Seasonal and Daytime Variation in Multiple Immune Parameters in Humans: Evidence from 329,261 Participants of UK Biobank

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Circadian and Seasonal Regulation of Immunity

Annual cycles are an established component of the dynamics of infectious disease. For example, most respiratory viruses and childhood infectious diseases (meningitis, mumps, pertussis, and varicella) cause winter-time infection.

There is experimental evidence that animals and humans are more resilient to inflammatory and infectious challenges during their active circadian phase. Such temporal modulation of immune function is conserved across the biological kingdoms - plants, fish, birds and mammals all align their immune defense with the time of day that pathogenic and physical challenge are most likely.

Nevertheless, the role of endogenous circadian and circannual variability in human susceptibility to infection is rarely considered.

The aim of this study was to investigate seasonal and daytime variability in the human immune system in participants of UK Biobank and to test for associations with demographic, lifestyle and environmental factors.

UK Biobank Participants

The UK Biobank is a general population cohort study that recruited over half a million UK residents continuously between 2006 and 2010.

Participants were allocated an appointment time between 8am-7pm and blood neutrophils, lymphocytes and monocytes and CRP were measured.

Data selected as covariables for inclusion in this study were: age, sex, ethnicity, socioeconomic position, physical activity, sedentary behaviour, alcohol intake, smoking status, outdoor temperature, blood analyser, vitamin D, sleep duration, day length, chronotype and UK Biobank assessment centre.

Data Analysis

Seasonality was assessed by fitting regression models that included a sine and a cosine transformation of the time variable for each outcome.

Segmented regression models were used to assess daytime variation since the absence of nighttime samples precluded assumption of circadian patterns.

Hierarchical multiple regression was performed to investigate the environmental and participant-related factors that predicted changes in the immune outcome variables.

Seasonal Variation

Neutrophil and lymphocyte counts, and CRP levels all showed significant seasonal variation.

Changes in neutrophil and lymphocyte counts, and CRP levels were directly related to day length, independent of covariables, including vitamin D and outdoor temperature.

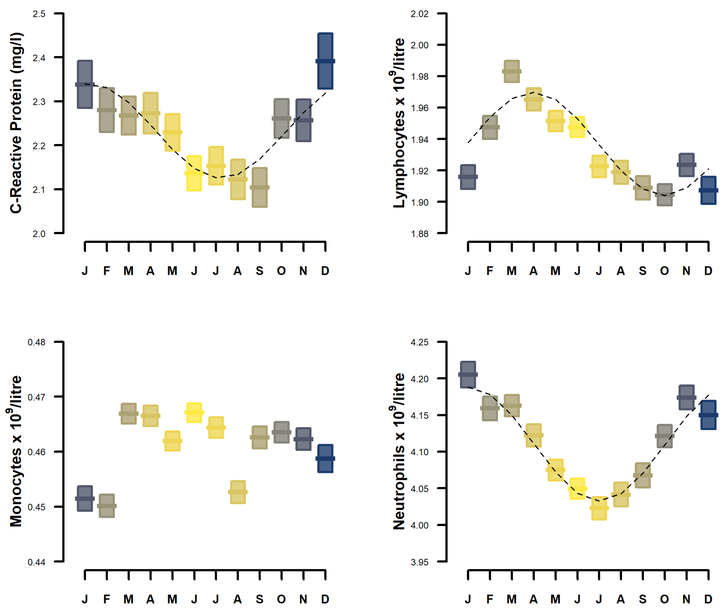


Figure 1. Annual variation in total monocytes, neutrophils, lymphocytes, and CRP. Data are mean (bars) and 95% confidence intervals (boxes), with fitted cosinor curves (dotted line). Daylength is indicated by the box color gradients

Table 3. Associations between day length and CRP, lymphocyte, neutrophil, and monocyte count

Day length	Model 1		Model 2		Model 3	
White blood cells (10^9/L)	−0.011***	[-0.013,-0.009]	−0.008***	[-0.011,-0.006]	−0.011***	[-0.015,-0.007]
Neutrophils (10^9/L)	−0.015***	[-0.017,-0.014]	−0.013***	[-0.015,-0.011]	−0.014***	[-0.018,-0.011]
Monocytes (10^9/L)	0.001***	[0.001,0.001]	0.001***	[0.001,0.001]	−0.000	[-0.001,-0.000]
Lymphocytes (10^9/L)	0.002***	[0.002,0.003]	0.003***	[0.002,0.004]	0.004***	[0.003,0.005]
CRP (mg/L)	−0.006***	[-0.007,-0.004]	−0.005***	[-0.006,-0.003]	−0.004***	[-0.007,-0.002]

Data are expressed as regression coefficients (B), with 95% confidence intervals in parentheses.
Model 1 was adjusted for age, sex, ethnicity, deprivation.
Model 2 was adjusted for Model 1 + BMI, physical activity, sedentary behavior, sleep duration, chronotype, shiftwork, smoking, alcohol.
Model 3 was adjusted for Model 2 + vitamin D, outdoor temperature, time of day, blood analyzer, and UK Biobank assessment center.

Daytime Variation

WBC counts were low in early morning, increasing as the day progressed, while daily patterns in CRP levels were more variable, peaking at 1pm and decreasing thereafter.

Daytime changes in WBCs and CRP were in most cases independent of lifestyle and environmental factors

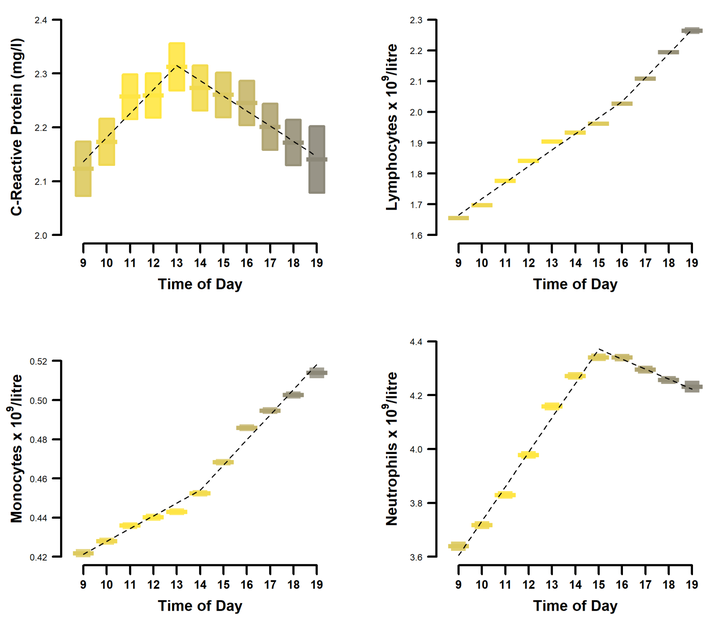


Figure 2. Daytime variation in monocytes, neutrophils, lymphocytes, and CRP. Data are mean (bars) and 95% confidence intervals (boxes), with fitted segmented regression lines (dotted black lines). The color gradient represents mean zenith angle of the sun at each time point is given to indicate daylight

Table 4. Segmented regression parameters showing predicted break points for each segment and regression coefficient for overall segmented linear model

Time of day	Break point time of day (se)	p*
White blood cells (10^9/L)	14.34 (0.069)	<0.001
Neutrophils (10^9/L)	14.62 (0.040)	<0.001
Monocytes (10^9/L)	13.27 (0.160)	<0.001
Lymphocytes (10^9/L)	16.12 (0.180)	<0.001
CRP (mg/L)	12.71 (0.220)	<0.01

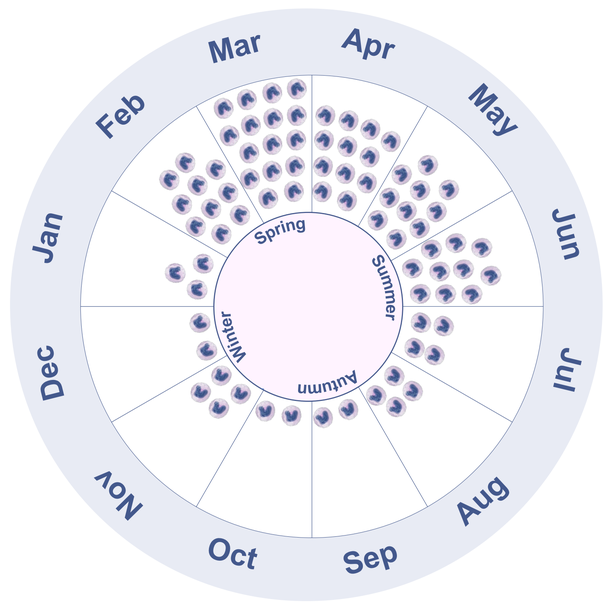
Conclusions

We report significant seasonal and daytime variability in multiple immune parameters in a large sample of the UK population

There was a statistically significant relationship between day length and neutrophils, lymphocytes and CRP that was not explained by temperature, vitamin D or any lifestyle factor.

These findings support the existence of photoperiod-dependent circadian and circannual patterns in the human immune system

The chronobiology of human immunity could impact susceptibly to infectious disease and the effectiveness of immunoprophylaxis and warrants further investigation.



Seasonality of Lymphocyte Counts

References

Halberg, F., Johnson, E., Brown, B.., and Bittner, J.. (1960). Susceptibility rhythm to E. coli endotoxin and bioassay. Proc. Soc. Exp. Biol. Med. 103, 142–144.
Dowell, S.F. (2001). Seasonal variation in host susceptibility and cycles of certain infectious diseases. Emerg. Infect. Dis. 7, 369–374.
Dopico, X.C., Evangelou, M., Ferreira, R.C., Guo, H., Pekalski, M.L., Smyth, D.J., Cooper, N., Burren, O.S., Fulford, A.J., Hennig, B.J., et al. (2015). Widespread seasonal gene expression reveals annual differences in human immunity and physiology. Nat. Commun. 6, 7000.
Yellon, S.M., and Tran, L.T. (2002). Photoperiod, reproduction, and immunity in select strains of inbred mice. J. Biol. Rhythm 17, 65–75.

Data Availability

The results of this study are published, Wyse *et al.*, iScience 24,102255, 2021 (https://doi.org/10.1016/j.isci.2021.102255). Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.102255. Code is available at https://github.com/cawyse9/Daily-and-Seasonal-Variation-in-Immune-Parameters-in-UK-Biobank. The data analysed in this study are available on application from www.ukbiobank.ac.uk.

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