

## General Reaction Score and CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> Cells Distributions Among Women with Aircraft Noise Stress

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### ABSTRACT

**Background:** One of the noise impacts is stress. The NK cells (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) are also one of the leukocyte subsets, which are responsive to the physiological stress and psychological stress. The aims of the research is to find out the correlation of the general reaction score with CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells distributions among women with aircraft noise stress in the area of Adi Sumarmo Airport of Solo, Indonesia.

**Methods:** The research design was an analytical survey with a cross sectional approach, taking location at the Dibal and Gagak Sipat Village, Boyolali District. The respondents who fulfilled the exclusive and inclusive criteria were selected by means of simple random sampling. The number of respondents was 39 and divided into 3 groups; Group 1 was exposed 92.29 dB of noise level (13 respondents); Group 2 was exposed 71.79 dB of noise level (13 respondents); and Group 3 was exposed 52.17 dB of noise level (13 respondents). The data were analyzed by Anova followed by post hoc test using LSD test completed with homogenous subsets and Pearson Correlation test.

**Results:** The Pearson Correlation test was showed that there was significant association between general reaction score with CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells distributions ( $r=0.589$ ;  $p=0.000$ ).

**Conclusion:** There is correlation of the general reaction score with CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells distributions among women with aircraft noise stress in the area of Adi Sumarmo Airport of Solo, Indonesia.

**Keywords:** Aircraft noise, CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>, women, Adi Sumarmo Airport

### ABSTRAK

General Reaction Score dan CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> pada wanita yang mengalami stres bising pesawat udara

**Latar belakang:** Salah satu dampak bising adalah stres. Natural killer cells (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) adalah salah satu subset leukosit yang sangat respon terhadap stres fisiologis maupun stres psikologis. Tujuan penelitian adalah untuk mengetahui hubungan antara general reaction score dengan jumlah sel NK (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) pada wanita yang memperoleh stres bising pesawat udara di sekitar Bandara Adi Sumarmo Solo, Indonesia.

**Metode:** Rancangan penelitian adalah survai analitik dengan pendekatan cross sectional. Lokasi di Desa Dibal dan Gagak Sipat, Kabupaten Boyolali. Responden yang memenuhi kriteria eksklusif dan inklusif diambil sejumlah 39 sebagai sampel dengan cara simple random sampling. Responden selanjutnya dibagi menjadi 3 kelompok; Kelompok 1 responden yang terpapar bising dengan intensitas 92,29 dB (13 responden); Kelompok 2 responden yang terpapar bising dengan intensitas 71.79 dB (13 responden); dan Kelompok 3 responden yang terpapar bising dengan intensitas 52.17 dB (13 responden). Data dianalisis dengan uji Anova dilanjutkan dengan post hoc test menggunakan LSD test completed with homogenous subsets dan Pearson Correlation test.

**Hasil:** Pearson Correlation test menunjukkan adanya hubungan yang signifikan antara general reaction score dengan jumlah sel NK (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) ( $r=0.589$ ;  $p=0.000$ ).

**Simpulan:** Penelitian ini menunjukkan bahwa ada hubungan antara general reaction score dengan jumlah sel NK (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) pada wanita yang mengalami stres bising pesawat udara di sekitar Bandara Adi Sumarmo Solo, Indonesia.

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## INTRODUCTION

An epidemiological research involving blue-collar workers, 1680 males and 688 females in Israel shows that for males, noise exposure level affected job dissatisfaction and post work irritability. For females it also intensified somatic complaints, anxiety and depression. All the distress symptoms were higher for females. Higher noise exposure levels were associated with increased accident and sickness absence for both sex.<sup>1</sup> This implies that in the twenty-first century noise exposure will still be a major public health problem.<sup>2</sup>

Around the International Airport of Adi Sumarmo Solo, Indonesia with the distance of less than 1,000 meters from the runway, the noise intensity of the high point activity ranges from 74.42 dB to 95.67 dB which was measured with weighted equivalent continuous perceived noise level (WECPNL). It is reported that 65% of the inhabitants in the region suffered sleeping disturbance, hearing impairment and annoyance.<sup>3</sup> At the same region, Hartono claims that the inhabitants exposed the aircraft noise with high intensity had the higher number of lymphocytes compared to those exposed with the low intensity aircraft noise.

There is sufficient scientific evidence that the noise influences on ischemic heart disease, hypertension, hearing impairment, sleeping disturbance, duodenum and gastric disorders. Other effects such as changes in the immune system, the evidence is limited.<sup>2</sup>

The noise of high intensity is more annoying than that of low intensity. The intermittent noise is more annoying than the continuous one.<sup>4</sup> Women are more sensitive in responding noise than men.<sup>1</sup> Statistically among the intermittent noise, the aircraft noise is significantly more annoying. The chronically exposed to noise is thought to bring about significant impacts if it happens more than a year.<sup>2,5</sup>

One of the impacts of exposure to noise is stress.<sup>2,6,7</sup> In response to a stressor, physiological changes are set into motion to help an individual cope the stressor. However, a chronic activation of these stress responses, which include the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis, results chronic production of glucocorticoid hormones and catecholamines.<sup>7,8</sup> Glucocorticoid receptors expressed on a variety of immune cells bind cortisol and interfered with the function of NF-kappa beta (NF-kB), which regulates the activity of cytokine in producing immune cells. Adrenergic receptors bind epinephrine and norepinephrine and activated cAMP response element binding protein, inducing the transcription of genes encoding for a variety of cytokines. The changes in gene expression mediated by glucocorticoid

hormones and catecholamines can disregulate the immune system. Lymphocytes, natural killer cells, macrophages and granulocytes exhibit receptors for many neuroendocrine products of the HPA and SAM axes, such as cortisol and catecholamines which may cause changes in cellular trafficking, proliferation, cytokine secretion, antibody production and cytolytic activity.<sup>9-11</sup>

General reaction score (GRS) was a rating scale with questionnaire to measure the annoyance level of the aircraft noise to the inhabitants who were exposed to it for years. The rating scale used to measure the annoyance level was questionnaire which was arranged and tested in terms of validity and reliability by Bullen and Hede.<sup>12</sup>

Natural Killer (NK) cells are important components of the innate immune systems, owing to their cytokine and chemokines production and ability to lyse target cells without prior sensitization. Human NK cells comprise  $\pm 15\%$  of all lymphocytes and are defined phenotypically by their expression of CD56 and CD16, lack of expression of CD3 (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>).<sup>13</sup> Among many indices of immune function, NK activity and NK cells subsets have been of interest to researchers because NK cells are known to be important in host defense against viral diseases and they appear to play a significant role in protection against neoplastic growth.<sup>14,15</sup> The NK cells are also one of the leukocyte subsets, which are responsive to the physiological stress and psychological stress.<sup>16</sup>

Based on the above elaborations, this research aims at finding out the correlation of the general reaction score with CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells distributions among women with aircraft noise stress in the area of Adi Sumarmo Airport of Solo, Indonesia.

## METHODS

### Research design

This research study was an analytical observational study with cross sectional design. It was conducted from July 2008 to June 2009 among residents in the neighborhood around of the runway of Adi Sumarmo International Airport of Solo, Indonesia, villages of Dibal and Gagak Sipat, Ngemplak subdistrict, Boyolali regency.

### Subjects

The study population comprised all residents of Dibal village and Gagak Sipat village, Ngemplak subdistrict, Boyolali regency who fulfilled the following criteria: female, married, housewife, 20-40 years old at age, and having lived in the area for at least 1 year. Exclusion

criteria were consumption of non-herbal or herbal medicines, pregnancy, hearing loss, infectious disease (colds, flu, and diarrhea), and diabetes mellitus.

The respondents who fulfilled the criteria were selected by means of simple random sampling. The sample size was calculated using the formula of Snedecor and Cochran or by using Win Episcopo 2.0 with estimated difference between means ( $\alpha=0.05$ ). For an expected confidence level of 95%, the expected significance level was 95%. Based on the results of previous studies in the area<sup>18</sup>, the number of lymphocytes  $S_D$  was 700;  $m_1$  was  $3.6 \times 10^3/\mu\text{l}$ ;  $m_2$  was  $2.5 \times 10^3/\mu\text{l}$ , and the number of subjects per group was 13. The total number of subjects were 39, who were divided into 3 groups, on the basis of the distance of their residential area from the runway. Group 1 respondents lived at a distance of less than 500 meters from the tip of the runway; group 2 respondents were subjects whose residential area was between 500 and 1,000 meters from the tip of the runway, while group 3 respondents lived at a distance of more than 1,000 meters from the tip of the runway.

**The noise measurement**

The noise exposure was measured using a sound level meter (Extech Model 407735, Japan) and rated according to WECPNL. In each of the two study areas measurement of noise was conducted at three different points with a portable sound level meter (SLM), and the acoustic physical parameter was measured in dB with A load. The SLM was placed with its filter parallel to the subject's ears. The SLM was set up at its maximum function of value to measure the peak noise level of aircraft passing over the areas so that the background noise level could be blocked. The acoustic physical parameter was recorded based on the peak noise level occurring at aircraft take-off and landing, and the time of occurrence of noise level was also recorded. The noise level was rated by using the WECPNL (weighted equivalent continuous perceived noise level) scale, according to the following equation:

$$\text{WECPNL} = \text{dB (A)} + 10 \log N - 27$$

$$N = N_1 + 3N_2 + 10N_3$$

dB (A) : Average decibel score of each peak level of aircraft activity in a day.

N : Number of aircraft arrivals and departures in 24 hours.

$N_1$  : Number of aircraft arrivals and departures between 07.00 and 19.00 Western Indonesia Time

$N_2$  : Number of aircraft arrivals and departures between 19.00 and 22.00 Western Indonesia Time

$N_3$  : Number of aircraft arrivals and departures between 22.00 and 07.00 Western Indonesia Time

The measurements in dB (A) were then converted into WECPNL in accordance with the number of aircraft passing over the area with in 24 hours.

**General reaction score**

General reaction score (GRS) was a rating scale with questionnaire to measure the annoyance level the aircraft noise to the inhabitants who were exposed to it for years. The rating scale used to measure the annoyance level was questionnaire which was arranged and tested in terms of validity and reliability by Bullen and Hede.<sup>12</sup>

**CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells**

The number of NK cells was calculated through the following: mononuclear cells/peripheral blood mononuclear cells (PBMC) were separated from 10 ml of the whole blood with Ficoll-Hypaque density-gradient centrifugate (30 minutes, 20°C, 400g). It was washed twice with PBS and stored in the medium of RPMI 1640 (GIBCO, Invitrogen) with 10% of fetal serum, penicillin (100 IU/ml) and streptomisin (100 µg/ml) at 4°C until analysis. NK cells were Enumerated with three-color immunophenotyping using suitable combinations of monoclonal antibodies (PharMingen, Sandiego, CA) conjugated fluorescein isothiocyanate (FITC), phycoerythrin (PE) and peridinin-chlorophyll protein (PerCP). Briefly, a sample of  $1 \times 10^6$  mononuclear cells (PBMC) was mixed with saturating amounts of monoclonal antibody conjugated with FITC (CD16), PE (CD56) and PerCP (CD3). After being washed twice with PBS, the stained cells were passed through a flow-cytometer (FACScan-Becton Dickinson). NK cells number in PBMC was determined as a percentage of CD16<sup>+</sup>CD56<sup>+</sup>CD3<sup>-</sup>.<sup>15-17</sup>

**Data analysis**

The study data analyzed by analysis of variance (Anova) to verify differences in general reaction score and number of NK cells, among the three groups of respondents. Pearsons product moment correlation test was used to investigate the correlation of general reaction score with number of NK cells.

**Ethical clearance**

The study participants were subject to the ethical clearance-related measures and procedures. Ethical clearance was obtained from the Ethical Review

Committee, Faculty of Medicine, Sebelas Maret University. The research study was also subjected to confidentiality and anonymity principles towards the data of the respondents.

## RESULTS

The data of noise intensity level (WECPNL), general reaction score (GRS) and  $CD56^+CD16^+CD3^-$  cells of each group is presented in Table 1 below.

The result of measurement on the intensity levels of the aircraft noise with WECPNL was not much different from that of measurement on the intensity levels of the aircraft noise with WECPNL conducted by before, where the intensity levels in area 1, 2, and 3 were 92.29 dB, 71.49 dB, and 52.17 dB respectively.<sup>3,18</sup>

The result of the measurement for each area as stated above was then followed up with the measurement of GRS towards 39 respondents. The result of measurement shows that there was a real difference between the groups tested with Anova followed up with

post hoc test ( $\alpha=0.05$ ) as indicated by the value of  $p=0.000$  (seen in Figure 1).

Based on Table 1, it can be seen that the average numbers of NK cells ( $CD56^+CD16^+CD3^-$ ) of the respondents in groups 1, 2, and 3 were 18.80%, 17.52%, and 12.88% respectively. Such a result of the Anova followed up with post hoc test ( $\alpha=0.05$ ) of the NK cell number ( $CD56^+CD16^+CD3^-$ ) indicates that there was a significant difference of the NK cell number ( $CD56^+CD16^+CD3^-$ ) among the three different groups as shown by the value of  $p=0.038$  ( $\alpha=0.05$ ). Meanwhile, the post hoc test shows that there was a significant difference of the NK cell number ( $CD56^+CD16^+CD3^-$ ) between group 1 and group 3, and between group 2 and group 3 as shown by the value of  $p<0.05$  (seen in figure 2).

Based on Table 2, the Pearson Correlation test was showed that there was significant association between GRS with  $CD56^+CD16^+CD3^-$  cells distributions ( $r=0.589$ ;  $p=0.00$ ).

Table 1. The result of noise intensity level (WECPNL), GRS, and the number of NK cells ( $CD56^+CD16^+CD3^-$ ) of each group

|                               | Group 1<br>(n=13)  | Group 2<br>(n=13)  | Group 3<br>(n=13)  | p     |
|-------------------------------|--------------------|--------------------|--------------------|-------|
| The intensity level (dB)      | 92.29              | 71.49              | 52.17              |       |
| GRS                           | $8.30 \pm 1.70^a$  | $4.85 \pm 2.03^b$  | $3.21 \pm 1.23^c$  | 0.000 |
| $CD56^+CD16^+CD3^-$ cells (%) | $18.80 \pm 6.85^a$ | $17.52 \pm 5.62^a$ | $12.88 \pm 5.17^b$ | 0.038 |

Notes: The different letters a, b, and c at one row show that there is a real difference in the test with Anova, which is followed up with post hoc test with  $\alpha=0.05$ .

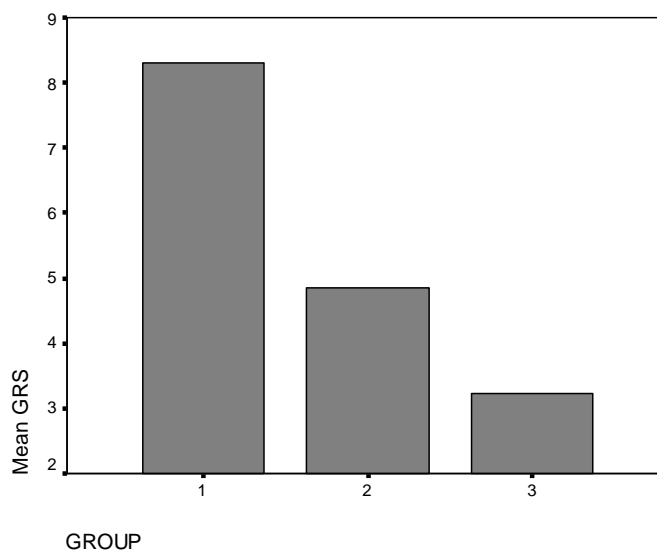


Figure 1. General reaction score (GRS) in the subjects group according to the tertile distribution of aircraft noise exposure (Anova;  $p=0.000$ ).

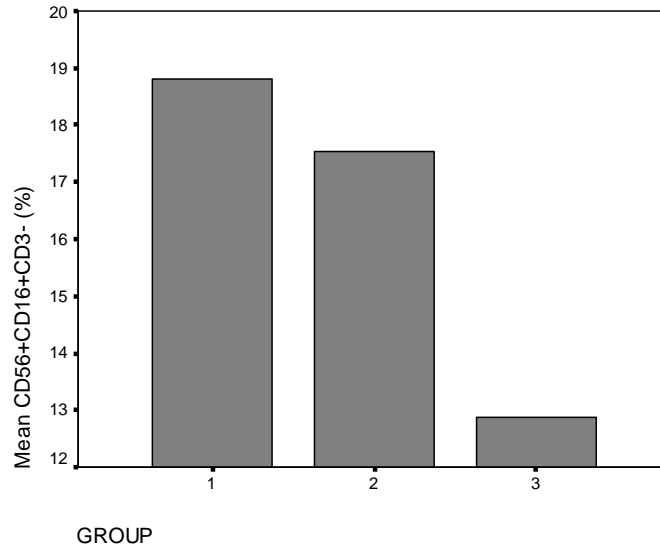


Figure 2. The cell numbers of CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> in the subjects group according to the tertile distribution of aircraft noise exposure (Anova: p=0.038)

Table 2. Pearson's correlation coefficient between GRS and the number of NK cells (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>)

| Variables              |                     | GRS    | The number of NK cells |
|------------------------|---------------------|--------|------------------------|
| GRS                    | Pearson correlation | 1      | 0.589*                 |
|                        | Sig. (2-tailed)     | .      | 0.000                  |
|                        | N                   | 39     | 39                     |
| The number of NK cells | Pearson correlation | 0.589* | 1                      |
|                        | Sig. (2-tailed)     | 0.000  | .                      |
|                        | N                   | 39     | 39                     |

\*p<0.01 (2-tailed)

**DISCUSSION**

Based on the result of the measurement, a conclusion can be drawn that the group of respondents in area 1 with the intensity level of 92.29 dB underwent higher general annoyance than those in area 2 with the intensity level of 71.49 dB and those in area 3 with the intensity level of 52.17 dB. Similarly, the group of respondents in area 2 underwent higher general annoyance than those in area 3. This is in compliant with the theories that the response to noise may partly depend on characteristic of sound. These include intensity, frequency, complexity of sound and duration (whether intermittent or continuous noise). The high intensity level of the noise is more annoying than the low intensity level.<sup>2,4,7,19</sup>

The results of the research above show that the respondents around the airport exposed to the aircraft noise with the intensity level of 92.29 dB measured with the scale of WECPNL for more than a year suffered more from annoyance (stress), which caused the increasing number of the NK cells (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>)

than the control group exposed to aircraft noise with the intensity level of 52.17 dB measured with the scale of WECPNL. The treatment group of respondents exposed to the aircraft noise with the intensity level of 71.49 dB measured with the scale of WECPNL also suffered more from annoyance which caused the increasing number of the NK cells (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) than the control group of respondents. Meanwhile, the number of NK cells (CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup>) of the group of respondents exposed to the aircraft noise with the intensity level of 92.29 dB and that of the group of respondents exposed to the aircraft noise with the intensity level of 71.49 dB were not significantly different.

It is known that the continuous recurrent aircraft noise will bring about stress. The chronic stress will increase the cortisol and catecholamine levels through HPA and SAM courses.<sup>8,9,10,20</sup> The increase of cortisol level and catecholamine levels through the glucocorticoid receptors (GR) and adrenergic receptors will inhibit several cytokines generated by NK cells (INF- , INF- ,

IFN- $\gamma$ , IL-10, GM-CSF, and TNF- $\alpha$ ). Interferon is major regulator of NK cells.<sup>9</sup> IFN- $\gamma$  functioned to inhibit the proliferation of NK cells through the inhibition of IL-4. The decreased INF- $\gamma$  production will cause the increasing of proliferation of NK cells.<sup>21,22</sup>

IL-2 takes a role to increase the proliferation of NK cells through the interleukin-2 receptors (IL-2R $\alpha$ ) which are expressed by NK cells of CD56<sup>bright</sup> and IL-2R $\beta$  receptors which are expressed by NK cells of CD56<sup>dim</sup>. In relation with the proliferation response, the two receptors have a high proliferation response toward IL-2 with a low dosage and do not have any responses if both receive a high dosage from IL-2 particularly for IL-2R $\alpha$  which was expressed by NK cells of CD56<sup>dim</sup>. The decrease of the level of IL-2 (low-dosage) due to the inhibition of the activity of glucocorticoid and catecholamine will cause the proliferation of NK cells to increase.<sup>13</sup>

## CONCLUSION

This study indicated that there was correlation of the general reaction score with CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells distributions among women with aircraft noise stress in the area of Adi Sumarmo Airport of Solo, Indonesia. The aircraft noise at the intensity level of 92.29 dB measured with WECPNL with the length exposure more than a year may cause a stress towards the inhabitants around Adi Sumarmo International Airport, Solo as shown by the increasing in the general reaction score and CD56<sup>+</sup>CD16<sup>+</sup>CD3<sup>-</sup> cells distributions.

## Recommendation

Based on the results of the research, preventive measures are needed in dealing with the aircraft noise so that it will not produce more bad impacts towards the inhabitants around Adi Sumarmo International Airport, Solo. One of the efforts that should be considered is to relocate the inhabitants to safer settlements.

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