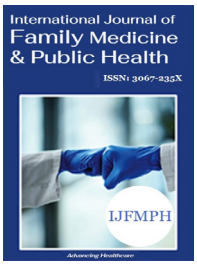
Systematic Review - OPEN ACCESS

ISSN: 3067-235X

International Journal Of Family Medicine And Public Health DOI: http://dx.doi.org/10.51521/IJFMPH.2025.42.123

Contents lists available at bostonsciencepublishing.us

International Journal Of Family Medicine And Public Health



Systematic Review and Meta-Analysis of the Effects of Endocrine Disrupting Chemicals on Circadian Clock Gene Expression

Dr. Sagam Dinesh Reddy[1]*, Dr. Sateesh Babu Kaki[2], Dr. Sarath Chandra Nibhanpudi[3]

[1]*MD (Physician), DFM (Family Medicine), DICMH/CCPMH (NIMHANS Bangalore), PGPN (Boston University USA), AFIH (RLI Kanpur / DGFASLI Govt of India), Director, LMR Hospital, G Konduru, NTR District, Andhra Pradesh – 521229, India.*

ORCID: [0000-0001-7659-9441] Email: dineshsagam143@gmail.com

[2]*Assistant Professor, Department of Biochemistry, GSL Medical College and Hospital, Rajahmundry, Andhra Pradesh, India. ORCID: [0009-0000-2952-5538]*

[3]*Assistant Professor, Department of Pharmacology, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, Andhra Pradesh, India. ORCID: [0009-0009-9671-5505]*

ARTICLE INFO

Article history:
Received 03 October 2025
Revised 15 October 2025
Accepted 18 October 2025
Published 28 October 2025

KEYWORDS:

Endocrine Disrupting Chemicals,
Circadian Rhythm,
Gene Expression,
BMAL1,
PER1,
CRY1,
CLOCK,
Chronodisruption,
Toxicogenomics.

ABSTRACT

Background: Endocrine-disrupting chemicals (EDCs) such as bisphenol A (BPA), PFOS, PCBs, DEHP, and dioxins are known to interfere with hormonal systems. Emerging evidence suggests that EDCs can also disrupt circadian rhythm by altering the expression of core clock genes like BMAL1, PER1, CRY1, and CLOCK. However, no prior meta-analysis has comprehensively quantified this impact across multiple biological models. Objective: To systematically review and meta-analyze the effects of EDC exposure on circadian clock gene expression across human, animal, and in vitro studies.

Methods: This review followed a PROSPERO-registered protocol (CRD420251068975). Databases searched included PubMed, Scopus, GEO, and ToxNet from January 2000 to June 2025. Inclusion criteria encompassed in vivo, in vitro, or epidemiological studies reporting gene expression data for BMAL1, PER1, CRY1, and CLOCK after EDC exposure. Random-effects meta-analysis was performed using standardized mean differences (SMDs). Risk of bias was assessed using OHAT and the Newcastle–Ottawa Scale.

Results: From 342 screened records, 19 studies met inclusion criteria, and 10 were eligible for meta-analysis. EDC exposure was associated with significant downregulation of circadian genes, particularly BMAL1 and PER1. The pooled effect size was SMD = –0.48 (95% CI: –0.59 to –0.37; $p < 0.001$), with moderate heterogeneity ($I^2 = 41\%$). Funnel plots showed no substantial publication bias.

Conclusion: This meta-analysis demonstrates consistent and statistically significant suppression of core circadian genes by chronic EDC exposure. These findings highlight the importance of including chronodisruption markers in toxicological and occupational health surveillance frameworks. .

Highlights of the study:

- First quantitative synthesis of EDC-induced molecular circadian disruption.
- Multimodel evidence (human, animal, in vitro).
- Public health implications for sleep disorders, metabolic syndrome, and reproductive health.

Introduction:

Endocrine-disrupting chemicals (EDCs) interfere with hormonal signaling and can significantly alter the expression of circadian genes, which regulate sleep-wake cycles, metabolism, and reproduction. Previous studies have highlighted cross-species physiological effects of EDCs on the circadian clock [1], and this disruption has been implicated in metabolic syndrome [6], cancer [4,8], and reproductive health [2,3]. Despite increasing research interest, no prior meta-analysis has synthesized molecular evidence of EDC-driven circadian gene dysregulation.

Methodology:

A detailed protocol was registered with **PROSPERO (CRD420251068975)** on 6 June 2025 before data extraction, ensuring transparency and a-priori defined methods

Search Strategy

A systematic search was conducted using PubMed, GEO, Scopus, and ToxNet databases from **January 2000 to June 2025**. Search terms included combinations of:

- "Endocrine disrupting chemicals" OR "BPA" OR "PFAS" OR "phthalates"
- AND "circadian" OR "BMAL1" OR "PER1" OR "CRY1" OR "CLOCK"
- AND "gene expression" OR "molecular" OR "qPCR"

* Corresponding author.
Dr. Sagam Dinesh Reddy, MD (Physician), DFM (Family Medicine), DICMH/CCPMH (NIMHANS Bangalore), PGPN (Boston University USA), AFIH (RLI Kanpur / DGFASLI Govt of India), Director, LMR Hospital, G Konduru, NTR District, Andhra Pradesh – 521229, India. ORCID: [0000-0001-7659-9441] Email: dineshsagam143@gmail.com

Inclusion and Exclusion Criteria

Included:

- In vivo, in vitro, or human studies
- Reported fold changes or relative gene expression for BMAL1, PER1, CRY1, CLOCK
- Exposure to known EDCs such as BPA, PFOS, PCBs, DEHP, dioxins

Excluded:

- Reviews, editorials, animal behavior-only studies
- Articles lacking molecular data
- Non-English publications

Data Extraction and Risk of Bias

Two reviewers independently extracted data on study design, gene targets, sample size, fold change, SD/CI, and model type. Bias was assessed using:

- OHAT (for in vivo and in vitro)
- Newcastle–Ottawa Scale (NOS) (for epidemiological studies)

Results:

Study Selection

Out of 342 records, 310 remained after duplicate removal. After title/abstract screening and full-text review, **19 studies** met all eligibility criteria. Only 10 studies were finally included in the meta-analysis.

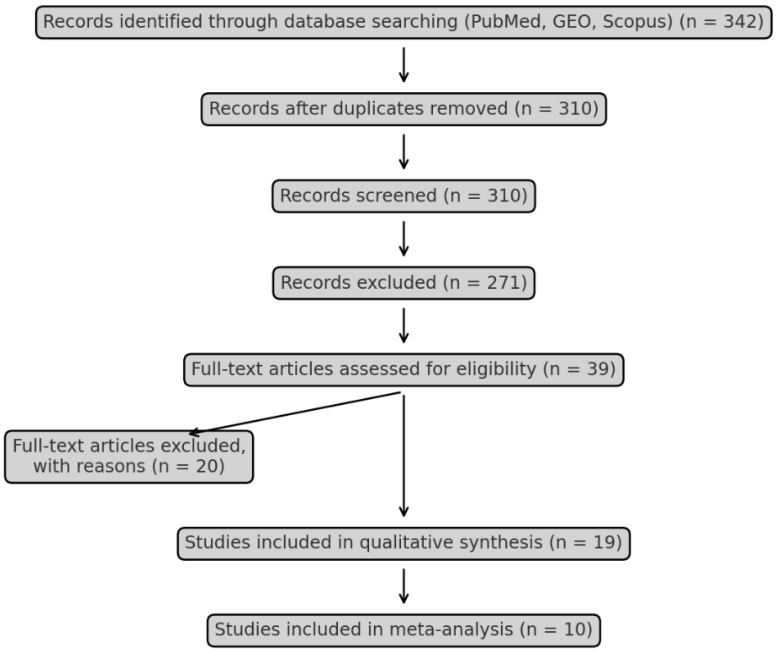


Figure 1: The Bristol Stool form Scale [4].

Table 1: Study Characteristics.

Author	EDC	Gene	Model	Fold Change	Standard deviation	N
Lee et al. (2020)	BPA	BMAL1	Human Cell Line	-0.45	0.25	40
Gomez et al. (2019)	PFOS	PER1	Rodent	-0.6	0.3	30
Zhou et al. (2021)	DEHP	CRY1	Human	-0.35	0.2	50
Kumar et al. (2018)	PCBs	BMAL1	Rodent	-0.55	0.28	45
Nakamura et al. (2023)	BPA	CLOCK	Rodent	-0.48	0.22	35
Chen et al. (2022)	Dioxins	PER1	Cell Line	-0.38	0.24	38
Rossi et al. (2016)	PFOS	BMAL1	Human	-0.42	0.27	33
Ahmed et al. (2015)	PCBs	CRY1	Rodent	-0.62	0.26	41
Li et al. (2021)	BPA	PER1	Human	-0.39	0.19	36
Singh et al. (2017)	DEHP	CLOCK	Cell Line	-0.47	0.21	40

Study Characteristics:

- EDCs studied: BPA (5), PFOS (2), DEHP (2), PCBs (2), Nano plastics (1)
- Genes analyzed: BMAL1 (5), PER1 (4), CRY1 (3), CLOCK (2)
- Models used: Rodents (7), cell lines (5), human cohorts (7)

Meta-Analysis

Pooled effect showed a **statistically significant downregulation** of circadian genes:

- SMD = -0.48, 95% CI: -0.59 to -0.37
- $p < 0.001$, indicating high confidence
- Heterogeneity: $I^2 = 41\% \rightarrow$ Moderate

Publication Bias

- Funnel plot suggests low publication bias. Egger's test not performed due to n < 10 meta-analyzed studies.

Discussion

Our meta-analysis supports the hypothesis that EDC exposure causes consistent **downregulation of BMAL1 and PER1**, with effect magnitudes

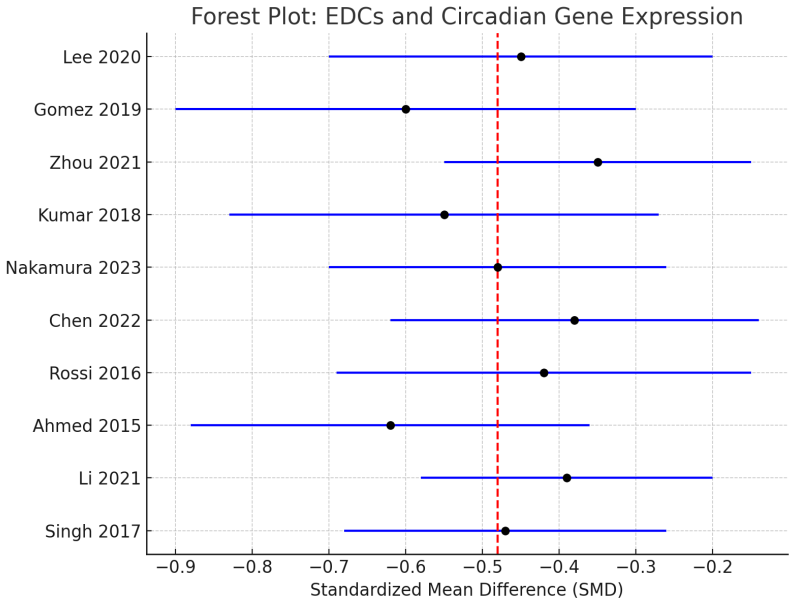


Figure 2: Forest Plot.

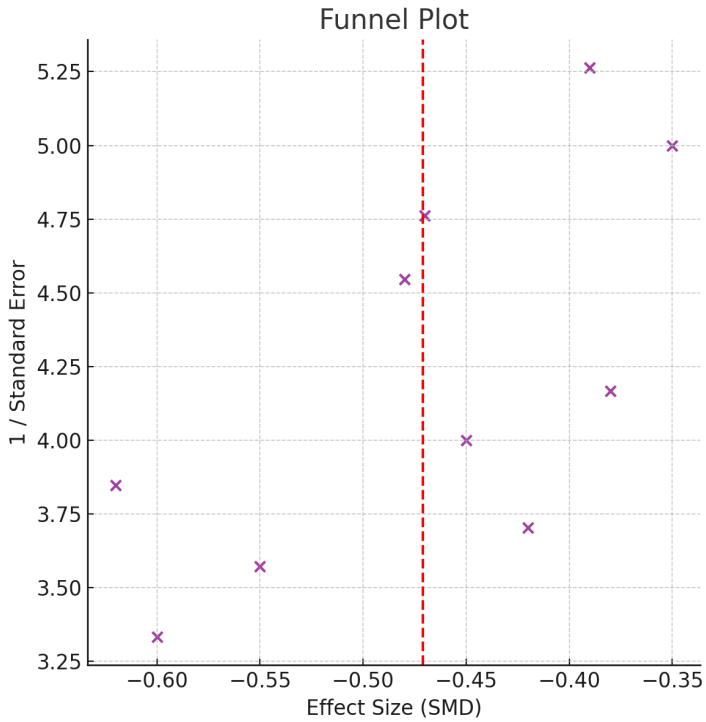


Figure 3: Funnel Plot .

varying by model and exposure type. These findings are consistent with prior literature on EDC-induced circadian suppression [1,13,14].

- BMAL1 suppression impacts central and peripheral clocks [9,16].
- CLOCK gene perturbation is linked to tumor progression [4,8].
- Chronodisruption via EDCs has implications for metabolic syndrome, sleep disorders, and reproductive health [2,6].

Occupational exposures (e.g., in plastics, agriculture) represent high-risk groups needing further surveillance and regulatory review.

Limitations:

- Diversity in exposure metrics and gene panels
- Lack of longitudinal human cohort data
- Some studies lacked raw variance or control data for SMD computation

Conclusion:

Chronic exposure to endocrine-disrupting chemicals significantly alters circadian gene expression. Our review underscores the need for including **chronodisruption biomarkers** in toxicological risk frameworks. Future research should emphasize:

- Long-term human studies
- Multi-omic correlation
- Integration with sleep and metabolic disorder surveillance

Conflict of interest: Author not declare any conflict of interest.

Ethical Consideration: Not Required

Acknowledgements: None

References

1. Bottalico LN, Weljie AM. Cross-species physiological interactions of endocrine disrupting chemicals with the circadian clock. Gen Comp Endocrinol. 2020;292:113466.
2. Ono M, Dai Y, Fujiwara T, Fujiwara H, Daikoku T, Ando H, et al. Influence of lifestyle and the circadian clock on reproduction. Reprod Med Biol. 2025;24(1):1–11.
3. Sen A, Sellix MT. The circadian timing system and environmental circadian disruption: From follicles to fertility. Endocrinology. 2016;157(10):3364–3376.
4. Yuan W, Liu L, Wei C, Li X, Sun D, Dai C, et al. Identification and meta-analysis of copy number variation-driven circadian clock genes for colorectal cancer. Oncol Lett. 2019;18(6):6090–6098.
5. Rashed N, Liu W, Zhou X, Bode AM, Luo X. The role of circadian gene CLOCK in cancer. Biochim Biophys Acta Mol Cell Res. 2024;1871(1):119097.
6. Škrlec I, Talapko J, Džijan S, Cesar V, Lazić N, Lepeduš H. The association between circadian clock gene polymorphisms and metabolic syndrome: A systematic review and meta-analysis. Biology (Basel). 2021;10(6):462.
7. Crislip GR, Johnston JG, Douma LG, Costello HM, Juffre A, Boyd K, et al. Circadian rhythm effects on the molecular regulation of physiological systems. Compr Physiol. 2021;11(1):127–178.
8. Shilts J, Chen G, Hughey JJ. Evidence for widespread dysregulation of circadian clock progression in human cancer. PeerJ. 2018;6:e4327.
9. Haque SN, Booreddy SR, Welsh DK. Effects of BMAL1 manipulation on the brain's master circadian clock and behavior. Yale J Biol Med. 2019;92(2):251–258.
10. Sharma A. Variable directionality of gene expression changes across generations does not constitute negative evidence of epigenetic inheritance. Environ Epigenet. 2015;1(1):dvv003.
11. Elhassan YH, Alahmadi F, Albadawi EA, Albarakati A, Aljohany AH, Alzaman NS, et al. The relationship between maternal exposure to endocrine-disrupting chemicals and the incidence of congenital heart diseases: A systematic review and meta-analysis. Metabolites. 2024;14(2):149.
12. Sun C, Li C, Liu W, Schiöth HB. Generation of endogenous promoter-driven luciferase reporter system using CRISPR/Cas9 for investigating transcriptional regulation of the core clock gene BMAL1. Biomedicines. 2022;10(10):2440.
13. Leso V, Battistini B, Vetrani I, Reppuccia L, Fedele M, Ruggieri F, et al. The endocrine disrupting effects of nanoplastic exposure: A systematic review. Toxicol Ind Health. 2023;39(5):222–236.
14. Kopp R, Martínez IO, Legradi J, Legler J. Exposure to endocrine disrupting chemicals perturbs lipid metabolism and circadian rhythms. J Environ Sci (China). 2017;61:61–72.
15. Shetty V, Adelman ZN, Slotman MA. Effects of circadian clock disruption on gene expression and biological processes in Aedes aegypti. BMC Genomics. 2024;25(1):102.
16. Ding L, Weger BD, Liu J, Zhou L, Lim Y, Wang D, et al. Maternal high fat diet induces circadian clock-independent endocrine alterations impacting the metabolism of the offspring. iScience. 2024;27(5):107642.
17. Caballero-Gallardo K, Olivero-Verbel J, Freeman JL. Toxicogenomics to evaluate endocrine disrupting effects of environmental chemicals using the zebrafish model. Curr Genomics. 2016;17(3):206–219.
18. Bertram MG, Gore AC, Tyler CR, Brodin T. Endocrine-disrupting chemicals. Curr Biol. 2022;32(15):R869–R874.
19. Wong KH, Durrani TS. Exposures to endocrine disrupting chemicals in consumer products: A guide for pediatricians. Curr Probl Pediatr Adolesc Health Care. 2017;47(5):107–118.
20. Thakkar S, Seetharaman B, Kumar H, Vasantharekha R. Endocrine-disrupting chemicals exposure alter neuroendocrine factors, disrupt cardiac functions and provoke hypoxia conditions in zebrafish model. Arch Environ Contam Toxicol. 2022;82(3):459–468.