Review Article

# Aging and Changes in White Blood Cells Count and Immunity: A Systematic Review


## Abstract

It is unclear why aging causes a drop in lymphoid-biased HSC numbers and a decline in lymphoid progenitor quality. One possibility is that stem and progenitor cells have inherently programmed processes at work, which would imply that these cells have an internal clock that controls their functionality and lifetime. This study aims to summarize current evidence regarding the Effect of aging on White Blood Cells Count and immunity. The PubMed database and EBSCO Information Services were utilised to choose the articles. In our review, all pertinent articles related to our subject and other publications were used. Other articles that have nothing to do with this subject were not included. The group members looked through a certain format in which the data had been extracted. The WBC count merits consideration as a potentially clinically helpful indicator of survival in individuals aged 75 and older, particularly in women. Monocyte count and total white blood cell count both peaked at the 50th and 97.5th quantiles at birth before significantly declining in the first six months of life. A relatively gradual decline persisted until the age of two. Contrary to the tendency for the neutrophil count, the lymphocyte count peaked in early childhood and subsequently fell as people aged. As the immune system is exposed to infections and environmental non-self-antigens more often after early infancy. This pattern appears to represent the development of acquired and adaptive immune responses.


**Keywords:** *Aging, White blood cells count, Immunity, Immune responses, Immune system.*


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## Introduction

Throughout at least part of their lifespan, white blood cells (WBC), a diverse collection of nucleated cells, can be present in circulation. Their average blood concentration ranges from 4,000 to 10,000 microliters. They are crucial to phagocytosis, immunity, and thus, the fight against infection.[1]

The loss of immunological function is among the most well-known effects of aging. While older people do not always have weak immune systems, they frequently have poor immune responses to new or previously encountered antigens. This is demonstrated by the greater susceptibility of those over the age of 70 to influenza, which is made worse by their suboptimal response to vaccination.[2-6]

While some particular immune responses decline with age, others remain unaltered or even worsen. Ironically, persistent low-grade inflammation is frequently seen in older people. When it was discovered that PBMCs from older individuals can produce higher levels of proinflammatory cytokines than those from younger subjects, an observation that on the surface seems to defy the prevalent hypothesis at the time—that elderly people are immunosuppressed—this chronic inflammatory state, known as "inflame-aging," was first described. Chronic antigenic stress causes inflammation-aging, which ultimately leads to the up-regulation of cellular and molecular functions and increases vulnerability to age-related disorders.[7]

The term "immunosenescence" refers to a condition in which the immune system has undergone significant aging-related alterations, which are characterized by a general loss in antigen-specific immunity. The most observable features of immunosenescence at the cellular level include a marked decline in the sum of lymphocytes as a result of a decrease in thymic yield of T cells, a reduction in bone marrow early progenitor B cells, and gathering of oligoclonally prolonged and functionally ineffectual memory lymphocytes These changes directly lead to a large decrease in the variability of the antigen-recognition repertoire with ageing.



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According to research on TCR V chain convention in human peripheral T cells, the antigen-recognition range of T cells declines from around 108 in young people to 106 in the aged.[8]

It is unclear why aging causes a drop in lymphoid-biased HSC numbers and a decline in lymphoid progenitor quality. One possibility is that stem and progenitor cells have inherently programmed processes at work, which would imply that these cells have an internal clock that controls their functionality and lifetime. However, mounting data indicates that aging-related environmental changes have an impact on lymphopoiesis decreases. Although variations in transforming growth factor -1 levels may be implicated, the specific age-related environmental variables that lead to the loss of lymphoid-biased HSCs remain unknown. B cell lineage aging has been linked to changes in the bone marrow microenvironment, presumably as a result of stromal cells secreting less IL-7.[2]

Aged mouse and human skin have both been shown to have a lower LC density. The issue of whether the number of human pDCs and cDCs decreased with age was investigated in many research. Two recent studies using flow cytometry analysis and DC subset-specific cell-surface markers demonstrated a substantial age-related numerical drop of pDCs but an unaltered number of cDCs in peripheral blood from healthy young and old volunteers.[9-11] Jing *et al.* intriguing.'s discovery that the diminishing health state of the elderly might have a significant detrimental influence on the conserved CDC frequency with age among healthy patients is noteworthy.[7, 12-20]

### Study objectives

This study aims to summarize current evidence regarding the Effect of aging on White Blood Cells Count and immunity

## Materials and Methods

In order to develop a consistent empirical research programme that builds on prior knowledge, a systematic assessment of the current evidence on ageing and immunity is observed as a dependable method of locating and synthesising the peer-reviewed papers for evidence in this field. Only an understanding could be made from the qualitative quantifiable in this review. A qualitative data fusion also strives to produce assumptions that are eloquent, pertinent, and proper for persons, to guide a study agenda, and finally to advance behaviours about the link between ageing and white blood cell count. The review mutual, cohesive, and, where proper, interpreted the data from the involved studies using qualitative synthesis methods.

The review attempts to go beyond the simple collection of data to offer further interpretive insights into obesity as a risk factor for various malignancies and to identify areas where more research can expand on what is already known.

### Study eligibility criteria

Peer-reviewed qualitative study were included in the evaluation. Mixed-methods studies' qualitative data was assessed for applicability before being added if it passed muster. We included those studies that have been conducted over twenty years. All peer-reviewed articles published in English, reporting the association between ageing and WBCs were included.

For the studies to be included for the review, papers were all published between 2002 and October 2022.. This would guarantee the work's currency and allow for the identification of developing issues from a wide range of perspectives.

### Study Inclusion and Exclusion criteria

The papers were chosen for the process focusing on their applicability, English, and consideration of a ten-year time limit. All additional articles, repeated studies, reviews of research, and articles with a primary purpose other than one of these areas were disregarded. The reviewers disqualified any studies that were not published in English, as well as any books, grey literature, or editorial comments. Additionally omitted were studies that solely provided qualitative data.

### Selection of study

The choice measures and outcomes were obtainable using the ENTREQ criteria for offering qualitative systematic reviews. To help with repetition removal, all retrieved studies were originally introduced into the Endnote library. After removing the copies, the two authors used a shared Endnote library to independently browse the papers by title and abstract while being led by the qualifying necessities. A full-text review of the studies that the two authors had selected was directed.

Any divergences between the two authors were determined by a third author. The whole texts of all qualifying studies were studied by the two authors autonomously. When the views of the two authors differ, an agreement was sought by conversation about the issues with the third authors. For the final agenda combination, the complete texts of all pertinent study that met the inclusion standards were kept.

### Data extraction

Two authors distinctly gathered data from qualifying studies onto a customised data abstraction form, filling it with material about the study population and relevant occurrences. The third review author double-checked and double-verified the pull out articles. The original author's name, the publication year, the duration of the data collection, and the geographical area of the study were all poised as study characteristics. Study-specific data was recorded, including the study's design, demographic, sample size, sampling techniques, and data collection methods.

### Data synthesis and analysis

Data examination was done lacking the use of any software package. The data was organised by theme by the authors, who then provided the themes as an analysis table (chart). The study

were epitomized in the table's columns and rows, and related topics allowed us to compare the results of the studies across various themes and subthemes.

## Results and Discussion

The selection and identification of research are shown in **(Figure 1)**. A whole of 286 studies were found after probing the aforementioned databases, which were then used for heading screening. 52 of them were excluded after 198 of them were involved for abstract screening. The whole texts of the outstanding 146 publications were surveyed. 137 papers were excluded from the full-text revision due to different study objectives, and 8 were enrolled for the final data extraction **(Table 1)**.

In Nilsson, G., *et al*. researchhigher WBC counts were strongly linked to noncardiovascular death in women and cardiovascular mortality in both sexes.[21] Moreover, In Li, K., *et al*. Study Monocyte count and total white blood cell count both peaked at the 50th and 97.5th quantiles at birth before significantly declining in the first six months of life. A relatively gradual decline persisted until the age of two. The lymphocyte count was low throughout infancy and rose to its peak at six months of age; after that, it gradually and steadily decreased until about nine years of age. In contrast to lymphocyte count, the pattern of neutrophil count altered with the age difference. Eosinophil and basophil numbers didn't seem to vary with age.[22]

According to Aminzadeh, Z., *et al*. study: in the case group, there were statistically significant correlations between age and past infection history, past hospitalization history, and source of infection (P 0.05).[23]

According to Sean Leng, *et al*. Significant correlations between total WBC, neutrophil, monocyte, and eosinophil counts and IL-6 levels were found, except lymphocyte and basophil counts. Even after accounting for age, race, and smoking status, these relationships were still extremely significant. In four rising quartiles of IL-6 levels, there were substantial stepwise increases in the total WBC, neutrophil, monocyte, and eosinophil counts. Additionally, there were differences in the associations of total and differential WBC counts and IL-6 levels with age, race, and cigarette smoking.[24]

The rest of the results are detailed in **Table 1**.

The included studies had different study designs.

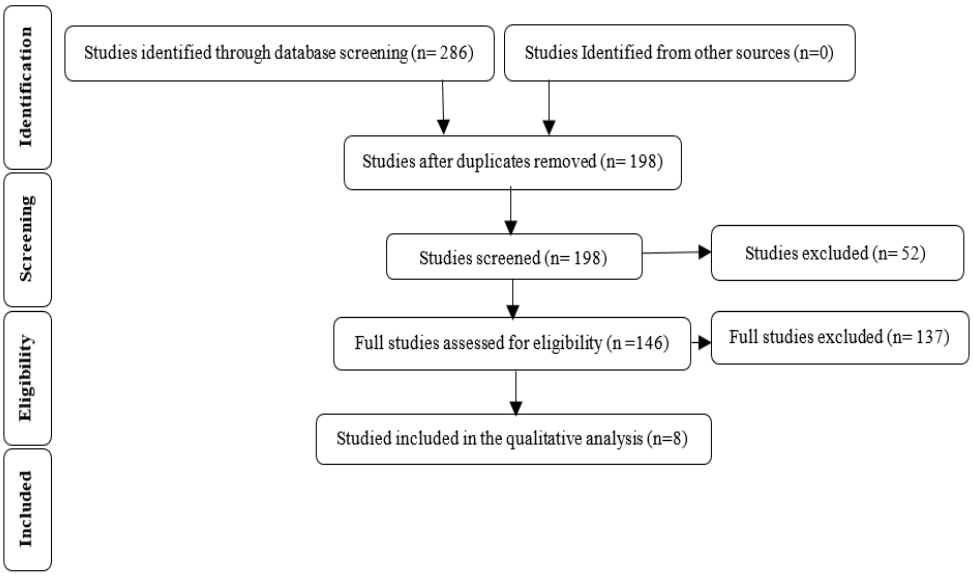


**Figure 1. selection and identification of research**

**Table 1. Included studies after exclusion:**

| Author, Publishing Year | Objective & Methodology | Outcomes |
|---|---|---|
| Nilsson *et al.* 2014[21] | Throughout an 11-year follow-up in a broad population of 75-year-olds, the predictive significance of WBC count on all-cause, cardiovascular, and noncardiovascular death was established. | For men, the median WBC count (109/L) was 6.3, while for women, it was 5.7. For every 109/L increase in WBCs, the hazard ratio (HR) for all-cause death was 1.16 for males and 1.28 for women. When risk variables were taken into account, their HRs remained substantially constant. Additionally, higher WBC counts were strongly linked to noncardiovascular death in women and cardiovascular mortality in both sexes. |

| | | |
|---|---|---|
| **Li *et al.* 2020**[22] | Total and differential white blood cell counts shift with age in children, with various numbers studied: The generalized additive models for location, shape, and scale technique were used to produce quantile curves. Both the total and differential white blood counts were determined using the 2.5th, 50th, and 97.5th quantile curves. The ratios of distinct white blood cells were shown using percentages of stacked area charts. R program was used to run every statistical analysis. | Monocyte count and total white blood cell count both peaked at the 50th and 97.5th quantiles at birth before significantly declining in the first six months of life. A relatively gradual decline persisted until the age of two. The lymphocyte count was low throughout infancy and rose to its peak at six months of age; after that, it gradually and steadily decreased until about nine years of age. In contrast to lymphocyte count, the pattern of neutrophil count altered with the age difference. Additionally, a locally weighted regression (LOESS) analysis revealed two inter-sections between lymphocyte count and neutrophil count during infancy and at around age 5. Eosinophil and basophil numbers didn't seem to vary with age. |
| **Aminzadeh *et al.* 2011**[23] | In sepsis patients who were young and old, researchers compared peripheral WBC levels. 130 hospitalized patients were split into two groups based on age: those under 65 (case group) and those over 65 (control group) for case-control research (control group). In two teaching hospitals in Tehran, Iran, from 2001 to 2006, sepsis was diagnosed in every patient. | The case group's mean WBC counts at admission were 17061.5 plus or minus 14240.2/l while the control groups were 13567.7 plus or minus 9888.0/ml. In the case group, there were statistically significant correlations between age and past infection history, past hospitalization history, and source of infection (P 0.05). Important risk factors in older people include a history of infection and a recent hospitalization for sepsis. |
| **Stervbo *et al.* 2015**[25] | Employing multi-parametric flow cytometry, complete immunophenotyping of innate leukocyte populations was done to look for age-related changes in various sub-populations. Researchers studied the peripheral blood mononuclear cells of 26 senior (aged 53–67) and 24 young (aged 19–30) donors. | The proportion of CD62L+CD57+ was lower in older donors compared to younger ones for classical CD16+CD56dim NK cells, while the other NK subsets under investigation were unaffected by aging. The elderly had higher levels of transitional monocytes and non-classical CD14+-CD16++ monocytes than the young did. The PDC and mDC2 populations were lower in the elderly. These findings indicate that reduced viral monitoring may be offset by the dynamics of the MDC subsets. These findings also suggest that NK cell maturation may eventually decrease. |
| **Sean Leng *et al.* 2005**[24] | Total and differential white blood cell counts in community-dwelling older women and their relationships to circulating interleukin-6 levels. Potential relationships between total and differential WBC counts, IL-6 levels, and age, race, and smoking were also investigated. | Significant correlations between total WBC, neutrophil, monocyte, except for lymphocyte and basophil counts. Even after accounting for age, race, and smoking status, these relationships were still extremely significant. In four rising quartiles of IL-6 levels, there were substantial stepwise increases in the total WBC, neutrophil, monocyte, and eosinophil counts. Additionally, there were differences in the associations of total and differential WBC counts and IL-6 levels with age, race, and cigarette smoking.<br>These results point to important roles for WBC and its subpopulations in circulating IL-6 levels as well as possible impacts of persistent elevations in IL-6 levels on the role of these mingling immune cells. |
| **Kim *et al.* 2013**[26] | The objective of this study was to assess the independent associations between mortality in an elderly population and the WBC count and each of its components. The study involved a total of 9996 people (age 65) who had normal medical examinations at the two hospitals associated to Seoul National University. From the Korean National Statistics Office, mortality information was acquired. The average age of the participants in the study was 69.7 years, and 5491 (54.9%) of them were men. There were 44.9 follow-up months on average. | 118 fatalities (1.2%) occurred throughout the follow-up period. Cancer was the top cause of death. Patients in various WBC and WBC subtype quartile groups had significantly varying death rates. In comparison to total WBC count, granulocyte count, and lymphocyte count, monocyte count was the best predictor of all-cause death. In the older population, higher monocyte counts were linked to an increased risk of death from cancer and cardiovascular disease. Although the overall WBC count is a reliable predictor of death in older persons, the monocyte subtype is more accurate. |
| **Nah *et al.* 2018**[27] | Complete Blood Count Reference Intervals and Change Patterns in Korean Children, Adults, and Seniors. After doing outlier testing, 22,766 examinees were eliminated from the reference population, which consisted of 804,623 health examinees. Researchers looked at the CBC parameters (platelet, white blood cell, and red blood cell parameters) from 781,857 test subjects. Researchers identified statistically significant age and sex groups and then computed them as following CLSI C28-A3 standards. | Male RBC parameters rose before puberty and then reduced with age, while female RBC parameters grew before puberty and then declined with age. Early infancy was when WBC and platelet counts were at their peak, and they fell as people aged. Age-related sex disparities were noted: Men had greater WBC counts than females during maturity, whereas females had higher platelet counts than males after puberty (P 0.001). Early infancy had the lowest neutrophil count, which rose as people aged. Early in childhood, the lymphocyte count peaked, and as people aged, it began to decline. In childhood, the eosinophil count peaked and was higher in men than in women. |
| **Nakanishi *et al.* 2004**[28] | To examine age-related changes in the strength of the association between features of the metabolic syndrome and white blood cell count (WBC), 5,218 Japanese male office workers were assessed for body mass index, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose, and uric acid (MS). | Except for HDL cholesterol, the WBC count exhibited a positive crude connection with the MS's constituents. As people got older, there was less of a connection between WBC count and each MS component, and there was less of an interaction with age. After adjusting for relevant confounders, individuals aged 23 to 39 years showed the greatest variations in WBC count for each category MS characteristic. The disparities in WBC count between the presence of no MS characteristics and each category of the number of clustered features were greatest in those aged 23 to 39 years, among both non-smokers and current smokers. The findings show that several MS characteristics are related to WBC count and that these trends are more prominent in younger people among both current and non-smokers. |

It is common knowledge that men have a greater WBC count than women. This gender disparity's origin is a mystery. One theory for the sex gap is that the need for female acceptance of the genetically distinct fetal tissue during pregnancy modifies the inflammatory response. WBC counts have a strong capacity to predict all-cause mortality, cerebrovascular

mortality, cardiovascular mortality, cancer mortality, as well as incident coronary heart diseases, according to several observational studies. Women have only been included in a handful of this research. These observational studies have examined wide age categories, primarily middle-aged individuals, as homogenous groups without the ability to differentiate prognoses for other age classes, such as the current study's 75-year-old participants.[21, 29-32]

In line with other studies, a study revealed that total and differential WBCs underwent significant alterations during childhood, particularly in the early years. Additionally, as compared to EO#, BASO#, and MONO#, LYMPH# and NEUT# showed more clear age-dependent alterations throughout childhood. LYMPH# showed its lowest level during infancy, increased to its highest level at 6 months of age, then gradually decreased until around 9 years of age. These patterns reflect the changes in children's exposure to foreign antigens with increasing age and are consistent with the general timing of paediatric diseases. In contrast to LYMPH#, the pattern of NEUT# varies with the age difference.[22]

Raz cited thrombocytopenia and leukocytosis as bacteremia risk factors and questioned the value of conducting blood cultures on elderly sepsis patients. In one study, the case group's history of recent infection during the past month was significantly correlated with age. This is in line with McBean and Meyers' findings that older patients both in hospitals and the community had a higher incidence of bacteremia.[23]

Even though aging is a continual process, the elderly (defined as those over 65) have received a lot of attention due to their increased vulnerability to diseases and reduced response to vaccinations. However, little is understood about the immunological profile of people in their late middle ages. Age-related changes may not be as noticeable in elderly people as they are in older people; for example, at the age of 70, the variety of T cells substantially declines. It is also evident that age and comorbidities have a high exponential correlation. Therefore, it is less probable that the age group included in the PRIMAGE research will be impacted by comorbidity.[25]

Contrary to the tendency for the neutrophil count, the lymphocyte count peaked in early childhood and subsequently fell as people aged. As the immune system is exposed to infections and environmental non-self-antigens more often after early infancy, this pattern appears to represent the development of acquired and adaptive immune responses. The neutrophil count also differed according to gender, being larger in females between adolescence and maturity. According to Verthelyi, sex hormones have an immunomodulatory effect: estrogen boosts immune responses, whilst testosterone reduces the body's reaction to infection. This validates a study demonstrating that females had greater neutrophil counts between puberty and maturity.[27]

Clinical decision limits for differential and total WBCs should be adjusted to account for children's growth and development. Such modifications can help with attempts to lessen missing and incorrect diagnoses in clinical practice. Notably, if the clinical decision limit was not changed for age, the diagnostic performance of WBCs in appendicitis exhibited a significant shift with increasing age. Furthermore, to assure disease diagnosis and control for novel infectious illnesses that have the potential to cause significant public health issues, it is crucial to have a timely and accurate understanding of clinical features.[22]

## Conclusion

The WBC count merits consideration as a theoretically clinically helpful indicator of survival in individuals aged 75 and older, particularly in women. Monocyte count and total white blood cell count both peaked at the 50th and 97.5th quantiles at birth before significantly declining in the first six months of life. A relatively gradual decline persisted until the age of two. Contrary to the tendency for the neutrophil count, the lymphocyte count peaked in early childhood and subsequently fell as people aged. As the immune system is exposed to infections and environmental non-self-antigens more often after early infancy, this pattern appears to represent the development of acquired and adaptive immune responses.

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None.

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