RESEARCH PAPER

Environmental Stress, Epigenetic Regulation, and Ageing Outcomes: A Secondary-Data Framework for Investigating Air Pollution, Noise, and Biological Ageing in Adolescents

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Abstract
Environmental exposures may influence health through biological pathways that connect oxidative stress, endocrine responses, inflammation, and epigenetic regulation. This paper examines the plausibility of associations between urban air pollution and environmental noise and ageing-related biomarkers among adolescents aged 15–18 years. It develops a secondary-data observational framework using ambient fine particulate matter ($PM_{2.5}$), environmental-noise estimates, DNA-methylation-based age measures, inflammatory markers, and cortisol. The proposed analytical strategy includes exposure-group comparisons, correlation analysis, multivariable regression, confounder adjustment, and sensitivity analyses. Evidence from human studies indicates that air pollution has been associated with some measures of epigenetic age acceleration, although estimates differ by pollutant composition, epigenetic clock, population, and study design. Childhood studies also suggest that early-life exposure may be associated with methylation-based ageing measures. Evidence concerning noise and cortisol is less consistent, underscoring the need for careful measurement and replication. A mechanistic framework is presented linking particulate exposure with oxidative stress and inflammatory signalling, and noise-related stress with hypothalamic–pituitary–adrenal-axis activity.

Keywords: Environmental stress; DNA methylation; Epigenetic ageing; Air pollution; Adolescents
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1. Introduction

Human health develops through interactions between inherited biology, behaviour, social conditions, and the physical environment. Urban residents may experience multiple exposures simultaneously, including fine particulate matter, traffic-related gases, transportation noise, limited access to green space, and socioeconomic stress. These exposures can act through overlapping physiological systems rather than as isolated hazards. Understanding whether cumulative environmental stress is associated with biological ageing is important because molecular changes may appear before clinical disease and may help explain how environmental disadvantage becomes embodied across the life course [1–3].

Epigenetics describes regulatory processes that influence gene activity without changing the underlying DNA sequence. DNA methylation, histone modification, and non-coding RNA regulation are among the mechanisms involved. DNA methylation at cytosine–phosphate–guanine (CpG) sites is particularly useful in population research because methylation patterns can be measured across the genome and used to estimate biological age. Epigenetic clocks combine methylation at selected sites to predict chronological age or related health characteristics. Horvath's multi-tissue clock demonstrated that methylation data could provide age estimates across diverse tissues, while later clocks were developed to capture healthspan, mortality-related risk, or pace of ageing [4–7].

Epigenetic age acceleration is commonly estimated as the difference or residual between methylation-predicted age and chronological age. It should not be interpreted as a direct measurement of every aspect of ageing, nor as a diagnosis. Different clocks capture different biological dimensions, and estimates can vary by tissue, cell composition, age range, and technical platform [5–7]. This distinction is particularly important in adolescence: many clocks were developed in broad age ranges or adult populations, and their validity in younger age groups must be assessed before their estimates are interpreted as evidence of accelerated ageing.

Air pollution is a plausible contributor to epigenetic change because inhaled particles and associated compounds can promote reactive oxygen species, oxidative stress, immune activation, and systemic inflammatory responses. Fine particulate matter ($PM_{2.5}$) can reach deep regions of the respiratory tract, and its biological effects depend not only on mass concentration but also on chemical composition and sources. Experimental and epidemiological studies have examined associations between particulate matter, inflammatory signalling, DNA methylation, telomere length, and methylation-based biological age [8–12]. Findings have not been uniform, which may reflect differences in exposure assessment, particle composition, participant characteristics, and the clock used.

Several human studies provide relevant evidence. In the KORA cohort, long-term air pollution exposure was associated with selected measures of biological ageing, although effect patterns differed by sex and ageing marker [8]. White and colleagues found that associations between $PM_{2.5}$ and methylation-based age varied across particulate-composition profiles, illustrating why a single pollutant concentration may not fully describe exposure-related risk [9]. A quasi-experimental panel study reported

short-term associations between $PM_{2.5}$ exposure and several methylation-based ageing measures in adults, with evidence consistent with inflammatory and oxidative pathways [10]. A study of prenatal and early-childhood exposure also reported associations between some pollutant exposures and epigenetic-age estimates in children, although direction and magnitude depended on exposure window and clock [11]. More recent longitudinal work has further examined traffic-related pollutants and ageing markers [12]. These findings support investigation but do not establish that the same associations occur in adolescents.

Environmental noise may operate through a partly different pathway. Perceived or measured noise can disturb sleep, increase annoyance, and activate stress-response systems. The hypothalamic–pituitary–adrenal (HPA) axis regulates cortisol release and adaptation to stress. Repeated activation may influence metabolic and immune regulation, although cortisol varies with time of day, sleep, medication, acute events, and sampling method [13–15]. Importantly, a recent analysis across European child cohorts did not find statistically significant associations between environmental noise and hair or urinary cortisol, indicating that a simple assumption of higher noise always producing higher measured cortisol is not justified [16]. This uncertainty makes noise exposure an important but empirically testable component of the proposed model.

Inflammatory mediators such as interleukin-6 (IL-6), tumour necrosis factor (TNF), and C-reactive protein (CRP) may provide complementary indicators of immune activation. Toll-like receptor (TLR) signalling and nuclear factor kappa B (NF-κB) are involved in inflammatory responses to environmental challenges. However, biomarker concentration is not specific to pollution: infection, adiposity, diet, physical activity, medication, and other conditions may also affect values [17–19]. DNA methylation is likewise influenced by age, sex, cell-type composition, smoking exposure, socioeconomic circumstances, and technical factors. A credible analysis therefore needs a prespecified confounder strategy and should avoid interpreting any single biomarker as proof of a causal pathway.

Life-course research also highlights the importance of social and environmental context. Exposure may cluster with housing quality, traffic proximity, access to green space, neighbourhood deprivation, family resources, and psychosocial stress. Studies of greenspace and stress suggest that the built environment may affect health through multiple pathways, potentially including epigenetic processes, but causal interpretation remains difficult [2,3]. Evidence from non-human systems, including studies of plant epigenetic responses and termite ageing, demonstrates that environmental stress can be linked to gene regulation and ageing-related biology; such findings are mechanistically informative but cannot be directly generalised to human adolescents [20,21].

Despite increasing interest in the environmental epigenome, several gaps remain. First, much of the epidemiological evidence on epigenetic age acceleration comes from adults, while adolescence is a period of rapid development and changing methylation patterns. Second, air pollution and noise are often analysed separately despite co-occurring in urban settings. Third, studies differ in their exposure windows, outcome clocks, biomarker assays, and confounder adjustment. Fourth, cross-sectional associations cannot determine whether exposure preceded the molecular outcome. The research gap is therefore not simply whether environmental stress is biologically plausible, but whether appropriately measured exposure is associated with reproducible ageing-related and inflammatory outcomes in adolescents.

The present paper develops a secondary-data observational framework to investigate adolescents aged 15–18 years living in higher- and lower-exposure urban settings. The primary research question is: are higher ambient $PM_{2.5}$ and environmental-noise exposures associated with epigenetic-age estimates, inflammatory markers, and cortisol concentrations in adolescents? The hypotheses are that higher exposure may be associated with altered methylation-based ageing measures and inflammatory biomarkers, while the direction and consistency of cortisol associations remain uncertain. The study is designed to assess associations, not to assume causal effects. By integrating environmental exposure assessment, biological outcomes, and confounder control, the framework aims to support a more rigorous understanding of environmental stress and biological ageing during adolescence.

2. Research Question and Hypotheses

Research question: Are higher ambient $PM_{2.5}$ and environmental-noise exposures associated with epigenetic-age estimates, inflammatory biomarkers, and cortisol concentrations among adolescents aged 15–18 years?

- H1: Higher $PM_{2.5}$ exposure is associated with differences in one or more inflammatory biomarkers after adjustment for prespecified confounders.
- H2: Higher $PM_{2.5}$ exposure is associated with methylation-based age estimates, although the direction and magnitude may differ by clock and exposure composition.
- H3: Environmental-noise exposure is associated with cortisol measures; the direction and consistency of this association are treated as uncertain.
- H4: Associations differ in robustness when exposure windows, clock measures, and confounder sets are varied.

3. Methodology

This paper uses a comparative observational framework based on secondary data and published cohort resources. The target population is adolescents aged 15–18 years, grouped by higher versus lower exposure to urban environmental stressors. No new participants were recruited for this manuscript, and no individual-level dataset or completed statistical output was supplied. Accordingly, the present paper specifies an analysis plan and synthesises existing evidence; it does not claim to

have completed a pooled analysis or generated new empirical estimates.

Exposure variables are annual or seasonally aligned ambient $PM_{2.5}$ concentrations and environmental-noise estimates obtained from documented public monitoring systems, government datasets, or validated geospatial exposure models. Biological outcomes, where compatible data are available, include DNA-methylation-based age estimates, inflammatory biomarkers (for example IL-6, TNF and CRP), and cortisol measured in a specified matrix such as saliva, urine, or hair. Measures from different matrices or assays should not be treated as interchangeable. Epigenetic clock selection must be justified for adolescent ages and the tissue sampled; clock algorithms and preprocessing procedures should be documented.

The analytical sequence begins with harmonisation of age, exposure period, units, assay methods, and covariate definitions. Descriptive summaries and distribution plots are used to inspect missingness, outliers, and group comparability. Pearson correlation is appropriate for approximately linear relationships with suitable distributions; Spearman correlation is used where rank-based analysis is more robust. Multivariable linear regression estimates associations between exposure and continuous outcomes. A general model is: $Y_i = \beta_0 + \beta_1 PM_{2.5i} + \beta_2 Noise_i + \beta_3 Age_i + \beta_4 SES_i + \beta_5 Lifestyle_i + \varepsilon_i$. Additional covariates may include sex, body mass index, smoking or second-hand smoke exposure, physical activity, diet, sleep, medication, infection status, and blood-cell composition, subject to availability and causal rationale.

Where data permit, pollutant and noise exposures are modelled jointly, with interaction terms considered only when prespecified and adequately powered. Repeated observations should be analysed using appropriate mixed-effects models. Missing data procedures must be reported transparently; imputation is appropriate only under defensible assumptions and with sufficient auxiliary information. Sensitivity analyses should compare exposure windows, alternative clock measures, complete-case and imputed analyses, and different confounder sets. A nominal target of 50–100 adolescents per exposure group was proposed in the source document, but a formal power calculation based on a defined primary outcome, expected effect size, variance, clustering, and missingness is required before finalising sample size. Ethical approval, data-use permissions, privacy protection, and special safeguards for minors are required for any new data linkage.

4. Results and Discussion

The first evidence theme is the association between air pollution and biological ageing. In a population-based KORA analysis, long-term exposure to $PM_{2.5}$ and traffic-related pollutants was associated with selected biological-ageing measures, but patterns varied by sex and by the marker used [8]. This result is important for the present framework because it indicates that environmental exposure may be reflected differently across ageing indicators. It also cautions against expecting every epigenetic clock to show the same response. White and colleagues reported that the association between $PM_{2.5}$ and methylation-based age varied across particulate-composition clusters, with positive, null, and inverse estimates across some comparisons [9]. The composition of pollution, not simply total mass, may therefore matter. These studies are consistent with an association between pollution and biological ageing in some settings, but they do not justify assuming a uniform effect in adolescents.

Evidence concerning early life is relevant but not definitive. A study of prenatal and early-childhood exposure examined several epigenetic clocks and found associations between some pollutant exposure windows and age acceleration in children; the observed pattern depended on the pollutant, timing, and clock [11]. Because developmental methylation changes differ from adult ageing patterns, this evidence supports age-appropriate analysis rather than direct extrapolation. A short-term quasi-experimental study in adults also reported associations between recent $PM_{2.5}$ exposure and several methylation-based ageing measures [10]. Such findings suggest that epigenetic markers may respond to environmental conditions over different time scales, but they do not establish whether short-term changes persist or indicate irreversible ageing.

More recent work continues to refine the exposure–ageing relationship. A longitudinal KORA analysis reported that increases in several traffic-related pollutants were positively associated with selected age-acceleration measures, with differences across clocks and subgroups [12]. A systematic review of chemical and climatic exposures and epigenetic ageing identified a substantial but heterogeneous body of human epidemiological evidence, emphasising that the exposure categories, study designs, populations, and clocks vary considerably [22]. Taken together, this literature suggests that the most defensible expectation is not a single universal pollution effect, but a possibility of clock-specific and exposure-specific associations that require replication and sensitivity analysis.

The second theme concerns the biological plausibility of oxidative stress and inflammation as intermediary processes. Particulate matter can promote oxidative stress and inflammatory responses, and NF-κB is a key regulator connecting cellular stress with inflammatory gene expression [17,18]. TLR-mediated recognition and immune activation may also contribute to pollutant-related inflammation [19]. IL-6 and TNF are relevant inflammatory mediators, while CRP provides a systemic marker that is often used in epidemiological research. Nevertheless, these biomarkers are nonspecific. An observed association between $PM_{2.5}$ and CRP would not, by itself, demonstrate that epigenetic changes mediate the relationship. Likewise, cross-sectional co-occurrence of exposure, inflammation, and methylation does not establish temporal ordering. Mediation would require stronger assumptions, well-timed measurements, and preferably longitudinal data.

The third theme is noise and endocrine stress. The proposed model suggests that chronic noise may disturb sleep and activate the HPA axis, potentially changing cortisol regulation. Experimental research has characterised HPA-axis and brain responses to loud noise, and broader reviews describe the complex human stress response [13,14]. However, cortisol is highly sensitive to sampling time, sleep-wake rhythms, acute stress, medication, and matrix. In the recent study using data from eight European birth cohorts, environmental-noise exposure was not significantly associated with hair or urinary cortisol in children [16]. This null finding should not be ignored. It suggests that any relationship may be modest, context-dependent, affected by measurement choices, or absent for particular exposure and outcome windows. The proposed study should therefore test rather than presuppose an increase in cortisol.

The fourth theme is the interpretation of DNA methylation and epigenetic clocks. Horvath's clock established the feasibility of methylation-based age estimation across many tissues [4], and later work has explained that clocks can capture overlapping but distinct biological dimensions [5–7]. Epigenetic age acceleration is generally defined relative to chronological age, often using residuals from a regression model. A positive residual indicates that the clock estimates an older age than expected for chronological age; it is not equivalent to a direct count of years of life lost. In adolescents, developmental calibration, tissue selection, cell composition, and algorithm suitability require special attention. The source proposal mentions the Horvath clock, but the final protocol should justify whether it is the most suitable clock for the available age range and specimen.

Table 1 summarises the principal variables and expected directions that would be evaluated. $PM_{2.5}$ is expected to relate to oxidative and inflammatory markers based on prior mechanistic and epidemiological evidence, while associations with methylation-based age may vary by clock and exposure composition. Noise–cortisol associations are treated as uncertain. DNA methylation changes are site-specific: global claims that all protective genes become hypermethylated or all inflammatory genes become hypomethylated would be overly broad. The direction and functional consequence of methylation depend on genomic location, cell type, regulatory context, and the gene involved.

Table 2 provides an evidence map. The most direct human evidence for the primary hypothesis comes from pollution–ageing studies and early-life cohort research [8–12]. Evidence on oxidative stress and inflammatory pathways provides mechanistic plausibility [17–19], while research on stress physiology and child noise exposure makes clear that endocrine findings need cautious interpretation [13,14,16]. Findings in plants and termites show that environmental stress can affect epigenetic or ageing-related biology in other organisms [20,21], but they are indirect evidence for human adolescents. The distinction between direct human evidence, mechanistic support, and cross-species analogy is necessary to avoid overstating the strength of the evidence.

Several analytical issues determine whether the proposed study can produce interpretable findings. Ambient exposure estimates can misclassify personal exposure because adolescents move between home, school, transport, and recreational settings. A single annual average may not capture exposure during a biologically relevant window. Noise estimates may describe outdoor levels rather than indoor exposure or perceived disturbance. Biological markers may be measured at different times and with different laboratory methods. In pooled secondary data, harmonisation should be performed before testing hypotheses, and study-specific differences should be handled through stratification, fixed effects, or random effects where appropriate. If sample size is small, a complex multi-pollutant model may be unstable; the primary exposure and outcome should be defined in advance.

Confounding and selection are equally important. Socioeconomic status can influence residential exposure and health-related outcomes, while diet, sleep, physical activity, adiposity, second-hand smoke, infection, and medication can influence biomarkers. Blood-cell composition is particularly relevant to methylation data because shifts in cell proportions can appear as methylation differences. Adjusting for every available variable is not necessarily appropriate: variables on the causal pathway may be mediators rather than confounders, and overadjustment can distort the target association. A directed acyclic graph and prespecified causal model would help distinguish confounders, mediators, and effect modifiers. Where feasible, repeated measurements and within-person comparisons can improve temporal inference.

Overall, the literature supports a biologically plausible but heterogeneous relationship between environmental exposures and ageing-related markers. The expected pattern is that higher $PM_{2.5}$ may be associated with selected inflammatory or epigenetic outcomes, while noise-related endocrine findings may be less consistent. Whether these relationships are detectable in adolescents remains an empirical question. The principal contribution of this paper is therefore a transparent, testable framework that links exposure measurement, biological outcomes, confounder control, and interpretation without presenting proposed results as observed facts.

Table 1. Variables, biological interpretation, and proposed direction

Variable / marker	Role in framework	Proposed expectation	Interpretive caution
$PM_{2.5}$ / traffic pollutants	Primary environmental exposure	Higher exposure may correlate with selected inflammat	Ambient measures may misclassify personal exposure

		ory or ageing markers	
Environmental noise	Co-exposure / stressor	Possible association with cortisol or sleep-related stress	Child cohort evidence for cortisol is not consistently positive
DNA methylation clock	Primary ageing-related outcome	Potential clock-specific age acceleration	Clock validity in adolescents and tissue must be justified
IL-6 / TNF	Inflammatory outcomes	Potential increase with inflammatory activation	Nonspecific; affected by infection and other factors
CRP	Systemic inflammation marker	Potential increase under sustained inflammation	Not specific to pollution or epigenetic mediation
Cortisol	Stress-response outcome	Direction uncertain; depends on timing and matrix	Circadian and sampling effects are substantial
Covariates	Confounding control	Age, sex, SES, diet, activity, sleep, smoke exposure, cell composition	Select using causal rationale; avoid overadjustment

Table 2. Evidence map and relevance to the proposed adolescent study

Evidence area	What prior research suggests	Relevance / limitation
Air pollution and biological ageing	Some long-term pollution studies report associations with selected ageing markers [8,9,12].	Direct human evidence, but heterogeneous and largely adult.
Early-life exposure	Some prenatal/childhood exposure windows are associated with selected clocks [11].	Supports developmental focus; clock and exposure timing matter.
Short-term $PM_{2.5}$ exposure	A quasi-experimental adult study reported changes in several methylation-age measures [10].	Suggests possible short-term responsiveness; persistence is uncertain.
Noise and cortisol	A multi-cohort child study did not find significant associations for hair or urinary cortisol [16].	Supports testing uncertainty rather than presuming a positive association.
Oxidative / inflammatory pathways	Mechanistic research supports oxidative stress and NF-κB/TLR-related inflammation [17–19].	Plausible mechanisms, not proof of mediation in adolescents.
Cross-species epigenetics	Plant and termite studies report stress-related epigenetic or ageing effects [20,21].	Indirect biological context; cannot be generalised directly to humans.

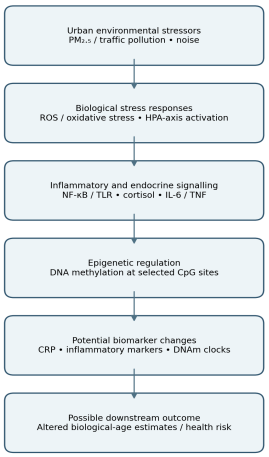


Figure 1. Proposed mechanistic pathway

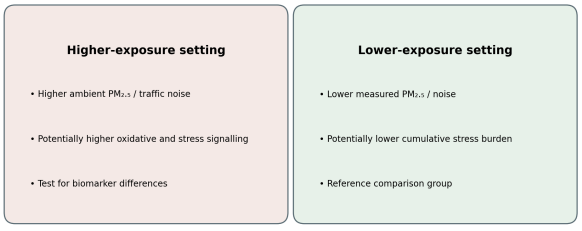


Figure 2. Proposed comparison of exposure groups

5. Limitations and Future Research

Residual confounding may remain even after statistical adjustment. Adolescents' sleep, diet, physical activity, second-hand smoke exposure, medication, infection,

socioeconomic conditions, and blood-cell composition may influence outcomes. The proposed sample-size range of 50–100 per group should be treated as provisional until formal power calculations are completed. Future studies should use longitudinal measurements, validated adolescent-appropriate clocks, repeated exposure assessment, and transparent preregistration. Independent replication and careful handling of multiple testing are also needed.

6. Conclusion

This paper develops a research framework for examining whether urban air pollution and environmental noise are associated with epigenetic-age estimates, inflammatory biomarkers, and cortisol among adolescents aged 15–18 years. Existing human studies provide evidence that air pollution can be associated with selected measures of methylation-based biological ageing, but the direction and magnitude of associations vary by pollutant composition, exposure window, population, and epigenetic clock [8–12,22]. Mechanistic literature supports potential links involving oxidative stress, inflammatory signalling, and stress-response systems [13,17–19]. Evidence concerning noise and cortisol in children is not uniformly positive, so that relationship should remain an open hypothesis rather than a presumed outcome [16]. The public-health implication is precautionary rather than causal: improving air quality, reducing avoidable traffic and environmental noise, and designing healthier urban environments are reasonable population goals even while specific epigenetic pathways are being investigated. Future research should integrate environmental monitoring with individual-level exposure information, protect minors' privacy, and avoid interpreting epigenetic clocks as diagnostic tests. With stronger longitudinal evidence, this framework may help clarify how environmental conditions become biologically embedded during development and inform policies aimed at healthier life-course outcomes.

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