The Impact of Sleep Deprivation on Sleepiness, Risk Factors and Professional Performance in Medical Residents

Oleg Pikovsky MD[1]*, Maly Oron MD[1]*, Arthur Shiyovich MD[2]*, Zvi H. Perry MD MA[3] and Lior Nesher MD[1]

[1]Division of Internal Medicine, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[2]Department of Medicine E, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[3]Department of Surgery and Soroka University Medical Center, Prywes Center for Medical Education, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

ABSTRACT: **Background:** Prolonged working hours and sleep deprivation can exert negative effects on professional performance and health.

Objectives: To assess the relationship between sleep deprivation, key metabolic markers, and professional performance in medical residents.

Methods: We compared 35 residents working the in-house night shift with 35 senior year medical students in a cross-sectional cohort study. The Epworth Sleepiness Scale (ESS) questionnaire was administered and blood tests for complete blood count (CBC), blood chemistry panel, lipid profile and C-reactive protein (CRP) were obtained from all participants.

Results: Medical students and medical residents were comparable demographically except for age, weekly working hours, reported weight gain, and physical activity. The ESS questionnaires indicated a significantly higher and abnormal mean score and higher risk of falling asleep during five of eight daily activities among medical residents as compared with medical students. Medical residents had lower high density lipoprotein levels, a trend towards higher triglyceride levels and higher monocyte count than did medical students. CRP levels and other laboratory tests were normal and similar in both groups. Among the residents, 5 (15%) were involved in a car accident during residency, and 63% and 49% reported low professional performance and judgment levels after the night shift, respectively.

Conclusions: Medical residency service was associated with increased sleepiness, deleterious lifestyle changes, poorer lipid profile, mild CBC changes, and reduced professional performance and judgment after working the night shift. However, no significant changes were observed in CRP or in blood chemistry panel. Larger prospective cohort studies are warranted to evaluate the dynamics in sleepiness and metabolic factors over time.

IMAJ 2013; 15: 739–744

KEY WORDS: medical residents, night shift, sleepiness, lipid profile, C-reactive protein (CRP), professional performance

For Editorial see page 768

A U-shaped association has been demonstrated between sleep duration and mortality risk [1]. Recent reports showed similar U-shaped associations between sleep duration and morbidity risk for patients with diabetes mellitus, hypertension, obesity, atherosclerosis, dyslipidemia and coronary artery disease [2-4]. Furthermore, sleep disorders have a negative impact on mood and quality of life, as found in studies comprising mostly middle-aged or older adults. Using sleep and health questionnaires, Steptoe et al. [5] studied 17,465 university students (young adults) in 27 countries and reported that short sleep duration (< 7 hours) increased the adjusted odds of poor health in both men and women, whereas no relationship was found between long sleep duration (> 8 hours) and health outcomes.

It has been indicated that sleep characteristics may exert powerful effects on immune function, which raises the possibility that inflammatory response to sleep deprivation is one mechanism linking short sleep duration as well as certain sleep disorders to cardiovascular, respiratory and metabolic disorders [6]. Other reports demonstrated that sleep loss might result in elevated C-reactive protein levels, an inflammatory marker of cardiovascular risk [7,8]. Physicians – during their residency training – constitute a unique population with long working hours and considerable sleep deprivation that are further aggravated by the medical workforce shortage around the world, including Israel [9]. Several studies have demonstrated the negative influence of long work shifts and sleep deprivation on residents' cognitive and professional performance, as well as increased risk of motor vehicle accidents [10,11]. Less is known about the effect of sleep deprivation on residents' health status and the possible risk of metabolic disorders. The aims of the current study were to assess the effect of sleep deprivation in medical residents on sleepiness level, lifestyle changes, lipid profile, CRP levels and professional performance.

***The first three authors contributed equally to this study**

CRP = C-reactive protein

SUBJECTS AND METHODS

A cross-sectional cohort study was conducted during the years 2009–2010 in 35 medical residents aged between 25 and 40 years who work at least six night shifts (approximately 26 hours) per month at the Soroka University Medical Center. The control group comprised 35 medical students in their 5th or 6th year of medical school (a 6 year program) without night shift duty. These students were chosen based on the assumption that the demographic characteristics of both groups in our institute are similar. Exclusion criteria were: a) ongoing medical treatment except for oral contraceptives, b) chronic disease, c) acute illness or surgical procedure within 2 weeks prior to the study, or d) pregnancy or less than 3 months postpartum. The study was approved by the Soroka Ben-Gurion University Medical Center Institutional Review Board. All the participants provided informed written consent after the purpose and nature of the study were explained to them.

ASSESSMENTS AND STUDY PROTOCOL

For evaluation, questionnaires were administered and blood tests were drawn from all the participants at 8 a.m. after a night shift for the residents or following a regular school day for the students. All subjects were asked to abstain from eating and drinking for 11 hours prior to the blood test. The questionnaire contained three parts:

- Demographic information, cardiovascular risk factors, and evaluation of working and sleeping characteristics
- The standard Epworth Sleepiness Scale questionnaire [12] in which the subject rated his or her probability of falling asleep on a scale of increasing probability between 0 and 3, during eight different activities that most people perform in their daily lives, though not necessarily every day. The scores for the eight questions were added together to obtain a single value. A score between 0 and 10 was considered normal while a value in the 10–24 range indicated that expert medical advice should be sought [12]
- Residents were asked to rate their performance and judgment after a night shift for six categories on a Likert-type scale (0 = low, 5 = high).

Blood testing included the following: a) complete blood count, b) a comprehensive metabolic panel (including liver function tests, kidney function tests, albumin), c) lipid profile, and d) CRP.

DATA ANALYSIS

Data were analyzed using SPSS V. 18 software (PASW, Chicago, IL, USA). Data are presented as mean ± standard deviation for continuous variables, as frequencies and as a percent of categories for other variables. Comparisons between groups were performed with Student's *t*-test for continuous variables and with the Mann-Whitney U test, and the chi-square test was used for categorical variables. Reliability was assessed using Cronbach's-alpha. $P < 0.05$ was considered significant for two-sided probability values.

RESULTS

The study comprised 70 participants: 35 medical residents and 35 medical students. The baseline characteristics of the study population are presented in Table 1. The two groups were similar in all parameters except for age, weekly working hours, reported rate of weight gain, and reduced extracurricular and aerobic physical activities [Table 1]. When residents were not working the night shift the number of hours slept a night was similar in the two groups; however, on a night shift the residents slept a mean of 2.3 ± 0.75 hours.

Analysis of the ESS questionnaires indicated a significantly higher risk of falling asleep during five of eight daily activities among residents compared to the students [Table 2]. Furthermore, while the mean total ESS score of the students was in the upper normal limit, the mean score of the residents was significantly higher and within the abnormal range. Internal consistency of the questionnaire was evaluated using Cronbach's-α coefficient, which showed a fair result: α = 0.79.

The laboratory tests of the two groups are presented in Table 3. The CBC demonstrated significantly lower mean corpuscular hemoglobin concentration and red cell distribution width, and higher mean platelet volume and monocyte and platelet count in residents compared to students. The blood

ESS = Epworth Sleepiness Scale
CBC = complete blood count

Table 1. Baseline characteristics; comparison between residents and students

	Residents	Students	*P*
Age (yr)	32.83 ± 2.995	28.51 ± 1.946	‹ 0.001
Gender: male	(62.9%) 22	48.6%) (17	0.229
Born in Israel	(70.6%) 24	(88.6%) 31	0.332
Smoker	(17.6%) 6	(8.8%) 3	0.283
Smoking pack-years	6.314 ± 10.51	4.333 ± 0.6667	0.643
Hours of sleep per night*	6.11 ± 0.796	6.23 ± 0.780	.5460
Hours of work per week**	68.97 ± 10.51	45.18 ± 6.384	‹ 0.001
Extracurricular activities	13 (39.4%)	20 (76.9%)	0.004
Aerobic physical activity	(47.1%) 16	80.0%) (28	0.014
Weight gain during residency/ medical school	17 (50%)	1 (3.1%)	‹ 0.001

Values are presented as n (%) or mean ± SD
*For residents: when not working the night shirt
**For students: formal study hours (and working hours if employed)

Table 2. Standard Epworth Sleepiness Scale results, comparison between groups (mean ± SD)

Activity	Residents	Students	*P**
Sitting and reading	2.12 (± 0.913)	1.51 (± 1.12)	0.024
Watching TV	2.09 (± 0.9)	1.26 (± 1.04)	0.001
Sitting inactive in a public place	1.15 (± 1.02)	1.03 (± 0.71)	0.871
As a passenger in a car for an hour without a break	1.76 (± 1.18)	1.83 (± 1.07)	0.861
Lying down to rest in the afternoon when circumstances permit	2.26 (± 1.02)	2.49 (± 0.83)	0.413
Sitting and talking to someone	0.62 (± 0.74)	0.23 (± 0.49)	0.014
Sitting quietly after a lunch without alcohol	1.65 (± 0.95)	1.20 (± 0.9)	0.050
In a car, while stopped for a few minutes in the traffic	0.58 (± 0.66)	0.18 (± 0.39)	0.005
Total score**	12.121 ± 5.122	9.8529 ± 3.84654	0.045

*Calculated using Mann-Whitney test

**Calculated using Student's *t*-test

chemistry analysis showed significantly higher alanine aminotransferase level and lower albumin in residents compared to students. With regard to the lipid profile, the residents displayed significantly low high density lipoprotein level and borderline elevation in triglyceride level as compared to the students. CRP levels were similar in both groups; however, a significant medium correlation was found between CRP levels and the number of hours worked a week (Pearson's correlation 0.315, $P = 0.011$). No other significant differences were found in the laboratory workup between residents and students. No correlation could be found between the ESS score and HDL (Pearson's correlation 0.009, $P = 0.944$) or triglyceride levels (Pearson's correlation 0.018, $P = 0.888$).

Sixty-three percent of the residents reported a low (0–2) professional performance level after the night shift while only 3% reported a high performance level (score 4–5) [Figure 1]. Similarly, 49% of the medical residents reported a low (0–2) level of professional judgment following the night shift, while only 14.3% reported a high level of professional judgment (score 4–5). Medical residents reported working an additional mean of 2 ± 1.18 hours after completion of their night shift. Twenty-nine residents (85%) reported driving regularly after working the night shift, 4 (11%) stated they tend to fall asleep while driving in such circumstances, and 5 (15%) admitted having been involved in a car accident during their medical residency.

DISCUSSION

The current study compared level of sleepiness, lifestyle changes, and blood testing (lipid profile, CBC, chemistry, CRP) of residents throughout their residency with a control

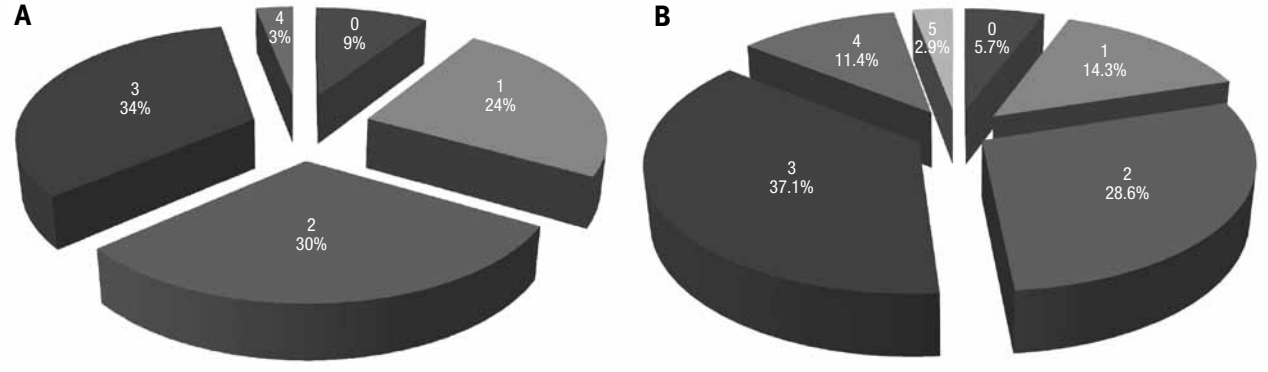
HDL = high density lipoprotein

Table 3. Laboratory results, CBC, chemistry and lipid profile in the two groups

	Residents (mean ± SD)	Students (mean ± SD)	Reference ranges	*P*
CBC				
Hemoglobin (g/dl)	14.348 ± 1.0955	14.386 ± 1.2857	M: 14–18 F: 12–16	0.898
Hematocrit (%)	43.070 ± 3.2904	42.051 ± 3.4617	M: 42–52 F: 37–47	0.219
Mean corpuscular volume (fl)	86.130 ± 4.6835	85.109 ± 4.4242	80–94	0.358
Mean corpuscular hemoglobin concentration (g/dl)	33.285 ± 0.7678	34.214 ± 0.6117	27–31	< 0.001
Red blood cell distribution width (%)	13.156 ± 0.7251	13.843 ± 0.6132	11.5–14.5	< 0.001
White blood cells (103/µl)	7.866 ± 2.055	7.15 ± 1.78	4.8–10.8	0.129
Neutrophils (%)	57.788 ± 8.5381	55.971 ± 9.0029	50–75	0.397
Lymphocytes (%)	32.05 ± 8.255	32.29 ± 8.424	18–42	0.904
Monocytes (%)	7.003 ± 1.6595	5.797 ± 1.5741	2–11	0.003
Eosinophils (%)	2.245 ± 1.0244	3.451 ± 3.4039	1–3	0.052
Basophils (%)	0.500 ± 0.2000	0.466 ± 0.3597	0–1.5	0.632
Platelets (103/µl)	262.15 ± 54.059	229.34 ± 47.229	130–400	0.010
Mean platelet volume (fl)	8.958 ± 1.2023	7.920 ± 0.8498	7.5–11.5	< 0.001
C-reactive protein (mg/L)	0.3226 ± 0.948	0.1289 ± 0.298	0–5	0.260
Chemistry				
Glucose (mg/dl)	86.81 ± 13.487	82.06 ± 7.384	70–100	0.075
Urea (mg/dl)	29.98 ± 7.300	28.89 ± 7.783	17–43	0.549
Creatinine (mg/dl)	0.832 ± 0.1319	0.850 ± 0.1388	0.67–1.17	0.581
Uric acid (mg/dl)	5.374 ± 1.2485	5.171 ± 1.3629	3.5–7.2	0.523
Sodium (mEq/L)	138.97 ± 2.695	139.66 ± 1.494	135–145	0.192
Potassium (mEq/L)	4.250 ± 0.3090	4.366 ± 0.3019	3.5–5.1	0.126
Calcium (mg/dl)	9.910 ± 0.3000	9.914 ± 0.2756	8.5–10.5	0.948
Phosphorus (mg/dl)	3.711 ± 0.5082	3.883 ± 0.3658	2.5–5	0.114
Magnesium (mg/dl)	2.132 ± 0.1449	2.097 ± 0.1248	1.6–2.6	0.287
Alkaline phosphatase (U/L)	74.38 ± 17.643	68.91 ± 17.272	30–120	0.198
Aspartate aminotransferase (U/L)	25.47 ± 15.343	23.43 ± 7.171	0–35	0.479
Alanine aminotransferase (U/L)	27.18 ± 21.628	19.23 ± 7.341	0–45	0.049
Creatine phosphokinase (U/L)	141.29 ± 134.893	145.88 ± 155.411	20–200	0.897
Lactate dehydrogenase (U/L)	398.50 ± 55.209	389.03 ± 96.521	230–480	0.620
Gamma-glutamyl transpeptidase (U/L)	23.62 ± 12.830	19.20 ± 5.373	0–55	0.070
Albumin (g/dl)	4.583 ± 0.2573	4.763 ± 0.3135	3.5–4.2	0.012
Total protein (g/dl)	7.731 ± 0.4243	7.874 ± 0.3776	6.6–8.3	0.142
Lipid profile				
Total cholesterol (mg/dl)	177.47 ± 37.497	188.86 ± 30.824		0.172
Triglycerides (mg/dl)	113.94 ± 72.746	87.54 ± 39.806		0.068
High density lipoprotein (mg/dl)	48.55 ± 12.613	60.97 ± 12.833		< 0.001
Low density lipoprotein (mg/dl)	106.97 ± 33.972	110.46 ± 23.543		0.628
Non-HDL (mg/dl)	129.94 ± 38.232	127.80 ± 26.905		0.792

M = male, F = female, HDL = high density lipoprotein

Figure 1. Residents' evaluation of their performance and judgment after working the night shift for six categories using a Likert-type scale (0 = low, 5 = high). **[A]** Professional performance after the night shift. **[B]** Professional judgment after the night shift



group of final year students from the same university center. In addition to the residents' expected higher mean age and more working hours per week, both groups were found to be similar in most baseline characteristics except for the lower rate of aerobic physical activity and extracurricular activities in the residents group. The latter findings are consistent with previous reports and could be attributed to the extended working hours [13]. Furthermore, the working hours of both students and residents exceeded those in the same age groups of the general population in the country: 39.2 hours (age 25–34 years) and 40.7 hours (age 35–44) respectively [14].

A higher and abnormal mean ESS score was found in the residents group, indicating increased sleepiness and higher risk of falling asleep during daily activities as compared with students. Nevertheless, the students' mean ESS score was also in the upper limit of normal, indicating increased sleepiness in many subjects in this group. These findings are in accordance with previous reports of excessive sleepiness among residents [10,15], which could have a deleterious impact on cognitive functioning and hence quality of patient care and clinical outcomes [10,11,15-18]. These results are also supported by the reported low professional performance and judgment of residents after working the night shift in the current study. Furthermore, the excessive sleepiness was reported to be associated with increased risk for motor vehicle accidents [15,19] and with the high rate of residents falling asleep while driving.

Overall, the CBC of the medical residents and students were similar, with moderate changes such as lower MCHC and RDW and higher volume of platelets and monocytes in residents. Although the latter two are of unclear clinical significance, increased monocyte count could be related to higher risk and severity of coronary atherosclerosis [20]. Platelets, which are an acute-phase reactant, rising in association with an increase in interleukin-6 and tumor necrosis factor-alpha levels could be an indicator of increased inflammatory processes [21]. Nevertheless, while CRP, an inflammatory marker of cardiovascular risk, was similar in residents and students, a medium correlation was found between CRP levels and the mean number of working hours per week. These findings are inconsistent with previous reports that suggested an increase in CRP as a result of sleep deprivation [7,8]; however, those reports evaluated the effects of acute or sub-acute sleep deprivation rather than chronic shift work-associated sleep deprivation reported here. Ramey et al. [22] conducted a study in police officers aged 20–63 years but did not find an association between CRP and shift or sleep duration. It is possible that physiological adjustment or compensating mechanisms prevent the overt pro-inflammatory state associated with acute sleep deprivation, when it becomes chronic. An increase in leukocyte levels (mostly neutrophils and monocytes) was found following acute as well as chronic sleep restriction [17]. Although changes in other markers (IL-6, IL-17, TNFα, myeloperoxidase) were found in chronic and acute sleep restrictions as well, but with different patterns [17], it seems clear that screening is needed for novel pro-inflammatory biomarkers altered specifically by sleep deprivation [17]. Considering the severity of sleepiness and neurobehavioral impairment in medical residents, it has been shown that short-term acute sleep loss and chronic partial sleep restriction have similar effects [18].

Residents displayed significantly lower HDL levels (by approximately 20%, $P < 0.001$) and higher triglycerides (by approximately 25%, $P = 0.068$), well-known cardiovascular risk factors, compared to students. These findings are consistent with reports of low HDL and high triglyceride levels associated with short sleep durations and shift work-

MSHC = mean corpuscular hemoglobin concentration
RDW = red cell distribution width
IL = interleukin
TNFα = tumor necrosis factor-alpha

ers [2,3,23]. Mechanisms such as a decrease in the blood concentration of leptin, which acts to suppress appetite, or an increase in the blood concentration of ghrelin, which promotes appetite due to sleep restriction, may be responsible for the associations between sleep restriction and these changes in lipid profile [2,24]. Furthermore, metabolic syndrome (a combination of visceral obesity, dyslipidemia, and abnormal blood pressure and glucose levels), in which insulin resistance plays a central role, has been prospectively shown to be causally linked to night shifts in health care workers [25]. In a 4 year prospective follow-up, visceral obesity was found to be the most prominent risk factor with increased frequency in health care night shift workers compared to daytime workers (14.2% vs. 7.7% respectively) [25]. A significant correlation between ESS score and HDL levels was not found in the current study. Other lifestyle changes in the medical residents group could also be responsible for the observed lipid abnormalities, e.g., lower rate of physical activity.

The blood chemistry test results of the residents and students were similar with slightly increased alanine aminotransferase and reduced albumin levels in the residents group, but this is unlikely to have major clinical consequences.

LIMITATIONS

This was a small cross-sectional pilot study that may have been underpowered to detect statistical significance in several of the parameters that were tested. Moreover, we were limited in choosing the parameters we would assess since some variables were not measured, such as insulin levels, coffee consumption, sleep quality and quantity, objective functioning tests, weight gain over time and hemodynamic values over time. Furthermore, a certain degree of bias due to the self-assessment nature of the study could not be ruled out. A larger prospective study with regular testing points in participants after a regular night sleep and after night shifts would shed light on the changes that the human body undergoes following chronic sleep deprivation.

CONCLUSIONS

The results of the current study indicate that medical residents working nearly 70 hours a week suffer from increased and abnormal sleepiness, lower HDL, higher triglyceride levels, and changes in monocytes and platelet count as compared to medical students. C-reactive protein levels, other lipid profile tests and blood chemistry analyses were found to be normal and similar in both groups. Residents reported reduced professional performance and judgment after working the night shift, as well as a high incidence of falling asleep while driving and of being involved in a motor vehicle accident after such shifts.

We propose that it is of public interest as well as safety that a larger prospective cohort study of medical residents throughout their residency be conducted, designed to evaluate fatigue characteristics and their relationship with metabolic parameters in this subgroup.

Acknowledgments

This study was supported in part by a grant from the Toman Faculty Fund for Medical Research of the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel. The authors are grateful to the students and the residents who willingly participated in the study.

Corresponding author:
Dr. A. Shiyovich
Dept. of Medicine E, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel
Phone/Fax: (972-3) 937-6506
email: arthur.shiyovich@gmail.com

References

1. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 2002; 59 (2): 131-6.
2. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004; 1 (3): e62.
3. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 2006; 29 (8): 1009-14.
4. Zee PC, Turek FW. Sleep and health: everywhere and in both directions. *Arch Intern Med* 2006; 166 (16): 1686-8.
5. Steptoe A, Peacey V, Wardle J. Sleep duration and health in young adults. *Arch Intern Med* 2006; 166 (16): 1689-92.
6. Faraut B, Touchette E, Gamble H, et al.Short sleep duration and increased risk of hypertension: a primary care medicine investigation. *J Hypertension* 2012; 30 (7): 1354-63.
7. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* 2004; 43 (4): 678-83.
8. van Leeuwen WM, Lehto M, Karisola P, et al. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PloS One* 2009; 4 (2): e4589.
9. Gofin Y, Afek A, Derazne E, Toker A, Shamiss A. A model for assessing the gap between physician residency demand and present status. *IMAJ* 2012; 14 (5): 275-80.
10. Kim HJ, Kim JH, Park KD, Choi KG, Lee HW. A survey of sleep deprivation patterns and their effects on cognitive functions of residents and interns in Korea. *Sleep Med* 2011; 12 (4): 390-6.
11. Suozzo AC, Malta SM, Gil G, Tintori F, Lacerda SS, Nogueira-Martins LA. Attention and memory of medical residents after a night on call: a cross-sectional study. *Clinics (Sao Paulo)* 2011; 66 (3): 505-8.
12. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14 (6): 540-5.
13. Jamal MH, Rousseau MC, Hanna WC, Doi SA, Meterissian S, Snell L. Effect of the ACGME duty hours restrictions on surgical residents and faculty: a systematic review. *Acad Med* 2011; 86 (1): 34-42.
14. Central Bureau of Statistics, Israel, 2009. Weekly work hours and average weekly work hours per employed person, by age, population, group and sex. http://www.cbs.gov.il/publications10/1417/pdf/t02_14.pdf
15. Reed DA, Fletcher KE, Arora VM. Systematic review: association of shift length, protected sleep time, and night float with patient care, residents' health, and education. *Ann Intern Med* 2010; 153 (12): 829-42.
16. Bhavsar J, Montgomery D, Li J, et al. Impact of duty hours restrictions on quality of care and clinical outcomes. *Am J Med* 2007; 120 (11): 968-74.
17. Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Med Rev* 2012; 16 (2): 137-49.
18. Veasey S, Rosen R, Barzansky B, Rosen I, Owens J. Sleep loss and fatigue in

residency training: a reappraisal. *JAMA* 2002; 288 (9): 1116-24.

19. Fruchtman Y, Moser AM, Perry ZH. Fatigue in medical residents – lessons to be learned. *La Medicina del lavoro* 2011; 102 (5): 455-63.
20. Huang G, Zhong XN, Zhong B, et al.Significance of white blood cell count and its subtypes in patients with acute coronary syndrome. *Eur J Clin Invest* 2009; 39 (5): 348-58.
21. Araneda M, Krishnan V, Hall K, Kalbfleisch J, Krishnaswamy G, Krishnan K. Reactive and clonal thrombocytosis: proinflammatory and hematopoietic cytokines and acute phase proteins. *South Med J* 2001; 94 (4): 417-20.
22. Ramey SL, Perkhounkova Y, Moon M, Budde L, Tseng HC, Clark MK. The effect of work shift and sleep duration on various aspects of police officers' health. *Workplace Health Safety* 2012; 60 (5): 215-22.
23. Thomas C, Power C. Shift work and risk factors for cardiovascular disease: a study at age 45 years in the 1958 British birth cohort. *Eur J Epidemiol* 2010; 25 (5): 305-14.
24. Chaput JP, Despres JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Quebec family study. *Obesity* 2007; 15 (1): 253-61.
25. Pietroiusti A, Neri A, Somma G, et al. Incidence of metabolic syndrome among night-shift healthcare workers. *Occ Environ Med* 2010; 67 (1): 54-7.

Capsule

The genesis and source of the H7N9 influenza viruses causing human infections in China

A novel H7N9 influenza A virus first detected in March 2013 has since caused more than 130 human infections in China, resulting in 40 deaths. Preliminary analyses suggest that the virus is a reassortant of H7, N9 and H9N2 avian influenza viruses and carries some amino acids associated with mammalian receptor binding, raising concerns of a new pandemic. However, neither the source populations of the H7N9 outbreak lineage nor the conditions for its genesis are fully known. Using a combination of active surveillance, screening of virus archives, and evolutionary analyses, Tsan-Yuk Lam et al. show that H7 viruses probably transferred from domestic duck to chicken populations in China on at least two independent occasions. The authors show that the H7 viruses subsequently reassorted with enzootic H9N2 viruses to generate the H7N9 outbreak lineage and a related previously unrecognized H7N7 lineage. The H7N9 outbreak lineage has spread over a large geographic region and is prevalent in chickens at live poultry markets, which are thought to be the immediate source of human infections. Whether the H7N9 outbreak lineage has, or will, become enzootic in China and neighboring regions requires further investigation. The discovery here of a related H7N7 influenza virus in chickens that has the ability to infect mammals experimentally suggests that H7 viruses may pose threats beyond the current outbreak. The continuing prevalence of H7 viruses in poultry could lead to the generation of highly pathogenic variants and further sporadic human infections, with a continued risk of the virus acquiring human-to-human transmissibility.

Nature 2013; 502: 241

Eitan Israeli

Capsule

Characterization of H7N9 influenza A viruses isolated from humans

Avian influenza A viruses rarely infect humans; however, when human infection and subsequent human-to-human transmission occurs, worldwide outbreaks (pandemics) can result. The recent sporadic infections of humans in China with a previously unrecognized avian influenza A virus of the H7N9 subtype (A(H7N9)) have caused concern owing to the appreciable case-fatality rate associated with these infections (more than 25%), potential instances of human-to-human transmission, and the lack of pre-existing immunity among humans to viruses of this subtype. Watanbe and associates have characterized two early human A(H7N9) isolates, A/Anhui/1/2013 (H7N9) and A/Shanghai/1/2013 (H7N9); hereafter referred to as Anhui/1 and Shanghai/1, respectively. In mice, Anhui/1 and Shanghai/1 were more pathogenic than a control avian H7N9 virus (A/duck/Gunma/466/2011 (H7N9); Dk/GM466) and a representative pandemic 2009 H1N1 virus (A/California/4/2009 (H1N1pdm09); CA04). Anhui/1, Shanghai/1 and Dk/GM466 replicated well in the nasal turbinates of ferrets. In non-human primates, Anhui/1 and Dk/GM466 replicated efficiently in the upper and lower respiratory tracts, whereas the replicative ability of conventional human influenza viruses is typically restricted to the upper respiratory tract of infected primates. By contrast, Anhui/1 did not replicate well in miniature pigs after intranasal inoculation. Critically, Anhui/1 transmitted through respiratory droplets in one of three pairs of ferrets. Glycan arrays showed that Anhui/1, Shanghai/1 and A/Hangzhou/1/2013 (H7N9) (a third human A(H7N9) virus tested in this assay) bind to human virus-type receptors, a property that may be critical for virus transmissibility in ferrets. Anhui/1 was found to be less sensitive in mice to neuraminidase inhibitors than a pandemic H1N1 2009 virus, although both viruses were equally susceptible to an experimental antiviral polymerase inhibitor. The robust replicative ability in mice, ferrets and non-human primates and the limited transmissibility in ferrets of Anhui/1 suggest that A(H7N9) viruses have pandemic potential.

Nature 2013; 501: 551

Eitan Israeli