REVIEW ARTICLE Nonstandard Shift Work and Subsequent Health Hazards : A Review

Surriya Jabeen

ABSTRACT:

Present age has moved into twenty four hours a day; seven days a week economy. Concept of 24-hour economy is based on the pattern of work; that for a given work, eight-hour working day can be carried out at any time during twenty-four hour day/night period, which is achievable by shift work (routine method being three shifts of eight hours each per day). According to international labor organization, shift work is defined (1990) as placement of an employee in schedule where workers succeed one another at job, hence the management can function more than the hours of work. The other term often available in 24-economy is shift sharing, and flexi-time. Over the years scientific research has been focused to explore relationship between organism and its environment to establish link between disease and man-made environment. The current review has addressed how de- synchronized physiological rhythm could lead to human pathophysiology by un-standardized shift work. **Keywords:** Shift work, Circadian rhythm, Sleep, Health hazards, Metabolic disease

INTRODUCTION:

The knowledge that effect does not depend on a single cause, but rather diseases are multifactorial in origin, resulted in wide spread interest towards preventive aspect, and concentrated research studies focusing all those questions which directly or indirectly have influence on health and well being of an individual. Scientific research has been trying to appreciate the measures to reach the goal of prevention rather than treatment. In the recent years, there is a growing concern on job related injuries such as the effect of de- synchronized sleep rhythm on health of an individual as observed in shift workers^{1,2,3}.

The social environment of an individual influences sleeping at different time and organizes daily activities during the light/dark cycle (Day/Night)^{4,5,6} which illustrates complexity of current life style, more heightened in rotating shift workers. The disaccord between social time and biological rhythm of the body in rotatory shift work results in a state when the body systems misalign the physiological norms, irregular meal time and hormonal control important to maintain the hemostasis in body⁷. Major progress has been made in understanding the physiology of circadian rhythm in humans with focus on "what is the time in brain". The fundamental pacemaker or the biological clock is the Suprachiasmatic nucleus (SCN) in the anterior hypothalamus. Sleep/wake rhythm in the human body is controlled by this endogenous clock^{8,9,10,11}. The oscillatory signal of biological clock is sent to metabolic systems via the efferent system from the SCN¹². SCN coordinates all the cellular circadian clocks as expression of ion channels throughout the body tissue which completely follow circadian principle¹³. Similarly Heart

Dr. Surriya Jabeen Professor and Head Department of Community Health Science Bahria Medical University & Dental College Karachi Received: 18-03-17 Revised: 20-05-17 Accepted: 20-06-17 rate variability (HRV) operates according to circadian rhythmicity as evidenced in morning-evening fluctuation, the lowest heart rate being observed in the morning, consequently physiological rhythm in the body is maintained^{14,15}.

Present life style has increased the need of rotating shift work and as for now prevalence of shift work has increased in both developed and developing countries¹⁶. In recent years, studies are channelizing circadian rhythm functioning from health perspective, leading to multiple disorders, one of which is Shift work disorder (SWD) observed in those people who work during normal sleep hours¹⁷. Human body is not meant for 24/7 work. This type of life style and health do not complement each other, instead there is degeneration^{18,19}. The pathological response such as metabolic syndrome(Met S); diabetes, hypertension and hyperlipidemia have been observed in conjure to the circadian stress of unnatural sleep schedule and irregular feeding time^{20,21,22}.

METHODOLOGY:

To observe the effect of shift work on Health, detailed medical literature search was made using multiple electronic data base like Pub Med, Google Scholar, Science direct. Extensive search was made in particular to those articles having a circadian component as their major substance. Inclusion criteria was studies involving only human subjects, published in English, in peer reviewed journals from 1994 to 2016. Abstract, editorials, commentaries and conference proceeding were excluded.

Different combination of key words were used to meet the relevant terms, starting from broader term and then confining it to the desired key word. The rationale of this article was to examine nonstandard shift work and its effect on health outcomes. Multiple research work was available internationally on this subject, however, insignificant work was available locally. Present search was able to identify 1000 articles, however it was shortlisted to 120 articles because of work duplication, some were not directly related to aim of the study, and others were based on animal models. Again 61 studies were removed since these articles did not incorporate

Surriya Jabeen

shift work as a key element of the study. Finally 59 articles were selected and included in this review.

LITERATURE REVIEW:

Shift work and sleep:

A common disorder presently defined in circadian sleep science is called shift work disorder $(SWD)^{23,24}$. This is a response of the body to mismatch endogenous rhythm and exogenous social time. Shift work sleep disorder (SWSD) is defined as the "report of difficulty falling asleep, staying asleep, or non-restorative sleep for at least one month" and it must be associated with "a work period that occurs during the habitual sleep phase"25. Employees working non-standard shifts observed to be sleep deficient were often more fatigued which subsequently effected work efficiency and increased vulnerability to errors and accidents. The symptoms reported from nonstandard shift workers with poor sleep quality were mostly somatic, such as headache, epigastric discomfort, neck and back pain, chronic fatigue, etc, which were eventually effecting their home life and triggering family conflicts. There was convincing evidence that sleep length in split shift workers was shortened by 2 -4 hours²⁶. Out of all the sleep stages, reduction was most evident in stage 2 and REM, however the slow wave sleep which comprises of Stages 3 and 4 was seldom affected. To assess the effect on sleep latency in nonstandard shift workers, it was observed that sleep latency was increased as compared to morning shift, and was decreased in night shift workers^{27,28} Present life style has contributed to 24-hour-economy at the cost of disturbed sleep pattern. Presently sleep deprivation has touched an epidemic magnitude. The prevalence of sleep deprived population was reported to be 25%²⁹.

Shift work and Obesity:

WHO defined obesity as abnormal or excessive fat accumulation which may impair health. Various studies have depicted direct relationship between sleep pattern and weight gain³⁰. Currently it became mandatory to evaluate the environmental contribution to increased weight³¹. Body mass index (BMI) is a practical indicator which incorporates weight and height (Kg/M2). If BMI ascended or descended from recommended ideal range, it was found to be related to diseases. Certain inappropriate practices were observed in shift workers like smoking³². However mostly their life style was due to the nature of jobs, resulting in irregular feeding habits, inability to participate in sports related activities etc. Moreover, the consequences of abnormal interaction of natural biologic cycle and behavioral cycle (feeding/fasting) was associated with altered appetite and hunger at wrong time of day/night cycle³³.

Shift work and gastrointestinal symptoms:

Multiple studies had established link between shiftwork and gastrointestinal symptoms, resulting in disordered digestive enzymes and acid-alkaline balance. Prior studies had established these disorders with sleep pattern and it was found to bear positive relation with the last night sleep³⁴. Another research observed that Shift-work should be considered as risk factor for duodenal ulcer, as it was shown that ulcer-genic ability of H-pylori infection was potent in infected shift workers³⁵. A research conducted in Iceland determined that nurses who were engaged sixteen hours in a day/night shift had more severe gastrointestinal symptoms³⁶.

Shift work and neuropeptides:

Orexin is one of the hypothalamic neuropeptide which is essential in regulation of sleep/wake cycle along with its pivotal role in energy metabolism. In adolescents, raised level of orexin had been found with weight reduction. Orexin deficiency seen in sleep disorders, like narcolepsy was found to be associated with increased body weight. If the release of orexin was affected as in shift work, it was invariably found to be associated with obesity³⁷. Importance of orexin signaling in energy metabolism and sleep was indicative of its control over other physiological processes in human body. The neuropeptide has significant role and assistance of central inflection of sleep, activity and energy metabolism³⁸.

Shift work and gut peptide :

Altered biological rhythm due to altered environmental signals (shift work) and metabolic strain, effect neuro-hormonal control of hunger and satiety, and subsequently influence energy balance which is routed by central mechanisms collaborating inhibitory hypothalamic stimuli of appetite control by adipose tissue (Leptin). Prior studies have observed influence of circadian oscillation and sleep on leptin circulatory level³⁹. Appetite regulating peptide from lower and upper gut with its significant role in obesity and metabolic dysfunctions namely Ghrelin had been observed to increase during fasting and its level tends to fall following meal. Leptin level was decreased in sleep restriction, concurrently it was negatively correlated to Ghrelin. Therefore circulatory level of ghrelin which is an appetite stimulant is increased suggesting that sleep restriction can increase apatite⁴⁰.

Shift work and Lipid metabolism:

Prior research had shown that feeding at night time tends to elevate LDL/HDL ratio⁴¹. Human body is not meant for nocturnal feeding. Several studies had reported elevated serum triglycerides and decreased HDL levels in shift workers than in fixed day workers. In addition, many prospective studies have evaluated association between shift work and coronary artery disease⁴². Some studies have linked shift work and lipid metabolism as a risk factor for hypercholesterolemia⁴³.

Shift work and cancer:

The international agency for research on cancer (IARC), a constituent agency of WHO (2007), related

circadian disruption with breast cancer. It was established that night shift work is a risk factor for this malignancy. With this new concept, multiple studies were conducted on this subject and positive relation was established. It was realized that chronic chronodisrupton was a long term factor associated with the risk of breast cancer and it was evidenced as an occupational disease^{44,45}. Night shift work (NSW) increased the risk of breast cancer by 1.9% for 5 years, 2.5% for 5–10 years, 7.4% for 10–20 years, and 8.8% for >20-years. Additionally, rotating NSW enhanced the morbidity of breast cancer by 8.9%⁴⁶.

Shift work and metabolic dysfunction:

Circulating currency in the blood is in the form of ATP, which is the energy body derived from various macronutrients after they are broken to smaller units. Metabolic syndrome characterizes group of risk factors which are metabolic in origin, and are forerunner and interconnected to serious outcomes in an individual⁴⁷. One proximate study which was conducted keeping duration of shift work as one of the variable, comprising of 4 groups; one who never worked, other worked for one year, next group for 10, and \geq 20 years. The findings suggested elevated all ratios for Met S in both gender workers after 10 years of shift work and demonstrated a gender difference on the relationship between shift work and Met S⁴⁸. Earlier research had determined dissimilarities in the development of Met S between men and women shift workers49. Another study discovered that Chinese males got increased frequency of Met S and its constituents complications, and faster development of Met S⁵⁰. Another study concluding that stroke, cardiovascular diseases and metabolic disorders were more prevalent in rotating shift work, has questioned the concept of occupational health and safety which were established issues that jeopardize worker health⁵¹.

Shift work and mental health:

According to WHO, mental health is a state of complete well-being in which person recognizes his or her own capabilities, can handle normal stresses of routine life and is productive to the community. Many studies had suggested that de-synchronization of circadian rhythm contributed to many chronopharmacologic alterations such as depression⁵². Depression may manifest differently in individuals, however, identification is based on the presence of a distinct change in mood (sadness or lack of pleasure) accompanied by change in appetite and activities, including decreased energy, psychomotor retardation or agitation, weight loss, change in sleep wake cycle, and depression rumination or thought of suicide for at least 2 weeks53. Cortisol, commonly described as stress hormone is secreted by adrenal cortex which is vital for life. Normally diurnal oscillation of cortisol is higher in the morning and gradually decreases by evening. However alternate response of adrenal cortex is the result of environmental stress⁵⁴. Daily emotions are related to cortisol⁵⁵. Multiple studies have established relationship between shift work

and depression⁵⁶.

Shift work and stress:

Stress is the response of the body to any situation that is threatening, frightening or exciting, however, this stress may be positive "Eustress" or it may be "Distress" which is unpleasant to the mind. Over the years, our knowledge on shift work and health grew exponentially. A series of findings began to identify harmful psychological effects of shift work, consequently it became mandatory to address the stress as a risk factor responsible for multiple diseases, for instance to find the mechanism to establish a causal relation between shift work and cardiovascular disease (CVD)⁵⁷. Human body in response to stress produces more catecholamines to prepare the body to flight and fight. These hormones increase heart rate, blood pressure and blood glucose level. If the person remains unable to cope with this state, the catecholamines remain permanently elevated⁵⁸ One prior study aimed to find relationship between shift stress and abortion. The Danish National Birth Cohort examined whether shift work, or job stress correlated with late fetal abortion. They had concluded in the findings a higher fetal loss in women working night shifts accompanied by habitual smoking⁵⁹.

CONCLUSION:

Present research has concluded that disturbed sleep pattern due to shift work has serious consequences. Relevant strategies should be planned based on circadian principles to minimize the adverse effects of unconventional shift system. Clockwise (morning, evening, night) rotation is favorable rather than counterclockwise, since delaying sleep time is easier as compared to advance sleep time, which elucidates that morning shift should enter to evening, and evening merges in night shift and then night workers should rotate to morning work.

REFERENCES:

- 1. Herrero MTV, Alberich JIT, García CL, Gómez IJ. Night shift work and occupational health. Spanish Journal of Legal Medicine. 2016; 42((4): 142-54
- 2. Liu H, Wang Q, Keesler V, Schneider B. Non-standard work schedules, work-family conflict and parental wellbeing: A comparison of married and cohabiting unions. Social science research. 2011; (40):473-84
- Merkus LS, Holte AK, Huysmans AM, van de Ven MP, Mechelen VW. Self-Reported Recovery from 2-Week 12-Hour Shift Work Schedules: A 14-Day Follow-Up. Safety and health at work. 2015;6:240-8
- 4. Broms U, Pennanen M, Patja K, Ollila H, Korhonen T, Kankaanpa A, et al. K. Diurnal Evening Type is Associated with Current Smoking, Nicotine Dependence and Nicotine Intake in the Population Based National finrisk 2007 Study. J Addict Res Ther. 2012; 2: suppl 002
- 5. Justice WA. Chronobiology and mood disorders. Dialogues Clin Neurosci. 2003;5(4):315-25
- 6. Garaulet M, Ordovás JM, Madrid AJ. The chronobiology, etiology and pathophysiology of obesity. Int J Obes.

Surriya Jabeen

2010; 34(12): 1667-83

- Eckel-Mahan K, Sassone-Corsi P. Metabolism and the circadian clock converge. Physiol Rev. 2013 Jan; 93(1): 107–35
- Ding JM, Chen D, Weber ET, Faiman LE, Rea MA, Gillette MU. Resetting the biological clock:Mediation of nocturnal circadian shifts by glutamate and NO .Science. 1994; 266(5191): 1713- 8
- 9. West CA, Bechtold AD. The cost of circadian desynchrony: Evidence, insights and open questions. Bioessay. 2015; 7: 777-88
- Mohawk AJ, Green C, Takahashi SJ. Central and peripheral circadian clocks in mammals. Annu Rev Neurosci. 2012; 35:445-62
- 11. Dijk DJ, Lockley SW. Functional genomics of sleep and circadian rhythm invited review: integration of human sleep wake regulation and circadian rhythmicity. J Appl Phsiol. 2002;92: 852-62
- Kalsbeek A, Scheer FA, Perreau-Lenz S, La Fleur SE, Yi CX, Fliers E, et al. Circadian disruption and SCN control of energy metabolism. FEBS Lett 2011; 585:14 12-26
- K GY-P, Shi L, Ko ML. Circadian regulation of ion channels and their functions. J Neurochem. 2009;110(4) :1150-202
- 14. Vanoli E, Adamson PB, Ba-Lin, Pinna GD, Lazzara R, Orr WC. Heart rate variability during specific sleep stages: a comparison of healthy subjects with patients after myocardial infarction. Circulation 1995; 91:1918-22
- 15. Kim SH, Yoon HK, CHO H J. Diurnal Heart rate variability fluctuation in normal volunteers. J Diabetes Technol. 2014; 8(2):431-3
- Atkinson G, Fullick S, Grindey C, Maclaren D, Waterhouse J. Exercise, Energy Balance and the Shift Worker. Sports Med. 2008; 38(8): 671–85
- 17. Drake LC, Roehrs T, Richardson G, James K, Walsh KJ, Roth T. Shift Work Sleep Disorder: Prevalence and Consequences Beyond that of Symptomatic Day Workers. Sleep. 2004; 27(8): 1453-63
- Egger G, Dixon J. Beyond Obesity and Lifestyle: A Review of 21st Century Chronic Disease Determinants. Bio Med Research International. 2014; 2014: ID 731685, 12 pages.
- Nigatu TY, van de Ven HA, van der Klink JJL, Brouwer S, Reijneveld SA, Bultman U. Overweight, obesity and work functioning: The role of working-time arrangements. Applied Ergonomics. 2016; 52: 128-34
- 20. An Pan A, Schernhammer SE, Qi Sun QI, Hu BF. Rotating Night Shift Work and Risk of Type-2 Diabetes: Two Prospective Cohort Studies in Women. PLoS Med 2011; 8(12): e1001141
- Reynolds CA, Paterson LJ, Ferguson AS, Stanley D, Wright Jr PK, Dawson D. The shift work and health research agenda: Considering changes in gut microbiota as a pathway linking shift work, sleep loss and circadian misalignment, and metabolic disease. Sleep medicine Reviews. 2017; 34: 3-9
- 22. Vetter C, Devore EE, Wegrzyn LR, Massa J, Speizer FE, Kawachi I, et al. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease

Among Women. JAMA. 2016; 315(16):1726-34

- Kimy J, Kim HJ, Woon H, Choi GK. Prevalence of Shift work sleep disorder and its impact on health and working. J Korean Sleep Res Soc. 2005; 2(1): 39-46
- 24. Sack RL, Auckley D, Auger RR, Carskadon MA, Wright KP, Vitiello MV, et al. Circadian Rhythm Sleep Disorders: Part-I, Basic Priciples, shift work and Jet Leg Disorders. Sleep, 2007;30(11):1460-83
- Åkerstedt T, Wright PK. Sleep Loss and Fatigue in Shift Work and Shift Work Disorder. Sleep Med Clin. 2009; 4(2): 257–71.
- 26. Costa G. Shift Work and Health current problems & preventive. Shift health work. 2010; 1(2) :112-23
- Åkerstedt T. Shift work and disturbed sleep/wakefulness. Occupational Medicine 2003;53: 89- 94.
- Akersted T. Shift work and disturbed sleep/wakedfullness. Sleep Medicine Review 1998;2(2):117-28
- Watson NF, Buchwald D, Vitiello MV, Noonan C, Goldberg J. A twin study of sleep duration and body mass index. J Clin Sleep Med 2010;6(1):11-7
- Watanabe M, Kikuchi H, Tanaka K, Takahashi M. Association of Short Sleep Duration with Weight Gain and Obesity at 1-Year Follow-Up: A Large-Scale Prospective Study. Sleep. 2010; 33(2): 161-7
- Pandalai PS, Schulte AP, Miller BD. Obesity and the occupational environment. Scand J Work Environ Health. 2013;39(3): 221-32
- Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. Chronobiol Int. 2008;25(2): 443-54
- Zimberg IZ, Fernandes SA, Crispim CA, Tufik S, de Mello MT. Metabolic impact of shift work. Work 2012 ;41:4376-83
- Caruso CC, Lusk SL, Gillespie BW. Relationship of work schedules to gastrointestinal diagnoses, symptoms, and medication use in auto-factory workers. Am J Indus Med 2004;46: 586-98
- 35. Pietroiusti A, Forlini A, Magrini A, Galante A, Coppeta L, Gemma G, et al. Shift work increases the frequency of duodenal ulcer in H pylori infected workers. Occup Environ Med. 2006; 63(11):773-5
- Sveinsdottir H. Self-assessed quality of sleep, occupational health working environment, illness experience and job satisfaction of female nurses working different combination of shifts. Scand J Caring Sci 2006; 20:229-37
- Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nature Reviews. Neuroscience. 2007; 8: 171-81
- Nixon JP, Mavanjia V, Butterick TA, Billington CJ, Kotz CM, Teske JA. Sleep disorders, obesity, and aging: the role of orexin. Ageing Res Rev. 2015; 20: 63–73
- Simon C, Gronfier C, Schlienger LJ, Brandenberger G. Circadian and Ultradian Variations of Leptin in Normal Man under Continuous Enteral Nutrition: Relationship to Sleep and Body Temperature. 1998; 83(6):1893-9
- 40. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007;8:21-34
- 41. Bøggild H, Knutsson A. Shift work, risk factors and

Nonstandard Shift Work and Subsequent Health Hazards : A Review

cardiovascular disease. Scand J Work Environ Health 1999;25:85-99

- 42. Dochi M, Suwazono Y, Sakata K, Okubo Y, Oishi M, Tanaka K, et al. Shift work is a risk factor for increased total cholesterol level: a 14-year prospective cohort study in 6886 male workers. Occup Environ Med. 2009;66 (9):592-7
- Akbari H, Mirzaei R, Nasrabadi T, Gholami-Fesharaki M. Evaluation of the Effect of Shift Work on Serum Cholesterol and Triglyceride Levels. Iran Red Crescent Med J. 2015;17(1): e18723.doi: 10.5812/ircmj.18723
- 44. Wang P, Ren F, Lin Y, Su F, Jia W, Su X, et al. Nightshift work, sleep duration, daytime napping, and breast cancer risk. Sleep Medicine. 2015;16(4): 462-8
- 45. Grundy A, Schuetz JM, Lai AA, Janoo-Gilani R, Leach S, Burstyn I, et al. Shift work, circadian gene variants and risk of breast cancer. Cancer Epidemiology. 2013; 37(5): 606–12
- 46. Lin X, Chen W, Wei F, Ying M, Wei W, Xie X. Nightshift work increases morbidity of breast cancer and allcause mortality: a meta-analysis of 16 prospective cohort studies. Sleep Medicine 2015; 16(11): 1381-7
- 47. Proper KI, van de Langenberg D, Rodenburg W, Vermeulen RCH, van der Beek AJ, van Steeg H, et al. The Relationship Between Shift Work and Metabolic Risk Factors. Am J Prev Med 2016;50(5):e147–e157. doi: org/10.1016/j.amepre.2015.11.013
- 48. Guo Y, Rong Y, Huang X, Lai H, Luo X, Zhang Z, et al. Shift Work and the Relationship with Metabolic Syndrome in Chinese Aged Workers. PLoS ONE. 2015;10(3): e01 20632. DOI: org.10.1371/journal.phone.0120632
- 49. Cooper DC, Trivedi RB, Nelson KM, Reiber GE, Zonderman AB, Evans MK, et al. Sex Differences in Associations of Depressive Symptoms with Cardiovascular Risk Factors and Metabolic Syndrome among African Americans. Cardiovasc Psychiatry Neurol. 2013; Article ID 979185, 10 pages. http://dx.doi.org/10.1155/2013/979185
- Canuto R, Garcez SA, Olinto M. Metabolic syndrome and shift work: A systematic review. Sleep Medicine. 2013;17(6):425-31

- Moreira FP, Jansen K, Mondin TC, Cardosoa T, Magalhães P, Kapczinski F, et al. Biological rhythms, metabolic syndrome and current depressive episode in a community sample. Psycho neuroendocrinology. 2016;72: 34-9
- 52. Baba VV, Galperin BL, Lituchy TR. Occupational mental health: a study of work related depression among nurses in the Caribbean. International Journal of Nursing Studies. 1999;36(2): 163-9
- 53. Kalmbach DA, Pillai V, Cheng P, Arnedt JT, Drake CL. Shift work disorder, depression and anxiety in the transition to rotating shifts :the role of sleep reactivity. sleep Medicine. 2015;16 (12):1532-8
- 54. Puterman E, Haritatos J, Adler NE, Sidney S, Schwartz JE, Epel ES. Indirect effect of financial strain on daily *cortisol* output through daily negative to positive affect index in the coronary artery risk development in young adults study. Psychoneuroendocrinology 2013;38(12): 2883-9
- 55. Goodday SM, Horrocks J, Keown-Stoneman C, Grof P, Duffy A. Repeated salivary daytime cortisol and onset of mood episodes in offspring of bipolar parents. Int J Bipolar Disord. 2016; 4:12 DOI 10.1186/s40345-016-0053-5
- Salma U, Rao K. Shift Work and Depression. International Journal of Environmental Research and Development. 2014;4(4): 417-22
- Puttonen S, Harama M, Hublin C. Shift work and cardiovascular disease-pathway from circadian stress to morbidity. Scan J work environ Health. 2010;36(2): 96-108
- 58. Fujiwara S, Shinkai S, Kurokawa Y, Watanabe T. The acute effects of experimental short-term evening and night shifts on human circadian rhythm: the oral temperature, heart rate, serum cortisol and urinary catecholamines level. Int Arch Occup Environ Health. 1992;63(6): 409-18
- 59. Zhu JL, Hjollund NH, Anderson AN, Oslen J. Shift work, Job Stress, and Late Fetal Loss: The National Birth Cohort in Denmark. Journal of Occupational and Environmental Medicine . 2004;46(11): 1144-9

