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Forensic Epigenetic Approaches in Human Biological Samples from Medico-Legal Investigations: A Systematic Review of Public Health

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ABSTRACT

Forensic epigenetics has emerged as a promising extension of conventional forensic genetics, enabling the inference of physiologically and socially relevant characteristics from biological evidence beyond individual identification. In particular, DNA methylation-based approaches have demonstrated utility in estimating age, sex, and lifestyle-related traits, with growing relevance for medico-legal investigations and public health intelligence. This systematic review synthesizes current evidence on forensic epigenetic methodologies applied to human biological samples, with a focus on their applications in age, sex, and lifestyle estimation.

A systematic literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar using predefined search strategies. Study selection was guided by the Population-Exposure-Outcome (PEO) framework, while methodological quality was appraised using the Critical Appraisal Skills Programme (CASP) checklist. Owing to methodological heterogeneity among included studies, a narrative synthesis approach was employed. Five studies met the inclusion criteria. DNA methylation-based age estimation emerged as the most robust and consistently validated application, particularly using age-associated CpG markers such as ELOVL2, although performance varied by tissue type. Epigenetic approaches to sex estimation and biological differentiation demonstrated potential, particularly in resolving complex forensic scenarios such as monozygotic twin discrimination but remain less mature than age prediction models. Additionally, lifestyle and environmental exposures were shown to modulate epigenetic signatures, underscoring their dynamic nature. Tissue specificity significantly influenced analytical accuracy, with blood and semen yielding more stable and reliable signals compared to touch DNA.

DNA methylation-based forensic epigenetic approaches represent a valuable tool for age estimation and supplementary biological inference in medico-legal contexts. Despite ongoing methodological and interpretative challenges, these approaches hold substantial promise for advancing forensic investigations and informing population-level public health applications.

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Introduction

Human biological samples from medico-legal investigations refer to biological materials obtained during legal enquiries, specifically in criminal, civil, or humanitarian contexts [1]. These samples could be blood, saliva, semen, hair, bone, teeth, skin cells, or other tissue pieces taken from crime scenes, disaster sites, unidentified human remains, or victims and suspects [2]. In forensic practice, these samples are frequently constrained in quantity, environmentally degraded, or temporally old, hence complicating traditional DNA profiling methodologies [3]. Medico-legal investigations necessitate contextual biological information, such as the probable age, sex, or lifestyle characteristics of an unidentified individual, to bolster investigative leads, victim identification, and population-level public health insights [4,5].

Forensic epigenetic methodologies have developed into efficient tools for deriving supplementary biological information from

human biological specimens [6]. Epigenetics denotes heritable yet reversible alterations that govern gene expression without affecting the fundamental DNA sequence, with DNA methylation being the most well examined mechanism in forensic research [7]. Epigenetic patterns, unlike genetic markers, are dynamic and influenced by developmental stages, environmental exposures, and behavioural factors [8]. Recent developments in high-throughput sequencing and methylation-specific assays have made it possible to study epigenetic markers in forensic materials that are of low quality or only a small amount [9]. Thus, forensic epigenetics enhances the application of biological evidence beyond identification verification, providing probabilistic assessments of biological characteristics pertinent to medico-legal scenarios [10,11].

Forensic epigenetics is especially useful for figuring out someone's age, sex, and lifestyle, which is important for public health [12]. DNA methylation-based age prediction algorithms have shown great accuracy in diverse tissues, which makes them useful for figuring out the age of people whose identities are unknown [5]. Estimating sex by epigenetic markers offers supplementary or alternative methods when genetic sex markers are compromised

or unclear [9]. Moreover, lifestyle-related epigenetic markers linked to smoking, alcohol intake, food, physical activity, and environmental pollutant exposure provide insights into the behavioural and social determinants of health [13]. In medico-legal and humanitarian investigations, these applications can assist in missing-person enquiries, disaster victim identification, and epidemiological surveillance, thereby integrating forensic science with public health [8,14,15].

Even though there has been methodological advancement, forensic epigenetics is still not widely used to study public health-related outcomes. Current research exhibits significant variability in study design, biological matrices, marker selection, analytical platforms, and population representation, hence constraining comparability and practical application [16,17]. There is little integrated evidence regarding how epigenetic estimations from medico-legal samples might contribute to overarching public health objectives, including understanding of population-level exposure patterns and health disparities. Ethical, legal, and interpretation problems further impede implementation, especially in low- and middle-income contexts [18]. So far, there has not been a full systematic review that brings together all the information on forensic epigenetic methods used on human biological samples, with an emphasis on their application for age, sex, and lifestyle for public health purposes. Consequently, the main aim of this review is to comprehensively assess and integrate the existing information about forensic epigenetic methodologies employed in medico-legal investigations and their utility in predicting age, sex, and lifestyle attributes relevant to public health.

Methods

Data Extraction, Quality Assessment and Synthesis

A standardised data extraction form was developed and pilot-tested to ensure consistency. Extracted data included bibliographic details, study aims, design, sample size, forensic context, epigenetic markers, analytical methods, and key findings on age, sex, and lifestyle estimation. Data extraction was conducted independently with cross-verification to minimise errors and ensure reliability.

Methodological quality was assessed using the Critical Appraisal Skills Programme (CASP) checklist a recognised tool for evaluating research rigour, validity, and relevance [22,23]. It examines key domains including study design, data collection, analysis, and validity of findings. Each study was independently appraised and classified as high, moderate, or low quality. Studies rated as low quality were excluded due to major methodological limitations, ensuring that only robust evidence informed the review.

A narrative synthesis approach was used to integrate findings [24]. This was appropriate given the heterogeneity in study design, sample types, epigenetic markers, and analytical methods, which limited the feasibility of meta-analysis [25]. This approach enabled systematic comparison and interpretation of patterns across studies, providing a coherent understanding of forensic epigenetic applications in medico-legal and public health contexts [24].

Eligibility Criteria

The Population–Exposure–Outcome (PEO) paradigm guided the criteria for including and excluding studies in this review (19). This framework is especially useful for reviews that focus on observational and applied research. The population (P) consisted of human biological specimens collected in medico-legal or forensic settings. The exposure (E) involved the utilisation of forensic epigenetic methodologies, specifically DNA methylation-based techniques. The outcomes (O) encompassed age estimation, sex estimation, and lifestyle or exposure-related inferences pertinent to public health. To make sure that the methods were sound and the results were useful, more criteria were added to the study design, timeframe, language, and type of publication. Table 1.0 shows the inclusion and exclusion criteria for this review.

Table 1.0: Inclusion and Exclusion Criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Human biological samples from medico-legal or forensic investigations (e.g. blood, saliva, semen, bone, teeth)	Animal studies; non-forensic or purely clinical samples
Exposure	Forensic epigenetic approaches, including DNA methylation or other epigenomic markers	Studies focusing solely on genetic (non-epigenetic) markers
Outcomes	Age, sex, and/or lifestyle or exposure estimation (e.g. smoking, alcohol, environmental exposures)	Studies without relevant estimation outcomes
Study design	Observational studies, experimental laboratory studies, validation studies	Editorials, commentaries, opinion pieces
Timeframe	Studies published from 2015 to 2025	Studies published before 2015
Language	English-language publications	Non-English publications without translation
Publication type	Peer-reviewed journal articles	Conference abstracts only, theses, grey literature (unless methodologically robust)

Result

Overview of Search Process

A search through PubMed/MEDLINE, EMBASE, CINAHL, Scopus, Web of Science, and the Cochrane Library yielded a total of 955 studies. Following record de-duplication and initial study screening, 331 studies were eligible for full text screening. Studies were excluded based on the predetermined eligibility criteria leaving 5 studies which met the review’s inclusion criteria. Figure 1 depicts the PRISMA flow chart, which shows the study selection process and reasons for exclusion of studies.

Figure 1: PRISMA Flow Diagram (21), Demonstrating the Study Selection Process

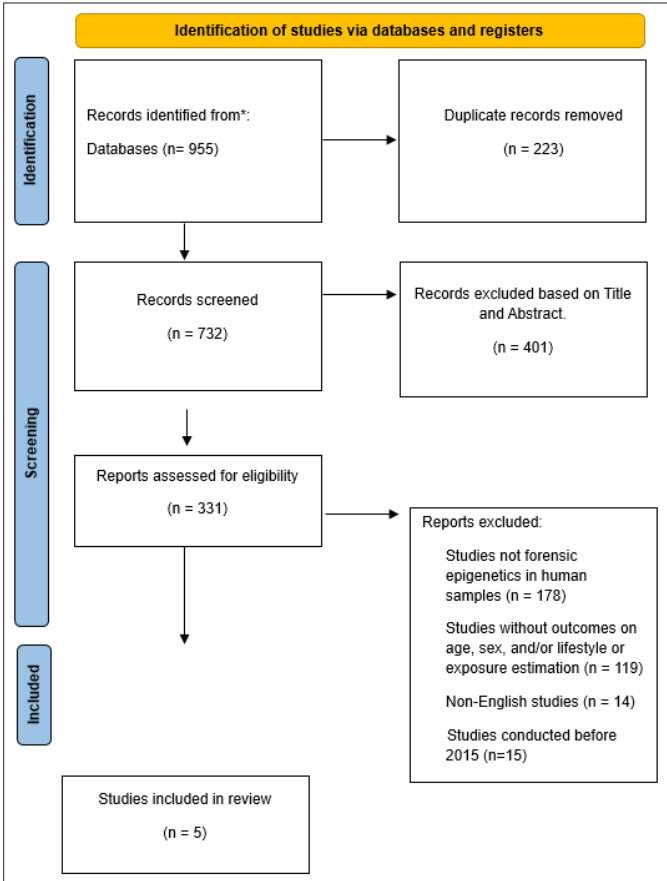


Table 2.0 details the characteristics of included studies. A total of five studies were included in the synthesis of this review. These studies were conducted in China, Japan, Indonesia, United States, and Serbia.

Table 2.0: Characteristics of Included Studies

Author(s) and year of publication	Study aim	Country and setting	Sample size and participant characteristics	Study design and methodology	Exposure variables	Outcome measures	Study findings
Xu et al., (26)	To assess whether LINE-1 DNA methylation can discriminate monozygotic twins in forensic contexts	China; forensic medicine laboratories in Hebei, Shanxi, and Yunnan provinces	176 twin pairs (119 monozygotic, 57 dizygotic); males and females aged 0–74 years; blood and buccal cell samples	Cross-sectional forensic epigenetic study; bisulfite conversion and pyrosequencing of three LINE-1 CpG sites; comparative twin-pair analysis	LINE-1 global DNA methylation levels; tissue type; age; sex	Ability to discriminate MZ twins; methylation differences across tissues; influence of demographic factors	LINE-1 methylation showed tissue-specific patterns and modest twin-to-twin variability. Approximately 12.6 % of MZ twin pairs could be differentiated. Findings support LINE-1 methylation as a complementary tool when STR profiling fails
Hamano et al., (27)	To develop and validate a practical forensic age-prediction model for saliva and cigarette butt samples	Japan; forensic medicine departments and police forensic laboratories	263 saliva samples from healthy donors aged 1–73 years; 16 cigarette butt samples; training set (n = 197), test set (n = 50)	Experimental validation study; methylation-sensitive high-resolution melting (MS-HRM); support vector regression modelling	DNA methylation scores of ELOVL2 and EDARADD; sample type; smoking status	Chronological age prediction accuracy (MAD, R ²)	Saliva-based model achieved MAD = 5.96 years (training) and 6.25 years (test). Application to cigarette butts yielded MAD = 7.65 years. Smoking had no significant impact, demonstrating forensic applicability to trace evidence

Suryani et al., (17)	To compare and validate tissue-specific DNA methylation models for forensic age estimation	Indonesia; forensic and biomedical research centres in Palembang, South Sumatra	150 healthy male volunteers aged 18–65 years; semen, saliva, and high-yield touch DNA samples	Laboratory-based validation study; bisulfite conversion and targeted pyrosequencing of five CpG markers; multiple linear regression with cross-validation	DNA methylation levels at ELOVL2, FHL2, TRIM59, KCNQ1DN, C1orf132; tissue type	Age-prediction accuracy (MAD, R ² , prediction intervals)	Semen and saliva models showed high accuracy (MAD = 3.19 and 3.55 years). Touch DNA model was less precise (MAD = 5.49 years) but informative. Highlights importance of tissue-specific epigenetic models
Anaya et al. (1)	To evaluate DNA methylation-based age prediction models using decedent blood samples for forensic casework	United States; academic and forensic science laboratories	264 decedent blood samples; adult age range; varying DNA quality and degradation indices	Observational forensic epigenetic study; bisulfite conversion and pyrosequencing of five age-associated CpG markers; training and test set modelling	CpG-specific DNA methylation levels; DNA degradation index; age group	Accuracy of age estimation; deviation between predicted and chronological age	The age-prediction model produced useful forensic estimates. Accuracy declined with increasing age, particularly >50 years. DNA degradation did not consistently predict methylation failure, supporting applicability in post-mortem samples
Pierre Louis, (28)	To examine the effects of age and sex on the discriminatory power of cg18562578 DNA methylation for monozygotic twin differentiation	Serbia (sample collection) and USA (laboratory analysis at John Jay College of Criminal Justice)	332 monozygotic twins from the Twin Identification Epigenetic Study (TIDES); males and females across multiple age groups; saliva samples	Cross-sectional forensic epigenetic study; bisulfite conversion followed by nested qPCR; relative quantification analysis	DNA methylation level at cg18562578; age; sex	MZ twin discrimination rate; association between methylation, age, and sex	cg18562578 showed strong discriminatory potential for MZ twins. Age significantly influenced methylation variability, while sex had a smaller effect, underscoring the need to account for demographic factors in forensic epigenetic analyses

Critical Appraisal of Included Studies

The CASP checklist was employed for the critical appraisal of the five studies that were included had a moderate to high level of methodological quality. All studies had clear research goals and employed the right forensic epigenetic designs to meet the objectives, age estimation and monozygotic twin discrimination [26,27,17,1,28]. The study samples, data collection methods, exposure variables, and outcome measures were all well-defined, and the analytical methods were strong, which adds to the credibility and forensic relevance of the results. A significant strength of the studies was their evident relevance to medico-legal investigations. Nevertheless, many limitations were recognised, especially the inconsistent identification and adjustment for potential confounding variables, including biological ageing variability, DNA degradation, lifestyle factors, and ancestry. Moreover, ethical considerations were inconsistently reported among the investigations. Even with these restrictions, the results of each study backed up its conclusions. In general, the evidence base was robust enough to support narrative synthesis, but it also showed that future forensic epigenetic research needs better control of confounding factors and clearer reporting. Table 3.0 shows the critical appraisal of the studies included.

Table 3.0 Critical Appraisal of the Included Studies

CASP appraisal questions	Xu et al., (26)	Hamano et al., (27)	Suryani et al., (17)	Anaya et al., (1)	Pierre Louis, (28)
1. Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
2. Was the research design appropriate to the aims of the study?	Yes	Yes	Yes	Yes	Yes
3. Was the recruitment strategy appropriate to the aims?	Yes	Yes	Yes	Yes	Yes
4. Were the study samples adequately described?	Yes	Yes	Yes	Yes	Yes
5. Was the data collection method clearly described?	Yes	Yes	Yes	Yes	Yes
6. Were the exposure variables measured accurately?	Yes	Yes	Yes	Yes	Yes

7. Were the outcome measures clearly defined and reliable?	Yes	Yes	Yes	Yes	Yes
8. Were confounding factors identified?	Can't tell	Yes	Yes	Yes	Yes
9. Were confounding factors adequately accounted for in the analysis?	No	Yes	Yes	Can't tell	Yes
10. Was the data analysis sufficiently rigorous?	Yes	Yes	Yes	Yes	Yes
11. Are the results clearly presented?	Yes	Yes	Yes	Yes	Yes
12. Are the findings precise and credible?	Yes	Yes	Yes	Yes	Yes
13. Are the findings applicable to forensic practice?	Yes	Yes	Yes	Yes	Yes
14. Were ethical issues considered and addressed?	Can't tell	Yes	Yes	Can't tell	Yes
15. Do the conclusions follow logically from the results?	Yes	Yes	Yes	Yes	Yes

Discussion

Five studies were included in this review, addressing DNA methylation for age estimation, epigenetic sex estimation and differentiation, the influence of lifestyle and environmental factors, tissue specificity, and public health applications. DNA methylation consistently emerged as the most robust and validated tool for forensic age estimation, particularly through CpG markers such as ELOVL2, FHL2, TRIM59, C1orf132, and KLF14 [1]. demonstrated strong correlations between methylation levels and chronological age in post-mortem samples, with mean absolute deviations (MADs) of 7.4–7.6 years, confirming applicability even in degraded specimens. Greater predictive accuracy was observed in living samples, particularly semen and saliva (MADs 3.19–3.55 years), although performance varied by tissue type. This tissue dependency was further supported by, while showed that trace samples such as cigarette butts could still yield reliable estimates [17,26,27]. However, reduced accuracy in older individuals was consistently reported, likely due to epigenetic plateauing [1-26].

Epigenetic variation also contributes to sex estimation and biological differentiation, although less reliably than age prediction. identified sex-specific LINE-1 methylation differences, attributed to X-chromosome inactivation, while demonstrated that methylation variability can aid in differentiating monozygotic twins, although age-related effects were more pronounced. noted sex as a potential confounder in methylation patterns, whereas limited their cohort to males, improving internal validity but restricting broader inference [26,28,1,17]. These findings highlight that epigenetic sex estimation remains supplementary but valuable in complex forensic scenarios.

Lifestyle, environmental, and biological factors were shown to influence epigenetic signatures, reinforcing their relevance to public health. reported context-dependent effects of lifestyle variables, while found no significant impact of smoking on age prediction accuracy [26,27,1]. observed discrepancies between chronological and epigenetic age, particularly in older individuals, suggesting the influence of cumulative environmental stressors. Similarly, supported the concept that epigenetic markers reflect combined internal and external influences. Environmental exposure, including UV and oral environmental variation, was also identified as a potential source of variability [17].

Tissue specificity emerged as a critical determinant of analytical performance [26]. demonstrated distinct methylation patterns between blood and buccal cells, reported highest accuracy in semen, followed by saliva, with reduced performance in touch DNA due to cellular heterogeneity [17]. Blood-based models remained useful in post-mortem contexts despite reduced accuracy in older individuals, confirmed the viability of non-traditional

samples. Overall, semen and blood provided the most stable signals, whereas touch DNA showed the greatest variability [1-27]. Beyond individual identification, the findings underscore the growing role of forensic epigenetics in public health. Population-specific models contribute to more equitable applications across diverse groups, while methylation markers may reflect cumulative exposures relevant to health further demonstrated discrepancies between biological and chronological age, indicating potential for assessing health status [17,26,1]. Collectively, these studies position forensic epigenetics as a bridge between medico-legal investigations and population-level health insights.

This review aligns with foundational studies demonstrating the reliability of DNA methylation-based age estimation, consistent with earlier work by, while extending applicability to degraded and trace samples [17,26,27,29]. However, reduced predictive accuracy in older populations remains a limitation, as also noted by [10]. Epigenetic approaches to sex estimation remain supplementary, with findings from [26,2]. supporting biological plausibility, and twin studies aligning with earlier evidence of epigenetic divergence [30]. Lifestyle and environmental influences observed in this review are consistent with epidemiological findings such as although forensic applications have yet to fully integrate these variables [31,32].

Overall, forensic epigenetics demonstrates strong potential for integration into medico-legal and public health systems. Nonetheless, challenges persist, including methodological variability, tissue dependency, limited population diversity, and ethical considerations. Future research should prioritize large, diverse, and longitudinal datasets, alongside the incorporation of lifestyle variables, to enhance both forensic applicability and public health relevance.

Conclusion

The aim of this review was to systematically synthesise data regarding forensic epigenetic approaches used on human biological specimens from medico-legal investigations, emphasising its public health applications for estimating age, sex, and lifestyle. The results indicate that DNA methylation-based techniques, particularly age estimate utilising well-validated CpG markers, constitute the most advanced and dependable application of forensic epigenetics to date, exhibiting consistent efficacy across various biological matrices. Epigenetic methods for sex estimate and biological differentiation serve as complementing tools rather than independent solutions, providing enhanced use in intricate identification contexts, such as the differentiation of monozygotic twins. The review also emphasises that epigenetic markers are influenced by lifestyle, environmental exposures, and biological

processes, hence strengthening their interpretation as dynamic indicators of cumulative life course impacts. Tissue specificity became a crucial factor influencing analytical performance, significantly affecting the selection and interpretation of forensic evidence. These findings establish forensic epigenetics as a potential conduit between medico-legal investigation and public health intelligence, capable of producing ethically grounded, population-relevant insights, while highlighting the necessity for tissue-specific, population-validated models and prudent implementation in practice.

Declarations

Ethics Approval and Consent to Participate

This study is a systematic review of previously published literature on forensic epigenetic approaches in medico-legal investigations. It does not involve direct interaction with human participants or the use of identifiable personal data. Therefore, ethical approval was not required.

Consent for publication

Not applicable

Availability of Data and Material

All data analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

ULU conceived and designed the study, conducted the literature search, performed data extraction and analysis, and drafted the manuscript. AGR contributed to study design, data interpretation, and critically revised the manuscript. NDA participated in data extraction, quality assessment, and manuscript review. AJ contributed to literature screening, data synthesis, and manuscript editing. IBO contributed to data interpretation and critically revised the manuscript for important intellectual content. All authors read and approved of the final manuscript.

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