of environmental temperature on human epigenome is a potential key to understand the health impacts of temperature and to guide acclimation under climate change. We performed a systematic review on the epidemiological studies that have evaluated the association between environmental temperature and human epigenetic modifications. We identified seven original articles on this topic published between 2009 and 2019, including six cohort studies and one cross-sectional study. They focused on DNA methylation in elderly people (blood sample) or infants (placenta sample), with sample size ranging from 306 to 1798. These studies were conducted in relatively low temperature setting (median/mean temperature: 0.8−13 °C), and linear models were used to evaluate temperature-DNA methylation association over short period (≤28 days). It has been reported that short-term ambient temperature could affect global human DNA methylation. A total of 15 candidate genes (ICAM-1, CRAT, F3, TLR-2, iNOS, ZKSCAN4, ZNF227, ZNF595, ZNF597, ZNF668, CACNA1H, AIRE, MYEOV2, NKX1-2 and CCDC15) with methylation status associated with ambient temperature have been identified. DNA methylation on ZKSCAN4, ICAM-1 partly mediated the effect of short-term cold temperature on high blood pressure and ICAM-1 protein (related to cardiovascular events), respectively. In summary, epidemiological evidence about the impacts of environment temperature on human epigenetics remains scarce and limited to short-term linear effect of cold temperature on DNA methylation in elderly people and infants. More studies are needed to broaden our understanding of temperature related epigenetic changes, especially under a changing climate.

1. Introduction

Environmental temperature is an important health determinant. As estimated by a multi-country study, 7.3% and 0.4% of mortality could be attributed to exposure to low and high temperatures, respectively (Gasparrini et al., 2015b). The attributable fraction was even higher in a recent study in China, where cold and heat were responsible for 12.6% and 1.8% of non-accidental mortality (Chen et al., 2018). In Brazil, a nationwide study has found that 6.2% of hospitalizations were attributable to heat exposure, corresponding to 132 cases per 100,000 residents (Zhao et al., 2019a).

As a major health determinant, environmental temperature is likely to be able to affect human epigenetic modifications which refer to changes of gene expression without alteration in the DNA sequence. Epigenetic modification includes DNA methylation, non-coding RNA (ncRNA),and chromatin regulation, while ncRNA mainly includes microRNA (miRNA) and long ncRNA, and chromatin regulation is mainly realized by histone modification (Alfano et al., 2018). It has been documented that epigenetic changes are

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associated with many human diseases, such as asthma, autism, diabetes, psoriasis and cardiovascular diseases (Petronis, 2010; Portela and Esteller, 2010). Meanwhile, the human epigenome can also be modified by environmental factors such as tobacco smoking (Li et al., 2018b) and air pollution (Alfano et al., 2018). However, it is still unclear whether exposure to suboptimal environmental temperature could affect epigenetic modifications related to human health.

By 2100, the global temperature is projected to increase by 2.7–4.8 °C (International Energy Agency, 2015). In a warming world, whether and how people could adapt to heat exposure is attracting increasing concern. A long-term decrease in the relative risks of heat-mortality association has been reported in the UK, USA, Czech Republic, Japan, and Spain (Barreca et al., 2016; Carson et al., 2006; Gasparrini et al., 2015a; Kysely and Plavcova, 2012), indicating substantial adaption of the human body to extreme temperatures. Meanwhile, epigenetic changes have been documented to play an important role in animals' and plants' adaptation to the temperature in their living environment (Liu et al., 2019; Platt et al., 2015; Su-Keene et al., 2018b; Yakovlev et al., 2010). However, whether the evidence is also true for human beings remains unclear.

This systematic review aims to summarize the existing epidemiological evidence of the effects of environmental temperature on human epigenetic modifications. Findings of the study might provide a better understanding of the underlying mechanism in temperature-health association and human's potential physiological adaptation to temperature. To our best knowledge, no systematic review on this topic has been published before. The present systematic review could serve as a timely guideline for this emerging field.

2. Materials and methods

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Text S1 for PRISMA checklist) (Liberati et al., 2009). Fig. 1 outlines the four main steps from literature identification to qualitative synthesis. The protocol of this review has been registered and become public available at PROSPERO (https://www.crd.york.ac.uk/prospero) with a registration number of CRD4201913692.

2.1. Literature search

Firstly, we performed a systematic search of four databases to identify epidemiological studies on the association between environmental temperature and epigenetic changes. The search was performed on PubMed, Web of Science, Science Direct and Scopus in English, without any time restriction. The search key words or MeSH terms for epigenetic changes included "epigenomics", "epigenetic*", "DNA methylation", "DNA hydroxyl-methylation", "non-coding RNA", "miRNA", "microRNA", "histon*", "chromatin remodelling," "chromatin," "chip-on-chip," and "chip seq". The search key words or MeSH terms for environmental temperature included "temperature", "climate", "weather", "heat wave*", "extreme heat", "extreme cold", and "cold spell*". We used Boolean operators to create all possible combinations on the terms of epigenetics and temperature. The detailed search terms varied slightly between databases and were described in **Supplementary material**. The latest search was conducted on August 5, 2019. Following the PRISMA flow diagram, the references from included studies were also considered.

2.2. Literature screening and selection

Secondly, two researchers (RX, QZ) independently screened the identified literature by reading the titles and abstracts. We excluded the following types of study: (1) studies for non-human species (animal, plants, etc); (2) *in vitro* studies (e.g., experiments on extracted human cells or tissues); (3) non-original investigations (e.g., reviews, meta-analysis, book chapters, editorials); (4) studies in which exposure or intervention was not environmental temperature (e.g., body temperature); (5) studies without any epigenetic bio-markers. Any records with uncertainty or inconsistency between two reviewers would be left to the next step.

Thirdly, two researchers (RX, SG) read the full texts of all remaining records to examine their eligibility. Eligibility criteria included: (1) the study was performed in human species; (2) the paper reported an original investigation (studies using first-hand data); (3) the paper reported an *in vivo* study; (4) the paper examined any epigenetic biomarker (DNA methylation, miRNA, non-coding RNA, histone modifications, and/or chromatin regulation) (5) the paper studied environmental temperature (e.g., ambient temperature, outdoor temperature, room temperature; not including body temperature); as exposure (for observational designs) or intervention (for experimental designs). Because all non-English papers had been excluded in the third step, all records left for the fourth step were published in English. We resolved disagreements in the final inclusion by consensus.

2.3. Data extraction and quality assessment

Finally, data extraction and quality assessment were performed by two researchers (RX, SG) independently for all included studies. Extracted data included authors, publication year, relevant country, study design and period, sample size, age, sex, exposure assessment of environmental temperature, epigenetic biomarkers and the detection technique, covariates adjusted, statistical methods and main findings.

Due to great heterogeneity in the time window of temperature exposure, epigenetic assessment technique, and statistical methods, we were not able to perform a quantitative meta-analysis. Consequently, we only performed qualitative synthesis of the main findings. We used the Newcastle Ottawa Scale (NOS) for cohort studies (Stang, 2010) and an adapted form of the NOS for cross-sectional studies (Herzog et al., 2013) to evaluate the quality of studies included (See Table S1). We resolved any disagreements in the data extraction and quality assessment by consensus.

3. Results

3.1. Basic characteristics of included studies

After a systematic searching and screening, we identified seven original articles that had examined the association between environmental temperature and human epigenetic modifications (Fig. 1) (Abraham et al., 2018; Baccarelli et al., 2009; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019; Lim et al., 2017). They were conducted between 1999 and 2015 and published between 2009 and 2019. Five studies actually originated from the same cohort - Normative Aging Study, a cohort consisting of more than 700 elderly male Veterans (median age 72 years) in Boston, United States (Baccarelli et al., 2009; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019). The other two studies, one cohort and one cross-sectional study, came from South Korea (Lim et al., 2017) and France (Abraham et al., 2018), respectively. The South Korean study involved 102 elderly people (mean

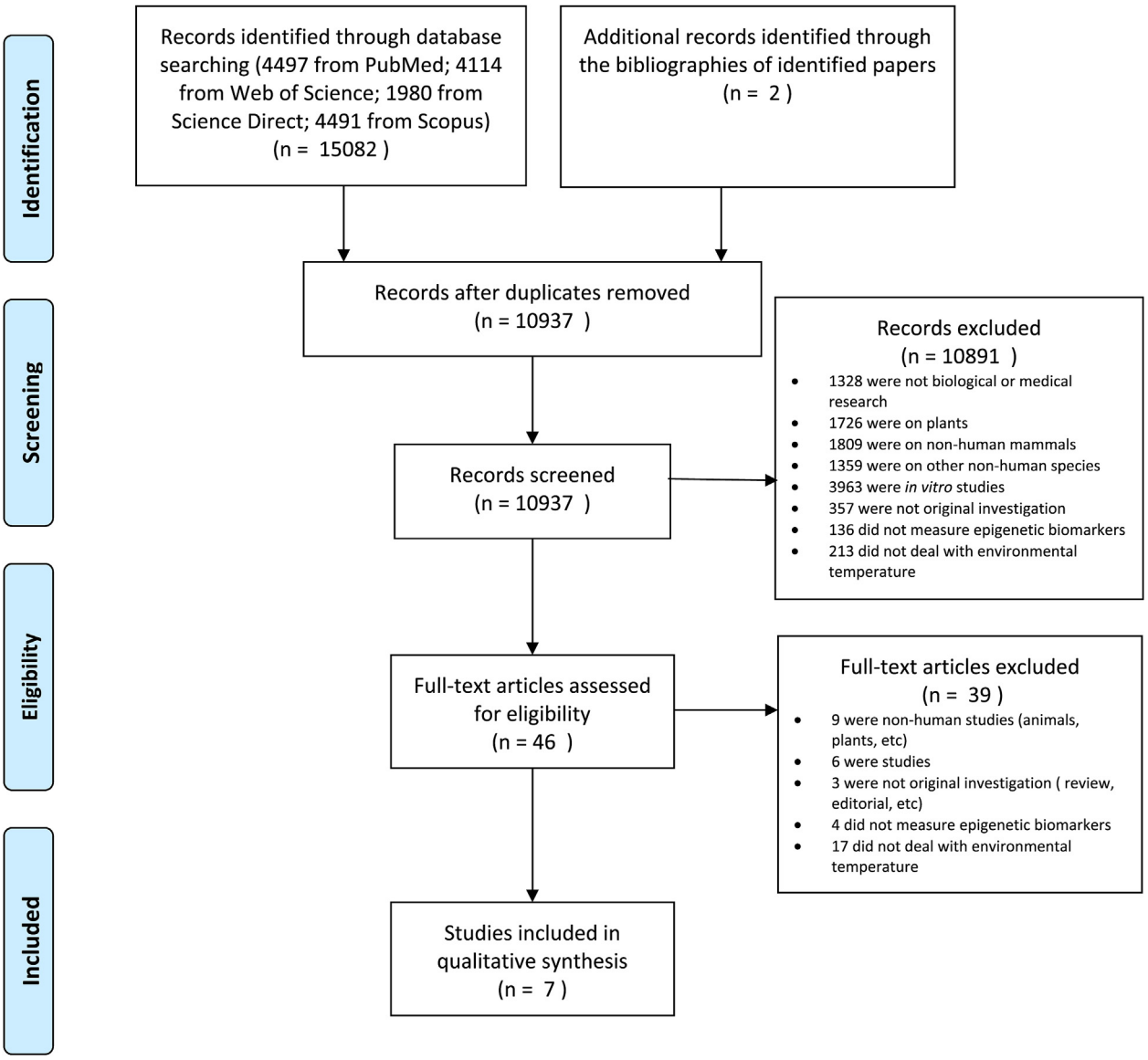

Fig. 1. Flow diagram for identifying relevant original articles on the association between environmental temperature and human epigenetic changes, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

age 72.8 years) predominantly females (92.2%). The French study included 668 newborns (48% female) from one hospital (Table 1). We reported the quality assessment of the included studies in Table S1. A major concern about those studies' quality is selection bias, because their participants were either dominated by single gender or all from one hospital. In addition, publication bias is also a concern since there might be some unpublished studies, particularly studies with null associations.

3.2. Methodological characteristics of included studies

For epigenetic bio-markers, all seven studies focused on DNA methylation. No study explored other epigenetic biomarkers such as non-coding RNA, miRNA or histone modification. The DNA methylation measurements were all performed with venous blood samples, except for the French study (Abraham et al., 2018) which measured DNA methylation in the placenta of newborns. Four early studies (Baccarelli et al., 2009; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b) published in 2009–2016 measured methylation in repetitive elements [long interspersed nuclear element-1 (LINE-1), *Arthrobacter luteus* (Alu)] and several candidate genes with PCR–pyrosequencing technology. The three most recent studies (Abraham et al., 2018; Gao et al., 2019; Lim et al., 2017) published since 2017 measured whole-genome DNA methylation using Illumina Infinium HumanMethylation450 K array, although the South Korean study investigated CpG (5′—C—phosphate—G—3′, cytosine and guanine separated by one phosphate group) sites of vascular disease-related genes only (Table 2).

For environmental temperature, all seven included studies used the outdoor ambient temperature recorded by nearby meteorological station as the exposure variable. However, different time windows of temperature exposure were used according to different assumptions or aims. The earliest study (Baccarelli et al., 2009) simply used the temperature of the present day of blood draw, because: 1) there was no previous knowledge about the time window; 2) their main study aim was to evaluate the impacts of traffic air pollution, so not too much attention was paid to the temperature (a covariate). The later four US studies in the same

Table 1
Basic characteristics of seven included studies.

No.	Authors, year	Country	Study design	Study period	Sample size	Sex	Age
1	Baccarelli et al., 2009	United States	cohort	1999–2007	718 individuals, 1097 visits (blood samples)	all males	55–100; mean 73.3, SD 6.7 years
2	Bind et al., 2014	United States	cohort	1999–2009	777 individuals, 1798 visits (blood samples)	all males	median 72, 5th percentile 62, 95th percentile 84 years
3	Bind et al., 2016 a	United States	cohort	1999–2009	777 individuals, 1798 visits (blood samples)	all males	median 72, 5th percentile 62, 95th percentile 84 years
4	Bind et al., 2016 b	United States	cohort	1999–2009	777 individuals, 1798 visits (blood samples)	all males	median 72 years, 5th percentile 62 years, 95th percentile 84 years
5	Lim et al., 2017	South Korea	cohort	2014–2015	102 participants, 306 measurements (3 visits per participant): discovery data (n = 50); replication data (n = 52)	94 (92.2%) females, 8 (7.8%) males	mean 72.8, SD 4.0; all ≥60 years.
6	Abraham et al., 2018	France	cross-sectional	2003–2006	668 newborns	319 (48%) females, 249 (52%) males	mean gestational duration was 40 (SD 1.7) weeks and 32 babies (5%) were born preterm (<37 gestational weeks); maternal age, mean 29.0 years, SD 5.1 years
7	Gao et al., 2019	United States	cohort	2003–2011	774 individuals, 1519 visits (blood samples)	all males	mean 74.6, SD 7.1 years

Note: SD, standard deviation.

cohort, which paid more attention to the impact of temperature, used daily mean temperatures averaged up to 28 days prior to the blood draw (Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019). They made this choice because they focused on blood immune profile or genes related to coagulation, inflammation, cortisol and metabolic pathways, and their previous study has found the relevant blood biomarkers (e.g. C-reactive protein) were associated with temperature averaged up to one month.

The South Korean study used mean ambient temperature during the visit time (9 a.m.–12 a.m.), in order to evaluate the immediate effects of temperature on blood pressure and DNA methylation (Lim et al., 2017). Because there was no previous knowledge about the most biological relevant time window of the effect of weather conditions on placenta DNA methylation, the study of newborns (Abraham et al., 2018) used the average ambient temperature during: 1–3 days before delivery, 1 week or 1 month before delivery, 1st-3rd trimesters, and the whole pregnancy. The five American studies (Baccarelli et al., 2009; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019) and the newborn study were conducted at moderate temperatures, with a median of 12–13 °C. In contrast, the South Korean study (Lim et al., 2017) was conducted in relatively cold temperatures ranging from −6 °C to 9 °C (mean 0.8 °C) (Table 2).

The statistical methods in the six cohort studies were mixed effect models or quartile regression for longitudinal data to account for repeat measurements of DNA methylation. Among them, the South Korean study (Lim et al., 2017) applied Bonferroni corrections to the p-values to account for multiple testing. The French study (Abraham et al., 2018) used linear regression, with a Benjamini and Hochberg False Discovery Rate (FDR) correction to the p-values to account for multiple testing. The earliest study (Baccarelli et al., 2009) did not adjust for any covariates when evaluating the association between temperature and epigenetic changes. Later studies (Abraham et al., 2018; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019; Lim et al., 2017) had some common adjusted covariates, such as age, sex, body mass index (BMI) and smoking status. Some of the studies also adjusted for relative humidity (Abraham et al., 2018; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019), and the potential technique bias in measuring DNA methylation (Abraham et al., 2018; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b) (batch effect and cell-type proportions). Only one adjusted for air pollution represented by $PM_{2.5}$ (particulate matter 2.5 μm or less in diameter) concentrations (Bind et al., 2016a). (Table 2).

Among the two studies that applied an epigenome-wide association study (EWAS) approach (Abraham et al., 2018; Lim et al., 2017), only the French study presented Q-Q plots, genomic inflation factor (lambda) and Bayesian inflation factor (BIF) to evaluate the inflation/deflation of p-values. The results indicated that the p-value distribution was close to theoretical distribution (with BIF close to 1, ranging from 0.96 to 1.15) (Abraham et al., 2018).

3.3. Temperature and global DNA methylation

Global DNA methylation is often represented by methylation level in repeat elements such as Alu and LINE-1 (Yang et al., 2004; Zhu et al., 2010). The earliest study (Baccarelli et al., 2009) did not find significant associations between ambient temperature and LINE-1 ($\beta = -0.04$; 95% confidence interval [95%CI]: −0.10 to 0.02 with a 9.2 °C increase in temperature; $p = 0.21$) and Alu ($\beta = 0.05$; 95%CI -0.01 to 0.11; $p = 0.09$) methylation. However these non-significant results could be due to several reasons: short exposure time window (1 day), limited sample size and bias caused by unadjusted confounders.

A later study (Bind et al., 2014) of the same cohort published in 2014, with a time window extended to 21 days, 63% greater sample size (1798 vs. 1097) and adjustment for many potential confounders, had different findings. In this study (Bind et al., 2014), every 5 °C increase in temperature in the first week prior to blood draw was significantly ($p < 0.05$) associated with about 0.25% decrease ($\beta \approx -0.25$) in LINE-1 methylation and about 0.1% increase ($\beta \approx 0.1$) in Alu methylation. The association for LINE-1 was also significant during the time window of the third week prior to visit but non-significant during the second week. Alu methylation was not significantly associated with temperature in the second and third weeks prior to visit. This suggests that Alu and LINE-1 methylation might have different time windows in response to environmental temperature. The French study (Abraham et al., 2018) found that temperature during pregnancy was not associated with LINE-1 or Alu methylation in newborn placenta, regardless the time window of exposure. However, global methylation represented by the overall DNA methylation distribution of all 425,878 CpG sites, was significantly associated with temperature during trimester 1 (Table 3).

3.4. Temperature and gene-specific methylation

The Normative Ageing Study has explored the association

Table 2
Summary of exposure measurement, epigenetic biomarkers and statistical methods of seven included studies.

No.	Authors, year	Environmental temperature exposure	Temperature level	Epigenetic biomarkers	Tissue	Detection technique	Adjusted covariates	Statistical models
1	Baccarelli et al. (2009)	Mean outdoor ambient temperature of the day of visit and blood draw, measured by nearby weather station.	mean 12.8 °C, SD 9.2 °C	Methylation at LINE-1 and Alu repetitive elements	Venous blood sample	Methylation analyses on bisulfite-treated blood leukocyte DNA using PCR −pyrosequencing technology	none	Linear mixed effect model
2	Bind et al. (2014)	Outdoor ambient temperature over 0−20 days (3 weeks) before each visit and blood draw, measured by nearby weather station.	median 13 °C, 5th percentile −1 °C, 95th percentile - 23 °C	Methylation at LINE-1 and Alu repetitive elements and 9 candidate genes related to coagulation, inflammation, cortisol, and metabolic pathway	Venous blood sample	Methylation analyses on bisulfite-treated blood leukocyte DNA using PCR −pyrosequencing technology	relative humidity, age, body mass index, smoking status, statin use, cell-type proportions, seasonal sine and cosine, season, and batch of methylation measurement	Generalized mixed-effects model; distributed lag model to account for lag effects.
3	Bind et al., 2016 a	Average outdoor ambient temperature over the 3-week period preceding each participant's visit and blood draw, measured by nearby weather station.	median 13 °C, 5th percentile −1 °C, 95th percentile 23 °C	Methylation at 9 candidate genes related to coagulation, inflammation, cortisol, and metabolic pathway	Venous blood sample	Methylation analyses on bisulfite-treated blood leukocyte DNA using PCR −pyrosequencing technology	relative humidity, age, body mass index, smoking status, statin use, sine and cosine terms as a function of day of the season, batch of methylation measurement, diabetes, cell-type proportions	Quantile regressions for longitudinal data
4	Bind et al., 2016 b	Average outdoor ambient temperature over the 3-week period preceding each participant's visit and blood draw, measured by nearby weather station.	median 13 °C, 5th percentile −1 °C, 95th percentile 23 °C	Methylation at ICAM-1	Venous blood sample	Methylation analyses on bisulfite-treated blood leukocyte DNA using PCR −pyrosequencing technology	$PM_{2.5}$ concentration, age, batch, body mass index, percentage of neutrophils in blood count, smoking, seasonal sine and cosine, and diabetes status	Generalized mixed-effect models
5	Lim et al. (2017)	The average ambient temperature during the blood draw time (9am-12.pm [noon]) on the visit day, measured by nearby weather station.	about −6−9 °C, mean 0.8 °C, SD 3.5 °C	Methylation at 24,490 CpG sites of 1294 vascular disease-related genes	Venous blood sample	Illumina Infinium HumanMethylation450 K array	Age, sex, body mass index, current smoking, drinking habits, and education and study year	Generalized linear mixed-effect models, with Bonferroni correction to the p-values
6	Abraham et al. (2018)	Mean daily ambient temperature measure by the nearest weather station to their home address. The exposure window included 1−3 days before delivery, 1 week or 1 month before delivery, 1st-3rd trimester, and the whole pregnancy.	about −7−30 °C, median about 12 °C	Whole-genome DNA-methylation	Placenta samples	Illumina Infinium HumanMethylation450 K array	relative humidity, child sex, parity (0, 1, ≥2 children), maternal age at end of education (≤18, 19−20, 21−22, 23−24, ≥25 years), season of conception, studycentre, maternal body mass index before pregnancy, maternal age at delivery, maternal smoking during pregnancy (continuous) and gestational duration, batch, plate, chip and cell-type proportions	Linear regression, accounting for multiple testing by applying a Benjamini and Hochberg False Discovery Rate (FDR) correction to the p-values. Differentially Methylated Regions (DMRs) analyses using comb-p method, with DMR p-values adjusted for multiple testing by Šidák correction
7	Gao et al. (2019)	Average outdoor ambient temperature on the same day of visit and up to 28 days (7, 14, 21, and 28 days) prior to visit and blood draw, measured by nearby weather station.	mean 12.58 °C, inter-quartile range 13.58 °C	The distribution of 10 types of leukocytes estimated by whole-genome DNA-methylation data	Venous blood sample	Illumina Infinium HumanMethylation450 K array	relative humidity, age, body mass index, smoking status, alcohol intake, total cholesterol, triglycerides, high-density lipoprotein, systolic diastolic blood pressure, hypertension, stroke, coronary heart disease, diabetes and cancer diagnosed by physician (yes/no), and season of medical visits	Linear mixed-effect regression model

Note: SD, standard deviation; $PM_{2.5}$, atmospheric particulate matter that have a diameter of less than 2.5 μm.

Table 3
The main findings of all included studies.

No.	Authors, year	Main findings
1	Baccarelli et al. (2009)	Ambient temperature was not significantly associated with LINE-1 [$\beta = -0.04$; 95% confidence interval (95% CI): −0.10 to 0.02 with a 9.2 °C increase in temperature; $p = 0.21$] and Alu ($\beta = 0.05$; 95% CI -0.01 to 0.11; $p = 0.09$) methylation.
2	Bind et al. (2014)	Ambient temperature increase within different time windows ranged from 1 to 3 week before blood draw were significantly ($p < 0.05$) associated with hypermethylation at Alu, ICAM-1, CRAT, hypomethylation at LINE-1, F3, TRL-2. No significant association with DNA methylation at OGG1, IFN-γ, IL-6, iNOS, and GCR was found. An interaction effect between temperature and relative humidity on ICAM-1 methylation was reported.
3	Bind et al., 2016 a	Ambient temperature increase was associated with hypomethylation at F3, TLR-2 and hypermethylation at CRAT, iNOS on participants in the lower quantiles of the methylation distribution. The association between temperature increase and hypermethylation at ICAM-1 was significant on participants in the higher quantiles of the methylation distribution. No heterogeneity and significant associations between temperature and the percentiles of the OGG1, IFN-γ, IL-6 and GCR methylation distributions were found.
4	Bind et al., 2016 b	The total effect of temperature on ICAM-1 was significant. A one-unit increase in standardized temperature exposure is associated with a 0.3472 ($\gamma = -0.3472$, 95% CI: −0.5323 to −0.1621) decrease in ICAM-1 protein. Direct ($\gamma = -0.206$; 95% CI: −0.508 to −0.014) and indirect ($\gamma = -0.059$; 95% CI: −0.191 to −0.037) effects (through increase in ICAM-1 methylation) of temperature rise on ICAM-1 protein were also significant. In other words, 22% [0.059/(0.059 + 0.206)] of effect of ambient temperature on serum ICAM-1 protein level could be mediated by change in ICAM-1 DNA methylation.
5	Lim et al. (2017)	Out of 24,490 CpG sites of vascular disease-related genes, 6 CpG sites showed significant increases in methylation with drops in ambient temperature in the discovery data ($p < 2.5 \times 10^{-6}$). One CpG site was located within a gene family of calcium channels (CACNA1H) and 5 CpG sites within ZNF genes (ZKSCAN4, ZNF227, ZNF595, ZNF597, and ZNF668)]. Two CpG sites (i.e., cg21194911 and cg21761427) were consistently shown significant associations with changes in DNA methylation in both discovery data ($p < 2.5 \times 10^{-6}$) and replication data ($P < 1.0 \times 10^{-2}$). 20.4% ($p = 0.0572$) of the association between temperature decrease and diastolic blood pressure elevation was mediated by increase in methylation at cg21761427 (CPG site at the promoter region of ZKSCAN4), but no significant mediation effect was found for cg21194911 ($p = 0.26$).
6	Abraham et al. (2018)	(1) Ambient temperatures during all time windows were not significantly associated with placental DNA methylation at LINE-1 (e.g., whole pregnancy: $\beta = -0.07$, p-value = 0.84) and Alu elements (e.g., whole pregnancy: $\beta = 0.03$, p value = 0.97); (2) temperature during trimester 1 was associated with placental overall DNA methylation distribution (p value = 0.03); (3) No single CpG site was found to be associated with ambient temperature during any time window of pregnancy (FDR p values ranged from 0.19 to 1); (4) The methylation levels of three regions mapped to AIRE (Šidák p-value $= 1.76 \times 10^{-5}$), MYEOV2 (Šidák p-value $= 3.25 \times 10^{-4}$) and NKX1-2 gene (Šidák p-value $= 4.93 \times 10^{-8}$), and one region mapped to CCDC15 (Šidák p-value $= 2.43 \times 10^{-5}$) were significantly associated temperature during whole pregnancy and temperature during trimester 3, respectively. The directions of the effects were not reported.
7	Gao et al. (2019)	The increase of average ambient temperature during all time windows was associated with the decreased proportion of $CD8^+$ T cell (change in z-score with interquartile range increase in temperature = −0.150; se = 0.064; $p < 0.05$) in blood sample estimated by DNA methylation data. Increased $CD8^+$ T cell is an indicator of systematic inflammatory response.

between ambient temperature and 9 candidate genes related to coagulation, inflammation, cortisol and metabolic pathways (Bind et al., 2014; Bind et al., 2016b). However, only five of them, namely Intercellular Adhesion Molecule 1 (ICAM-1, 3 CpG sites measured), Carnitine O-acetyltransferase (CRAT, 2 CpG sites), Tissue Factor (F3, 5 CpG sites), Toll-Like Receptor 2 (TLR-2, 5 CpG sites), and inducible Nitric Oxide Synthase (iNOS, 2 CpG sites) showed significant associations with temperature. Different candidate genes showed different effective time windows of temperature exposure. For example, F3 and TLR-2 hypomethylations were significantly associated with the temperature increase during the first week prior to visit. By contrast, ICAM-1 and CRAT hypermethylations showed significant associations with the temperature increase during the whole three weeks prior to visit. DNA methylation at iNOS was not significantly associated with temperature when using a generalized mixed effect model. Interestingly, when performing quantile regression of the same dataset, Bind et al. found a significant association between temperature rise and hypermethylation at iNOS on participants in the lower quantile of the methylation distribution (Bind et al., 2016b). This indicated that quantile regression could be an important method to discover new environment related candidate gene methylation.

The South Korean study (Lim et al., 2017) focused on 24,490 CpG sites of 1294 vascular disease-related genes. It identified 6 CpG sites related to temperature using EWAS approach. Five of them were located in Zinc Finger (ZNF) genes [Zinc Finger With KRAB And SCAN Domains 4 (ZKSCAN4), Zinc Finger Protein 227 (ZNF227), Zinc Finger Protein 595 (ZNF595), Zinc Finger Protein 597 (ZNF597), and Zinc Finger Protein 668 (ZNF668)], and one located in a gene family of calcium channels [Calcium Voltage-Gated Channel Subunit Alpha1 H (CACNA1H)].

The French study (Abraham et al., 2018) of placental samples did not identify any single CpG site associated with ambient temperature during any time window of pregnancy (FDR p-values ranged from 0.19 to 1) using EWAS approach. However, they identified four Differentially Methylated Regions (DMR) that were significantly associated with temperature during pregnancy, using comb-p (a software for combining, analysing, grouping and correcting spatially correlated P-values (Pedersen et al., 2012)). These regions could be mapped to Autoimmune Regulator (AIRE, 4 CpG sites, Šidák p-value $= 1.76 \times 10^{-5}$), Myeloma-overexpressed 2-like protein (MYEOV2, 5 CpG sites,Šidák p-value $= 3.25 \times 10^{-4}$), NK1 Homeobox 2 (NKX1-2, 4 CpG sites, Šidák p-value $= 4.93 \times 10^{-8}$) and Coiled-Coil Domain Containing 15 (CCDC15, 6 CpG sites, Šidák p-value $= 2.43 \times 10^{-5}$) genes (Table 3).

Two studies (Bind et al., 2016a; Lim et al., 2017) suggested a mediation role for gene-specific methylation in the effect of low temperature on cardiovascular health. Bind et al. (2016a) estimated that 22% of effect of ambient temperature on serum ICAM-1 protein level could be mediated by change in ICAM-1 DNA methylation. High plasma ICAM-1 protein levels have been associated with high risks of coronary artery disease and death (Luc et al., 2003; Postadzhiyan et al., 2008). In summary, low temperature would induce hypomethylation of ICAM-1, resulting in over expression of the protein, and increase the risk of cardiovascular events. Similarly, the South Korean study found 20.4% of the effect of low temperature on high diastolic blood pressure (DBP) was mediated by the hypermethylation of CpG site at the promoter region of ZKSCAN4 (also known as ZNF307) (Lim et al., 2017).

The detailed information about the 15 identified genes whose methylation status associated with ambient temperature was reported in Table 4. According to the gene functions and related health outcomes, it seems that the results for ICAM-1, CRAT, F3, TLR-2, iNOS, ZKSCAN4, CACNA1H could be biologically relevant, which was consistent with the observed impacts of cold temperature on cardiorespiratory health (Turner et al., 2012). The fact that high expression (low methylation) of ZNF227 was related to aggression phenotype could be consistent with the observation

Table 4
Detailed information about the 15 candidate genes whose methylation status was significantly associated with ambient temperature.

Author year	Gene name	Full name	CpG sites measured in the study	Analysis method	Tissue	Change in methylation with temperature increase	Gene functions	Related health outcomes
Bind et al. (2014); Bind et al. (2016a); Bind et al. (2016b)	ICAM-1	Intercellular Adhesion Molecule 1	cg10242236, cg10242225, cg10242218	Candidate gene	Blood	↑	This gene encodes a cell surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system.	Coronary artery disease and myocardial infarction (PMID: 30290609); Type 2 diabetes (PMID: 30798334); Diabetic nephropathy (PMID: 30587209); Hepatocellular carcinoma (PMID: 28894136); Colorectal cancer (PMID: 28816939).
Bind et al. (2014); Bind et al. (2016a)	CRAT	Carnitine O-acetyltransferase	cg130912824, cg130912806	Candidate gene	Blood	↑	This gene encodes a key metabolic pathway enzyme which plays an important role in energy homeostasis and fat metabolism.	Insulin resistance (PMID: 27931032); Obesity and diabetes (PMID: 24395925); Lung function (PMID: 22430802);
Bind et al. (2014); Bind et al. (2016a)	F3	Coagulation factor III, Tissue Factor	cg94779947, cg94779950, cg94779956, cg94779958, cg94779974	Candidate gene	Blood	↓	This gene encodes coagulation factor III which is a cell surface glycoprotein. This factor enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII. The resulting complex is responsible for initiation of the coagulation protease cascades by specific limited proteolysis.	Thrombosis (PMID: 30278301 and 29789989);
Bind et al. (2014); Bind et al. (2016a)	TLR-2	Toll-Like Receptor 2	cg154824709, cg154824713, cg154824715, cg154824723, cg154824727	Candidate gene	Blood	↓	The protein encoded by this gene is a member of the Toll-like receptor (TLR) family which plays a fundamental role in pathogen recognition and activation of innate immunity. These cell-surface proteins recognize molecules derived from microorganisms known as pathogen-associated molecular patterns (PAMPs). Activation of TLRs by PAMPs leads to an up-regulation of signalling pathways to modulate the host's inflammatory response.	Arterial Thrombus Formation (PMID: 30261531). Essential hypertension (PMID: 28560381); Type 2 diabetes (PMID: 28536605); Asthma (PMID: 28514297); Alzheimer (PMID: 28087373); Tuberculosis Susceptibility (PMID: 30733958 and 29486365); Human glioma (PMID: 30898699); Refractory periapical granuloma (PMID: 30631444); Multiple sclerosis (PMID: 30043528). *Helicobacter pylori* infection and peptic ulcer (PMID: 29755012 and 28844484); Intracranial aneurysm (PMID: 29066233); Inflammatory bowel disease (PMID: 28388655).
Bind et al. (2016a)	iNOS (or NOS2)	inducible Nitric Oxide Synthase	cg23149929, cg23149936	Candidate gene	Blood	↑	Nitric oxide is a reactive free radical which acts as a biologic mediator in several processes, including neurotransmission and antimicrobial and antitumoral activities. This gene encodes a nitric oxide synthase which is expressed in liver and is inducible by a combination of lipopolysaccharide and certain cytokines.	Asthma (PMID: 29518423); Hypertension (PMID: 28685250 and 26579803); Ovarian cancer (PMID: 30970628); Cerebral palsy (PMID:29931509); Malaria (PMID: 30118498); Fracture non-union (PMID: 29518099); Chronic periodontitis (PMID: 28617311); Prostate cancer (PMID: 28162285). Breast cancer (PMID: 27464521);
Lim et al. (2017)	ZKSCAN4 (or ZNF307)	Zinc Finger With KRAB And SCAN Domains 4	cg21761427	EWAS	Blood	↓	This gene encodes one of Zinc-finger proteins (ZNFs), ZNF307. ZNFs function as transcription factors and are involved in several cellular processes including transcriptional regulation, ubiquitin-mediated protein degradation, signal transduction, actin targeting, DNA repair, and cell migration. They play a key role in development and differentiation of several tissues. ZNFs are involved in tumorigenesis, cancer progression and metastasis formation (Cassandri et al., 2017).	Tumor-suppressor in hepatocellular carcinoma (PMID: 28765950); Negative regulator of pressure overload-induced cardiac hypertrophy (PMID: 28223477); Schizophrenia (PMID: 22037552); Rheumatoid arthritis (PMID: 27898717);
Lim et al. (2017)	ZNF227	Zinc Finger Protein 227	cg21194911	EWAS	Blood	↓	This gene encodes Zinc Finger Protein 227.	High expression associated with aggression phenotype (PMID: 20553618)
	ZNF595		cg25173401	EWAS	Blood	↓		

(*continued on next page*)

Table 4 (*continued*)

Author year	Gene name	Full name	CpG sites measured in the study	Analysis method	Tissue	Change in methylation with temperature increase	Gene functions	Related health outcomes
Lim et al. (2017)		Zinc Finger Protein 595					This gene encodes Zinc Finger Protein 595.	Carotid Paragangliomas (PMID: 31397435); Sporadic lung cancer (PMID: 29054765); Gastric cancer (PMID: 25422082).
Lim et al. (2017)	ZNF597	Zinc Finger Protein 597	cg24333473	EWAS	Blood	↓	This gene encodes Zinc Finger Protein 597.	Imprinting diseases (PMID: 27632690); Brain development (PMID: 19968752); Silver-Russell syndrome characterised by growth failure and dysmorphic features (PMID: 30242100).
Lim et al. (2017)	ZNF668	Zinc Finger Protein 668	cg01700035	EWAS	Blood	↓	This gene encodes Zinc Finger Protein 668.	Tumor suppressor of non-small cell lung cancer (PMID: 29556277); Breast cancer (PMID:21852383); Nodular melanoma (PMID: 21343389).
Lim et al. (2017)	CACNA1H	Calcium Voltage-Gated Channel Subunit Alpha1 H	cg07940218	EWAS	Blood	↓	This gene encodes a T-type member of the alpha-1 subunit family, a protein in the voltage-dependent calcium channel complex. The alpha-1 subunit has 24 transmembrane segments and forms the pore through which ions pass into the cell.	Prostate cancer (PMID: 31527367); Aldosteronism (PMID: 27729216); Abdominal pain in irritable bowel syndrome patients (PMID: 27196538); Pediatric chronic pain (PMID: 26706850); Hypertension and blood pressure (PMID: 19609347 and 25907736); Cardiac hypertrophy (PMID: 20699644); Epilepsy (PMID: 24277868, 17215393, 17156077, 16905256, 26216687 and 17696120); Headache with neurological deficits and lymphocytosis (PMID: 23111027); Autism spectrum disorders (PMID: 16754686); Diabetic peripheral neuropathy (PMID: 29581247).
Abraham et al. (2018)	AIRE	Autoimmune Regulator	cg09510531, cg11923631, cg16501323, cg27251412	DMR analysis	Placenta	not reported	This gene encodes a transcriptional regulator that forms nuclear bodies and interacts with the transcriptional coactivator CREB binding protein. The encoded protein plays an important role in immunity by regulating the expression of autoantigens and negative selection of autoreactive T-cells in the thymus.	Autoimmune diseases including pernicious anaemia, vitiligo and autoimmune thyroid disease, systemic lupus erythematosus, and type 1 diabetes (PMID: 27504588, 31563273 and 29417186).
Abraham et al. (2018)	MYEOV2	Myeloma-overexpressed 2-like protein	cg06717460, cg08045488, cg12495591, cg17342071, cg26306091	DMR analysis	Placenta	not reported	This gene encodes Myeov2, which regulates subnuclear localization of ribosomal protein L11, leading to regulation of p53 (a tumor suppressor) stress response pathway (Ebina et al., 2013).	Breast cancer (PMID: 26103053).
Abraham et al. (2018)	NKX1-2	NK1 Homeobox 2	cg02043951, cg10095938, cg14233800, cg16019809	DMR analysis	Placenta	not reported	This gene encodes a homeodomain-containing transcription factor Nkx1-2 (also known as Sax1), which is a critical component of the gene regulatory network that operates downstream of Wnt/β-catenin signalling to regulate the formation of mesoderm and endoderm (Tamashiro et al., 2012).	Adipogenesis (PMID: 31615896); Transposition of the great arteries (PMID: 26655555);
Abraham et al. (2018)	CCDC15	Coiled-Coil Domain Containing 15	cg01243246, cg02513924, cg05468346, cg12136126, cg24050671, cg24403578	DMR analysis	Placenta	not reported	The gene encodes a protein that might be involved in DNA damage repair and cell cycle progression (Tripp, 2017).	Mantle cell lymphoma (PMID: 29755111)

Note: EWAS, epigenome-wide association study; DMR, differentially methylated region. The information on gene functions and their related health outcomes came from https://www.ncbi.nlm.nih.gov/gene/. PMID refer to the unique identifier number of a paper in PubMed.

that violent crime increased along with temperature rise (Tiihonen et al., 2017). However, whether the results for the other 7 genes (ZNF595, ZNF597, ZNF668, AIRE, MYEOV2, NKX1-2, CCDC15) make biological sense remains unclear.

3.5. Other findings

The most recent study (Gao et al., 2019) based on Normative Ageing Study used the Illumina Infinium HumanMethylation450 K chip to estimate the proportions of leukocyte subtypes in blood samples. They found that the average ambient temperature during all time windows (7–28 days prior to blood draw) was negatively associated with the proportion of $CD8^+$ T cell ($p < 0.05$). This study provided a good example of how to utilize HumanMethylation450 K data to evaluate the effects of environmental exposures on human immune system.

4. Discussion

We did a systematic review of the epidemiological studies on the association between environmental temperature and human epigenetics. To our best knowledge, this is the first systematic review of this topic. Generally, this is quite a new area with a small amount of evidence available, although both epigenetics and temperature-health association have been intensively studied. The main findings of the seven studies included could be summarized as follows:

- Short-term ambient temperature could affect global DNA methylation;
- A total of 15 candidate genes (ICAM-1, CRAT, F3, TLR-2, iNOS, ZKSCAN4, ZNF227, ZNF595, ZNF597, ZNF668, CACNA1H, AIRE, MYEOV2, NKX1-2 and CCDC15) with methylation status associated with short-term ambient temperature have been identified;
- DNA methylation on ZKSCAN4, ICAM-1 partly mediated the effect of short-term cold temperature on high blood pressure and ICAM-1 protein (related to cardiovascular events), respectively;
- Short-term ambient temperature might affect the human's proportions of leukocyte subtypes estimated by Illumina 450 k data in blood sample.

Although existing studies have provided some useful information, a lot of questions are yet to be answered. Here, we present a mind map to summarize the current evidence, and more importantly, the future directions to gain deeper understanding of the effects of environmental temperature on human epigenetics (Fig. 2). In the next paragraphs, we discuss this mind map with our findings and focus on three aspects: epigenetic modifications, environmental temperature (exposure), and methodological issues.

4.1. Epigenetic modifications

4.1.1. Multi-omics integration

The existing studies have solely focused on DNA methylation - the most widely studied and well understood epigenetic biomarker. The impacts of environmental temperature on DNA methylation profile have also been reported in animals (Cramer et al., 2018; Marsh and Pasqualone, 2014; Weyrich et al., 2018) and plants (Lai et al., 2018; Munzbergova et al., 2019; Pan et al., 2011; Platt et al., 2015; Yu et al., 2018; Zhou et al., 2015). However, DNA methylation is only one of several epigenetic regulation mechanisms. Other epigenetic mechanisms may also play an important role in human's response to environmental temperature. Several studies have revealed the involvement of non-coding RNA (mainly miRNA) (Liu et al., 2017; Liu et al., 2019; Radhakrishnan et al., 2018; Su-Keene et al., 2018a, b; Wang et al., 2019; Zhang et al., 2018; Zhu et al., 2019), histone (Ishihara et al., 2019), and chromatin remodelling (Liu et al., 2015; Sung and Amasino, 2004) in the adaptation to environmental temperature for animals or plants. Whether similar findings could be observed for human beings is waiting to be tested by future epidemiological studies. In recent years, increasing attention has also been attracted to mitochondrial epigenetics in addition to nuclear epigenetics (Stimpfel et al., 2018). Studying the impacts of environment temperature on human mitochondrial epigenetics is also a promising field.

From a broader perspective, epigenetic regulation is only a part of the multiple biological networks from human genomic to health outcomes. The integration of multi-omics data would provide more useful information than just focusing on epigenetics. One important reason for multi-omics integration is that the relationship between epigenetic changes, gene expression and health outcomes is often not straightforward. For example, DNA methylation at transcriptional start sites is usually associated with gene silencing while methylation in the gene body is often positively associated with gene expression (Jones, 1999).

Two existing studies have set good examples of how to integrate protein level and health outcome data (blood pressure) (Bind et al., 2016a; Lim et al., 2017). Both animal and plant studies have integrated gene expression data (e.g. mRNA profile) when studying the effect of environmental temperature on epigenetic status (Barati et al., 2018; Zhu et al., 2019). The integration of genomic and epigenetic data (e.g., GWAS and EWAS) is also a promising approach (Zhao et al., 2019b). Study has shown that the methylation status of about 32% CpG sites could be regulated by genetic variation or methylation quantitative trait loci (mQTLs) (Cheung et al., 2017). It is possible that temperature induced epigenetic modifications might also be affected by such kinds of genetic variation, such as a mQTL nearby the CpG site associated with ambient temperature. A similar gene-environment interaction was clearly reported in a previous study which evaluated the smoking-mQTL interaction on methylation of smoking related CpG sites (Gao et al., 2017).

4.1.2. Further study of DNA methylation

Due to practical problems such as cost, many studies rely on DNA methylation, mostly Illumina 450 k or Illumina 850 k data. Given the scarcity of evidence on the relationship between environmental temperature and human epigenetics, there is still much work to do even to focus on DNA methylation. Firstly, despite the 15 candidate genes identified by existing studies, none of them has yet been replicated by any other study. Without sufficient replication, those identified candidate genes tend to be less convincing. Moreover, existing studies often have small sample size, leading to potential low statistical power to identify new CpG sites. Therefore, more EWAS studies, embedded in different populations, are needed to either replicate previous findings or identify new CpG sites.

Because epigenome-wide DNA methylation data are highly-dimensional, using certain approaches to reduce the dimensions are often useful and could reveal new information. Taking Illumina 450 k data as an example, the methylation status of more than 450,000 CpG sites would be measured for each individual using this technique. Although EWAS approach could often identify many single CpG sites, it cannot evaluate the overall effect of environmental factors on DNA methylation status across the whole genome.

Furthermore, in epigenetic regulations, the gene expressions and health outcomes may be not just regulated by methylation level of single CpG site, but by a set of CpG sites (e.g., genes within same biological pathway). Several dimension reduction approaches, including DMR (Abraham et al., 2018), global methylation

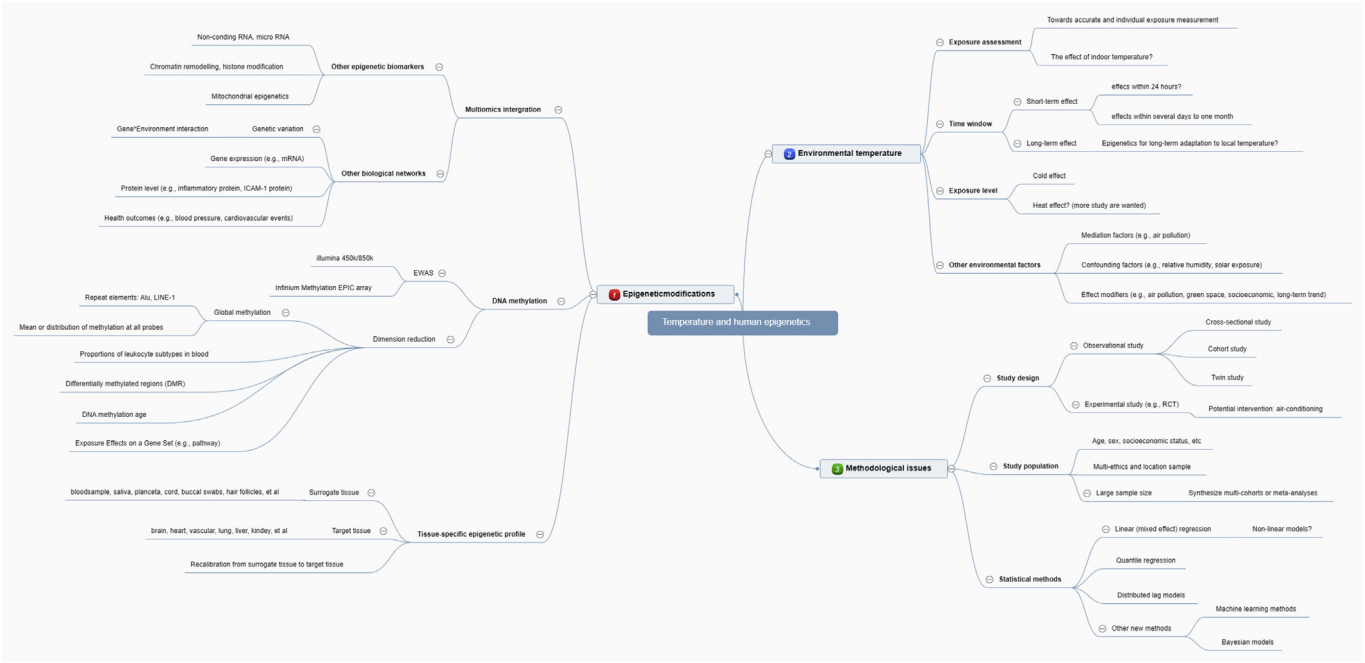

Fig. 2. Mind map of the current and future epidemiological studies on the association between environment temperature and human epigenetics.

(Abraham et al., 2018; Baccarelli et al., 2009; Bind et al., 2014), proportions of leukocyte subtypes (Gao et al., 2019) in blood have been applied in the studies included. There are still other dimension reduction approaches, such as DNA methylation age (McEwen et al., 2018), exposure effect on a gene set (e.g., pathway) (Sofer et al., 2012), yet to be explored.

4.1.3. Tissue-specific epigenetic profile

Last but not the least, human epigenetic profiles are tissue-specific (Slieker et al., 2013). Most epidemiological studies rely on easily accessible tissues such as peripheral blood samples, saliva, buccal swabs and/or hair follicles (Slieker et al., 2013). Findings based these tissues have the advantage of being easy for population health translation. However, epigenetic profiles in surrogate tissues like blood samples may not actually reflect epigenetic status in the target organ. For example, Lim et al.'s study explored the mediation role of DNA methylation in the association between low temperature and high blood pressure (Lim et al., 2017). In this study, methylation measured in white blood cells did not necessarily represent the methylation of target organs (e.g., vessels, kidney) to regulate blood pressure.

Cross-tissue concordance in environment induced epigenetic changes might be higher in early development (Heijmans et al., 2009), but might be lower in old age due to tissue-specific epigenetic drift (Mill and Heijmans, 2013; Thompson et al., 2010). The concordance also depends on specific tissues and CpG sites (Davies et al., 2012; Dick et al., 2014; Huang et al., 2016; Slieker et al., 2013; Sullivan et al., 2006). Therefore, we need to be careful to interpret results based on surrogate tissues like blood samples or placenta. In this scenario, epigenetics in surrogate tissues might only serve as a biomarker of environmental exposure, rather than the true mediator between exposure and health outcomes (Ladd-Acosta, 2015). However, a method with the potential to recalibrate the DNA methylation in a surrogate tissue to the DNA methylation in the target tissue has been developed (Ma et al., 2014). This method might be applied in future studies to gain more robust insights into the underlying epigenetic mechanisms between temperature and health.

4.2. Environmental temperature

4.2.1. Exposure assessment

The measurement of temperature exposure in existing studies was restricted to outdoor ambient temperature measured by a nearby meteorological station. Because the exposures were not measured at an individual level, the underestimation of the association due to non-differential measurement error could not be excluded. Future studies may move towards accurate personal temperature measurement (e.g. through wearable monitors) (Kuras et al., 2017) just as some air pollution studies have done (He et al., 2010). In addition, although all existing studies focused exclusively on outdoor temperature, indoor temperature is equally or even more important (White-Newsome et al., 2012). People living in developed nations spend about 90% of their time indoors, and indoor temperature has also been linked to respiratory and cardiovascular distress (Uejio et al., 2016). Unfortunately, the effects of indoor temperature on human epigenetics remains unknown, which needs further research.

4.2.2. Time windows

The time window of temperature exposure varied slightly between studies, but they mainly focused on the short-term effects within one month. However, both short-term and long-term suboptimal temperatures have been linked to health outcomes (Costello et al., 2009; Ye et al., 2012; Zanobetti and O'Neill, 2018). Future research should also explore the effect of long-term temperature on human epigenetics. This will have important implications for the biological adaptation to climate change (Barreca et al., 2016; Carson et al., 2006; Gasparrini et al., 2015a; Kysely and Plavcova, 2012). Meanwhile, studies have also suggested the effect of hourly temperature on health (Cheng et al., 2017; Guo, 2017). Therefore, to explore the epigenetic effects of temperature functions within 24 h is another promising direction. However, epigenetic status might fluctuate naturally within one day (Lim et al., 2014). It is important to consider adjusting for the circadian rhythm by study design (e.g., by taking the blood or tissue at similar time) or statistical methods (e.g., by including a natural cubic spline

of the exact clock time of taking tissue) when evaluating the epigenetic impacts of temperature on hourly or shorter scales.

4.2.3. Exposure level

The exposure levels in the seven studies included were restricted to moderate and low temperatures. The implications of existing studies mainly suggested the adverse health impacts of low temperature rather than high temperature. For example, Bind et al. (2016a) found that temperature decrease was associated with hypomethylation of ICAM-1, leading to increased expression ICAM-1 protein related to higher risk of cardiovascular events (Luc et al., 2003; Postadzhiyan et al., 2008). Similarly, Lim et al. (2017) revealed the mediation role of hypermethylation of ZKSCAN4 in the link between low temperature and high diastolic blood pressure. Although both low and high temperatures are associated with increased health risk (Chen et al., 2018; Gasparrini et al., 2015b), limited understanding of the effect of high temperatures on human epigenetics could be obtained from existing studies. However, interest in heat effects has been and will be increasing given the global warming trend (International Energy Agency, 2015). This is a major research gap that needs future studies to fill.

4.2.4. Other environmental factors

There are other environmental factors that also need to be considered when evaluating the effects of temperature on epigenetic regulation. They may confound, mediate or modify the effect of temperature on human epigenome. Air pollution has been frequently adjusted for in epidemiological analyses of the association between temperature and health outcomes. However, as argued by Buckley et al. (2014), in most scenarios, ambient temperature affects air pollution rather than the converse. Therefore, air pollution is more likely to be a mediator rather than confounder between temperature and health. Adjusting for air pollution would lead to biased estimation of the health impacts of ambient temperature. Since epigenetic changes are similar with health outcomes, we should also not adjust for air pollution when evaluating the association between ambient temperature and human epigenetic changes (Bind et al., 2014). Nevertheless, many studies have linked human epigenetic changes to air pollution exposure (Alfano et al., 2018), so it would still be interesting to include air pollution data to evaluate its mediating effect between temperature and epigenetics.

Relative humidity and solar exposure are potential confounders which need adjustment if with available data. Previous studies have also suggested many factors that could modify people's vulnerability to cold and heat, including air pollution, green space, socioeconomic status et al. (Romero-Lankao et al., 2012; Vicedo-Cabrera et al., 2019). Stratification analyses or adding interaction terms would provide some interesting information on whether epigenetic effects of temperature could be modified by those factors. For example, the impacts of high temperature on DNA methylation might be stronger with higher air pollution or less surrounding green space, as suggested by epidemiological studies (Parry et al., 2019; Schinasi et al., 2018). Given the observed long-term decrease in the heat-mortality association (Barreca et al., 2016; Carson et al., 2006; Gasparrini et al., 2015a; Kysely and Plavcova, 2012), whether there is a long-term trend in temperature-epigenetics association would also be an interesting topic.

4.3. Methodological issues

4.3.1. Study design

The seven studies included are all observational, either cohort or cross-sectional studies. A cross-sectional design has the advantages of low cost and being easy to conduct. However in a cross-sectional study, the exposure, epigenetic biomarkers, and health outcomes are all measured at one time point or within a short period, without repeat measurements. It is difficult to make causal inferences from this design because the temporality between exposure, epigenetic changes and health outcomes cannot be determined. For example, we can hardly know whether the epigenetic changes caused the high blood pressure or the reverse. Also, it remains uncertain about whether the epigenetic changes arose before or after the exposure time window.

A cohort study with repeat measurements could help to solve the problem of temporality or reverse causation, if the epigenetic status is measured after the exposure and before the onset of phenotype. This design could help establish the potential mediating role of epigenetic changes between temperature exposure and health outcomes. However, a cohort study usually costs much more than a cross-sectional study, and new bias may arise because of attrition during follow-up.

Another observational design in epigenetic epidemiology is twin study, especially of monozygotic twins. This design could well adjust for the potential confounding effects of genetic background and the shared environment of twins (Bell and Saffery, 2012; Mill and Heijmans, 2013). The Inference about Causation through Examination of FAmiliaL CONfounding (ICE FALCON) based on twin study is a powerful method to perform causal inference (Bui et al., 2013; Stone et al., 2012). ICE FALCON analyses have performed as well as Mendelian Randomisation (MR) in establishing the causal effects of smoking and body mass index (BMI) on DNA methylation (Li et al., 2019; Li et al., 2018b).

Differing from observational designs, an experimental design especially randomized controlled trial (RCT) could provide high-quality evidence, although at a high cost. In an RCT, participants are assigned to intervention or control group in a random manner. A good randomisation procedure ensures that both measured and unmeasured confounders are evenly distributed across groups, thereby limiting bias that could hardly be eliminated in observational designs. Li et al. performed a randomized double-blind crossover trial (a type of RCT) to evaluate the association between short-term exposure to fine particulate air pollution and genome-wide DNA methylation (Li et al., 2018a). This trial is a good example of how to perform a RCT to evaluate epigenetic effects of environmental exposure. Future studies may use similar design to evaluate the causal effect of environmental temperature on human epigenetics if ethical requirements are met. In such studies, air-conditioning might serve as a potential intervention.

4.3.2. Study population

The studies included focused on either elderly people or infants. Future studies may do more work in children, adolescents and young adults. Some epidemiological evidence have suggested that both children and elderly people are vulnerable population subgroups to temperature-related morbidity (Zhao et al., 2018; Zhao et al., 2019a). It would be interesting to test whether children and the elderly higher vulnerability also holds for temperature-related epigenetic changes. The existing studies also have limited diversity of ethnicity (six mainly in people of European ancestry (Abraham et al., 2018; Baccarelli et al., 2009; Bind et al., 2016a; Bind et al., 2014; Bind et al., 2016b; Gao et al., 2019), and only one in Asian people (Lim et al., 2017)), locations (five in USA, one in France, and one in South Korea, see Table 1). The diversity in ethnicity and locations need to be improved by future studies, which will provide more generalized implications.

Sample size is a key issue of epigenetic epidemiology. The final choice of sample size is a trade-off between budget and statistical power. Some researchers have tried to estimate suitable sample size for EWAS study based on case-control and monozygotic twin

design (Tsai and Bell, 2015). However, this may not apply to studies on temperature and epigenetics, given the largely unknown effect size. Many epidemiological studies on the association between air pollution and human epigenetics might serve as a good reference on the selection of sample size (Alfano et al., 2018). With increasing evidence in future, synthesising data from multiple cohorts or using meta-analyses to combine published studies are promising approaches to increase the statistical power and detect relatively small epigenetic changes induced by temperature.

4.3.3. Statistical methods

Linear regression and linear mixed effect regression were the most widely used statistical model in the seven studies included. However, the relationships between temperature and health (e.g. mortality (Chen et al., 2018; Gasparrini et al., 2015b), blood pressure (Li et al., 2016)) are often non-linear. Future studies may consider using non-linear models to evaluate the effect of temperature on human epigenetic modifications. Moreover, linear (mixed effect) regression models can only evaluate the mean difference in epigenetic changes at different temperature. However, the distribution of epigenetic changes at different temperature may not differ only by their means, but also (even only) by their lower or upper quantiles (Beyerlein, 2014). In that case, quantile regression would be an important method to identify temperature related epigenetic changes omitted by linear regression. Taking the study of Bind et al. as an example, methylation at iNOS was not significantly associated with temperature when using linear mixed effect model (Bind et al., 2014), but the association became significant for iNOS methylation in the lower quantiles when using quantile regression (Bind et al., 2016b). Another important consideration when modelling epigenetic impacts of temperature is the lag effects. For example, the impacts of low temperature on mortality may lag for around 21 days, while the impacts of high temperature may lag for up to 10 days (Chen et al., 2018; Gasparrini et al., 2015b). The lag effects of temperature on epigenetic changes could be captured by distributed lag models (DLM) (Gasparrini, 2011) which was used by Bind et al. (2014). In addition, there are some other new statistical methods have been introduced to epigenetic studies, such as Bayesian models (Lock and Dunson, 2017) and machine learning models (Holder et al., 2017; Ladd-Acosta et al., 2016).

5. Conclusions

Epidemiological evidence for the impacts of environment temperature on human epigenetics remains scarce. They are limited to short-term linear effect of cold temperature on DNA methylation in elderly people and infants. More studies are needed to broaden our understanding of temperature related epigenetic changes, especially under a changing climate. A huge space has been left for future studies, including more EWAS study, deeper mining of DNA methylation data, effects on other epigenetic biomarkers, integration of multiple biological networks, epigenetic profiles in tissues other than blood and placenta sample. The effect of long-term exposure to local temperature, potential non-linear effect, the effect of hot temperature, the interaction between temperature and other environmental factors are also yet to be explored. Improvements could also be made in regard to study design, study samples and statistical models.

Main findings

Existing epidemiological evidence about the impacts of environment temperature on human epigenetics remains scarce and limited, and more studies are wanted.

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Declaration of competing interest

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Appendix A. Supplementary data

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