

# Day Care in Infancy and Risk of Childhood Acute Lymphoblastic Leukaemia: Findings from UK Case - Control Study

Eiman Hamid

Calderdale and Huddersfield Foundation Trust, NHS, England

**Abstract:** *This is a critical appraisal of the article titled "Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case - control study". This study aimed to explore the potential connection between early - life exposure to infections during infancy and its impact on the risk of developing Acute Lymphoblastic Leukemia ALL. Using daycare attendance as a proxy for childhood infection exposure, this research delved into existing hypotheses, particularly Greaves hypothesis, to investigate whether reduced exposure to infections during early childhood heightens the likelihood of ALL development. The study included a large sample size of 3838 cases and 7629 controls, obtained from pediatric oncology units and national registers. The methodology involved careful matching for various factors and adjusting for confounders. Results showed a significant association between reduced exposure to infections and increased ALL risk, meeting Bradford Hills criteria for causality. Despite some limitations in the methodology, this research contributes valuable insights into the relationship between childhood infections and ALL risk. Further investigations are warranted to validate these findings and address remaining uncertainties in this complex association.*

**Keywords:** Early - life infections, Acute Lymphoblastic Leukemia, Daycare attendance, Childhood infections, Case - control study

## 1. Study title/ Question/ Introduction/ Design

The primary objective of this research was to investigate the potential link between early - life exposure to infections during infancy and its influence on the risk of developing Acute Lymphoblastic Leukemia (ALL). Specifically, the central inquiry of this study pertains to whether diminished exposure to infections during early childhood, leading to a state of immunological isolation, heightens the likelihood of ALL development. Daycare attendance served as a surrogate measure, indirectly indicative of childhood infection exposure.

This review of the literature sought to address the prevailing ambiguities within existing hypotheses and, in particular, the scholarly interest in the hypothesis proposed by Greaves. Greaves's hypothesis provided the theoretical framework for the execution of this study. However, the review did not provide a comprehensive discussion of the implications and significance of investigating this hypothesis.

The title of the study might have been more descriptive with regard to the anticipated association (whether inverse or direct) between infant daycare attendance and the risk of childhood ALL. Nevertheless, the study's hypothesis was explicitly stated in both the abstract and the introductory sections.

The primary objective of this study was to test the hypothesis that a reduced exposure to common infections during the first year of life increases the susceptibility to developing acute lymphoblastic leukemia. However, the study eventually involved a comparative analysis between ALL and non - ALL malignancies. This comparative approach entailed the testing of multiple hypotheses, potentially introducing the risk of false positive results due to the increased likelihood of chance findings. Furthermore, the formulation of a hypothesis based on subgroup analysis

(ALL group vs. non - ALL) was, although intriguing, considered to be less reliable.

The employment of a case - control study design was deemed appropriate for addressing research questions aimed at elucidating causality and establishing the relationship between exposure to a risk factor (daycare attendance) and the resulting outcome (development of ALL).

## 2. Methods/ Participants/ Measures

There were no power calculations to predict the appropriate sample size but 3838 cases and 7629 controls is fairly a large number. Data on cases were extracted from paediatric oncology units at 10 regional centres but they did not mention their sampling technique, how cases were chosen, whether they had a reliable system to choose cases or they included all diagnosed children. It is not clear who extracted the data (under the acknowledgement section they thanked local hospital staff, GPs, and UKCCS interviewers, but their role was not mentioned in the methods section), and whether blinding has taken place or not. Controls were chosen from the national register to allow generalisation and representation.

To avoid confounding, they've done pairing (2: 1) ratio and they've matched for age, sex, month of birth (to avoid seasonality being an influence), year of birth, and region of residence at diagnosis. I think they should have matched for socio - economic status and parental work as it may influence daycare attendance. To avoid further confounding, they've done restrictions which is obvious in their exclusion criteria. They excluded children who were diagnosed with malignancy below the age of 2, to overcome overlapping symptoms and diminish the possibility of being under - involved in social activity due to malignancy and ascertain that exposure has happened a long time before the outcome. Diagnoses of Down syndrome is a huge confounder which

Volume 12 Issue 10, October 2023

[www.ijsr.net](http://www.ijsr.net)

Licensed Under Creative Commons Attribution CC BY

was properly excluded, due to its strong association with leukaemia and its impact on activity and exposure to infection.

Although a structured questionnaire was used to interview parents, they did not mention the interview timing, setting, location, number of interviews per case, whether it was held at the time of diagnosis or follow - up, who performed the interviews and whether interviewers were transcribed/blinded or not. Measurement methods were different between cases and controls, the time from diagnosis to interview was 6 months in cases and 14 months in controls.

Exposure was clearly defined and they standardised parents' understanding of social interaction by creating definitions and categories for different degrees of social involvement. However, recall bias <sup>(1)</sup> is of significant concern in such studies as parents may over - report or under - report the exposure.

The researchers used daycare as a reflection of social activity and used the social activity as an indicator of exposure to infection. However, this association is not confirmed and may not truly reflect exposure to infection. I am wondering whether it would have been better to use a more objective/accurate indicator of childhood infections, such as GP visits within the first year or absence from daycare due to illness. Moreover, children may encounter infections from within the household without getting involved in social activity. Although the exposure was clearly defined it was neither accurately measured nor truly reflected.

Ethical Consideration has been touched on briefly in the methods section with the fact that they sought ethical approval and patient consent but no detailed mention of the circumstances, approval body, or principles.

### 3. Presentation of Results

- The analysis of results reported in table 2 as Odds ratio is appropriate to the study design of case - control study. The table seemed cluttered, but the labelling and results were clearly displayed. A different number of cases/controls than what was mentioned in the script due to missing values (i. e.: ALL cases 1272 instead of 1286, control 6238 instead of 6305). To calculate the result of the primary outcome (social activity in ALL cases vs controls):

	ALL cases	Control
Social involvement	1020	5343
No involvement	252	895

Odds ratio =  $(1020/252) \div (5343/895) = 4/6 = 0.66$  (resemble study result) or  $6/4 = 1.5$

Since leukaemia/malignancy is a rare event, the odds ratios are approximately the same as the risk ratio, therefore, we can interpret OR in terms of RR <sup>(1)</sup>

- The proper wording would be "children in this study who did not sustain social interactions during their first year

of life are 1.5 times as likely to develop ALL than children who didn't have social interactions. or "children who sustained social interactions (rather than not) during their first year of life are 0.66 times (two third times) as likely to get ALL" and we are 95% confident that the plausible value of risk reduction lies between the range of (0.56 to 0.77) ". Another way of phrasing would be "Having social interaction within the first year of life will decrease the risk of having ALL by 44%". Hence, as the study mentioned "activity was associated with a reduced risk of ALL" is acceptable.

- The estimate of daycare attendance appears to be precise and statistically significant. The 95% CI does not include null value of 1 and is narrow (0.56 to 0.77) and less than 1 implying the reduced risk and the protective effect. the P is <0.001 which confidently rejects the null hypothesis <sup>(1)</sup> Results have been similar across different ALL subgroups and non - ALL malignancies. And the risk of malignancy was inversely related to the increased daycare involvement. I have doubts regarding the case - case analysis (ALL VS non - ALL) since it was not considered within the initial study aims and whether is considered a sub - category analysis. Apart from formal daycare OR 0.69, 95% CI (0.51 to 0.93) P value 0.04, the OR ratios have been close to 1 and the 95% CI contained 1 which is plausible to be of non - significance. I choose to disagree with the authors and relate the protective effect of social activity for non - ALL malignancies to bias.
- Adjustment for confounders was considered in the analysis as odds ratio calculations were, adjusted for age at diagnosis/pseudo diagnosis, sex, region, maternal age, mother working at the time of birth, and deprivation. It was not mentioned whether this adjustment has made a difference to the odd ratio.

Ordinal logistic regression has been appropriately used to produce odds ratios for outcome variable <sup>(2)</sup>. Missing values were mentioned to be excluded but were not quantified. Underreporting has been counted for in the analysis and reported that did not affect the results.

### 4. Study Discussion and Conclusions

The discussion started appropriately with a recap of the study's nature, aim and main goal of the study. In the summary, they compared to previous studies but not systemic reviews which may pose selection bias. They've pointed towards shortcomings of the study in terms of methodology, mismatching of cases and controls, and the uncertain possibility of reverse causation between the exposure and outcome which set out the implications for further research work.

Apart from ALL to non - ALL analysis (with the presumed protective effect), assuming that daycare interaction can truly reflect childhood disease exposure, the results of the main outcome seem significant and the limitation of methodology did not flaw the result significantly. The proposed risk - outcome association has time sequence, does - response gradient, strength and biological plausibility which fulfils Bradford Hills criteria <sup>(3)</sup> and is consistent with other research results.

## References

- [1] David Bowers B. Understanding Clinical Papers. Wiley - Blackwell; 2020.
- [2] White G. A Survival Guide for Health Research Methods. Vol.13, Nurse Education in Practice.2013. e30 p.
- [3] Bradford Hill criteria - Oxford Reference [Internet]. [cited 2023 Jan 2]. Available from: <https://www.oxfordreference.com/display/10.1093/oi/authority.20110803095523346;jsessionid=9D57DFC4FAB76BA7A51B40ACE9655296>