NSIDRC Journal Article Alert – April 2007

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• Mitochondrial tRNA genes and flanking regions in sudden infant death syndrome.
• A mitochondrial DNA polymorphism associated with cardiac arrhythmia investigated in sudden infant death syndrome.


Background: There is inconsistent evidence as to whether work schedule (including rotating shifts and night work) can affect reproductive outcomes. Methods: We investigated the association between work schedule and risk of spontaneous abortion in U.S. nurses. The Nurses' Health Study II is a prospective cohort study established in 1989. In 2001, information about occupational activities and exposures during pregnancy was collected from female nurses for the most recent pregnancy since 1993. Of 11,178 eligible respondents, 9547 (85%) indicated willingness to participate in the occupational study, and 8461 of those (89%) returned the questionnaire, for an overall participation rate of 76%. Of these, 7688 women had pregnancies that were eligible for analysis. Results: Participants reported 6902 live births and 786 (10%) spontaneous abortions. Compared with women who reported usually working "days only" during their first trimester, women who reported usually working "nights only" had a 60% increased risk of spontaneous abortion (RR = 1.6; 95% confidence interval [CI] = 1.3-1.9). A rotating schedule, with or without night shifts, was not associated with an increase in risk (RR = 1.2 [CI = 0.9-1.5] and 1.0 [CI = 0.8-1.2], respectively). Women who reported working more than 40 hours per week during the first trimester were also at increased risk of spontaneous abortion (1.5; 1.3-1.7) compared with women working 21-40 hours, even after adjustment for work schedule. Conclusions: Nightwork and long work hours may be associated with an increased risk of spontaneous abortion. Further studies are needed to determine whether hormonal disturbances attributed to night work affect pregnancy outcome.

Full-text available at: http://www.epidem.com (not a U.S. Government site)

A sire-maternal grandsire threshold model was used for genetic evaluation of stillbirth in US Holsteins. Calving ease and stillbirth records for herds reporting at least 10 dead calves were extracted from the Animal Improvement Programs Laboratory database. About half of the 14 million calving ease records in the database had a known livability score, mostly from herds processed by Dairy Records Management Systems (Raleigh, NC). Calf livability scores of 2 and 3, representing calves born dead and calves that died within 48 h of parturition, respectively, were combined into a single category. The model included effects of herd-year, year-season, parity-sex, sire, birth year group of sire, maternal grandsire (MGS), and birth year group of MGS. Herd-year, sire, and MGS were random effects. Mean predicted transmitting abilities, expressed as the expected percentage of stillbirths, were 7.9 and 8.6 for direct and maternal stillbirths, respectively. Mean reliabilities for both the direct and maternal effects were 45%. Correlations among domestic and Interbull stillbirth solutions on the underlying scale for bulls with at least 90% reliability ranged from 0.63 to 0.90 across countries for direct stillbirths and from 0.69 to 0.96 for maternal stillbirths, indicating that results were generally consistent with those from other countries. There was no evidence of a genetic trend for either trait. More complete recording of stillbirth scores would improve reliabilities and could allow for evaluations of other breeds.

Full-text available at: http://jds.fass.org/ (not a U.S. Government site)


Internal validation data offer a well-recognized means to help correct for exposure misclassification or measurement error. When available, external validation data offer the advantage of cost-effectiveness. However, external data are a generally inefficient source of information about misclassification parameters. Furthermore, external data are not necessarily "transportable", for example, if there are differences in the design or target populations of the main and validation studies. Recent work has suggested weighted estimators to simultaneously take advantage of internal and external validation data. We explore efficiency and transportability in the fundamental case of estimating the odds ratio for binary exposure in a case-control setting. Our results support the use of closed-form weighted log odds ratio estimators in place of computationally demanding maximum likelihood estimators under both types of validation study designs (using internal data only, and combining internal and external data). We also provide and assess a formal test of the transportability assumption, and introduce a new log odds ratio estimator that is inherently robust to violation of that assumption. A case-control study of the association between maternal antibiotic use and sudden infant death syndrome provides a real-data example.

Full-text available at: http://www.epidem.com (not a U.S. Government site)
Hoffman JM, Brown JW, Sirlin EA, Benoit AM, Gill WH, Harris MB, Darnall RA. 
**Activation of 5-HT1A receptors in the paragigantocellularis lateralis decreases shivering during cooling in the conscious piglet.**
Am J Physiol Regul Integr Comp Physiol. 2007 Apr 4; [E-pub ahead of print]

Activation of 5-HT1A receptors in the medullary raphe decreases sympathetic outflow to thermoregulatory mechanisms, including brown adipose tissue (BAT) thermogenesis and peripheral vasoconstriction when these mechanisms are previously activated with leptin, prostaglandins, or cooling. These same mechanisms are also inhibited during REM sleep. It is not known whether shivering is also modulated by medullary raphe neurons. We previously showed in the conscious piglet that activation of 5-HT1A receptors with 8-OH-DPAT (DPAT) in the paragigantocellularis lateralis (PGCL), a medullary region lateral to the midline raphe that contains 5-HT neurons, decreases heart rate, body temperature and muscle activity during NREM sleep. We therefore hypothesized that activation of 5-HT1A receptors in the PGCL would also attenuate shivering and peripheral vasoconstriction during cooling. During REM sleep in a cool environment, shivering, carbon dioxide production and body temperature decreased, and ear capillary blood flow and ear skin temperature increased. Shivering associated with rapid cooling was attenuated after dialysis of DPAT into the PGCL. In animals maintained in a continuous cool environment, dialysis of DPAT into the PGCL attenuated shivering and decreased body temperature, but there were no significant increases in ear capillary blood flow or ear skin temperature. We conclude that both naturally occurring REM sleep and exogenous activation of 5-HT1A receptors in the PGCL are associated with a suspension of shivering during cooling. Our data are consistent with the hypothesis that 5-HT neurons in the PGCL facilitate oscillating spinal motor circuits involved in shivering but are less involved in modulating sympathetically mediated thermoregulatory mechanisms.


Mitchell EA, Hutchison L, Stewart AW.
**The continuing decline in SIDS mortality.**
Arch Dis Child. 2007 Apr 3; [E-pub ahead of print]

The "Back to Sleep" campaign resulted in a dramatic decrease in SIDS worldwide. SIDS mortality has continued to decline (in New Zealand by 63% from 1993 to 2004), but this has not been explained. A postal survey found that the proportion of infants sleeping on their back has increased substantially (from 24.4% in 1992 to 72.3% in 2005), and this could account for 39% - 48% decrease in SIDS mortality.

Full-text available at: [http://adc.bmj.com/cgi/rapidpdf/adc.2007.116194v1](http://adc.bmj.com/cgi/rapidpdf/adc.2007.116194v1) (not a U.S. Government site)

Reddy UM, Wapner RJ, Rebar RW, Tasca RJ.
**Infertility, assisted reproductive technology, and adverse pregnancy outcomes: Executive Summary of a National Institute of Child Health and Human Development Workshop.**
The National Institute of Child Health and Human Development held a workshop on September 12-13, 2005, to summarize the risks for adverse pregnancy outcomes after assisted reproductive technology (ART), develop an approach to counseling couples regarding these risks, and establish a research agenda. Although the majority of ART children are normal, there are concerns about the increased risk for adverse pregnancy outcomes. More than 30% of ART pregnancies are twins or higher-order multiple gestations (triplets or greater) and more than one half of all ART neonates are the products of multifetal gestations, with an attendant increase in prematurity complications. Assisted reproductive technology singleton pregnancies also demonstrate increased rates of perinatal complications-small for gestational age infants, preterm delivery, and perinatal mortality-as well as maternal complications, such as preeclampsia, gestational diabetes, placenta previa, placental abruption, and cesarean delivery. Although it is not possible to separate ART-related risks from those secondary to the underlying reproductive pathology, the overall increased frequency of obstetric complications, including preterm birth and small for gestational age neonates, should be discussed with the couple. Significant gaps in knowledge were identified, and the basic science and clinical and epidemiologic research required to address these gaps is outlined.

Full-text available at: http://www.greenjournal.org/cgi/content/full/109/4/967 (not a U.S. Government site)


Objectives: This study examines changing patterns of inequalities in US infant, neonatal, and postneonatal mortality rates between 1969 and 2001 by area deprivation and maternal education. Methods: A deprivation index was linked to county vital records data to derive annual infant mortality rates by deprivation quintiles from 1969 to 2000. Rates by maternal education were computed for 1986, 1991, 1996, and 2001 using national linked birth/infant death files. Log-binomial regression was used to estimate relative risks of infant mortality by deprivation and time period. Cox regression was used to model overall and birth weight-specific infant mortality risks by maternal education after adjusting for covariates. Temporal disparities were summarized by log-linear regression and inequality indices. RESULTS: Although absolute disparities have narrowed over time, relative socioeconomic disparities in infant mortality have increased since 1985. In 1985-1989, infants in the most deprived group had, respectively, 36% and 57% higher risks of neonatal and postneonatal mortality than infants in the least deprived group. The corresponding relative risks increased to 43% and 96% in 1995-2000. The adjusted risk of infant mortality was 22% higher in 1986 for mothers with < 12 years of education than for those with > or = 16 years of education, with the relative risk increasing to 41% in 2001. Disparities were greatest among normal birth weight infants, with education-
specific relative risks of neonatal and postneonatal mortality increasing significantly between 1986 and 2001. Conclusions: Dramatic declines in infant mortality among all of the socioeconomic groups during 1969-2001 represent a major public health success. However, substantial socioeconomic disparities persisted in both neonatal and postneonatal mortality. Relatively larger declines in infant and postneonatal mortality among higher socioeconomic groups have contributed to the widening gap in mortality since 1985. Persistent disparities in infant mortality may reflect increasing polarization among socioeconomic groups in material and social conditions, smoking during pregnancy, and health care services.

Full-text available at: http://www.pediatrics.org (not a U.S. Government site)

Claudius I, Keens T.
Do all infants with apparent life-threatening events need to be admitted?

Objective: The goal was to identify criteria that would allow low-risk infants presenting with an apparent life-threatening event to be discharged safely from the emergency department. Methods: We completed data forms prospectively on all previously healthy patients <12 months of age presenting to the emergency department of an urban tertiary care children's hospital with an apparent life-threatening event over a 3-year period. These patients were then observed for subsequent events, significant interventions, or final diagnoses that would have mandated their admission (eg, sepsis). Results: In our population of 59 infants, all 8 children who met the aforementioned outcome measures, thus requiring admission, either had experienced multiple apparent life-threatening events before presentation or were in their first month of life. In our study group, the high-risk criteria of age of <1 year and multiple apparent life-threatening events yielded a negative predictive value of 100% to identify the need for hospital admission. Conclusions: Our study suggests that >30-day-old infants who have experienced a single apparent life-threatening event may be discharged safely from the hospital, which would decrease admissions by 38%.

Full-text available at: http://www.pediatrics.org (not a U.S. Government site)

Gamble C, Ekwaru PJ, Garner P, Ter Kuile FO.
Insecticide-treated nets for the prevention of malaria in pregnancy: A systematic review of randomised controlled trials.

Background: Protection from malaria with insecticide-treated bednets (ITNs) during pregnancy is widely advocated, but evidence of benefit has been inconsistent. We undertook a systematic review of randomised trials. Methods And Findings: Three cluster-randomised and two individually randomised trials met the inclusion criteria; four from Africa (n = 6,418) and one from Thailand (n = 223). In Africa, ITNs compared to no nets increased mean birth weight by 55 g (95% confidence interval [CI] 21-88),
reduced low birth weight by 23% (relative risk [RR] 0.77, 95% CI 0.61-0.98), and reduced miscarriages/stillbirths by 33% (RR 0.67, 0.47-0.97) in the first few pregnancies. Placental parasitaemia was reduced by 23% in all gravidae (RR 0.77, 0.66-0.90). The effects were apparent in the cluster-randomised trials and the one individually randomised trial in Africa. The trial in Thailand, which randomised individuals to ITNs or untreated nets, showed reductions in anaemia and fetal loss in all gravidae, but not reductions in clinical malaria or low birth weight. Conclusions: ITNs used throughout pregnancy or from mid-pregnancy onwards have a beneficial impact on pregnancy outcome in malaria-endemic Africa in the first few pregnancies. The potential impact of ITNs in pregnant women and their newborns in malaria regions outside Africa requires further research.


Vennemann MM, Hoffgen M, Bajanowski T, Hense HW, Mitchell EA. Do immunisations reduce the risk for SIDS? A meta-analysis. Vaccine. 2007 Mar 16; [E-pub ahead of print]

Background: There are claims that immunizations cause sudden infant death syndrome (SIDS), but some studies have found either no association or that they are associated with a reduced risk of SIDS. Aims: To conduct a meta-analysis examining the relationship between immunization and SIDS. Methods: Nine case-controls studies were identified examining this association, of which four adjusted for potential confounders. Results: The summary odds ratio (OR) in the univariate analysis suggested that immunizations were protective, but the presence of heterogeneity makes it difficult to combine these studies. The summary OR for the studies reporting multivariate ORs was 0.54 (95% CI=0.39-0.76) with no evidence of heterogeneity. Conclusions: Immunizations are associated with a halving of the risk of SIDS. There are biological reasons why this association may be causal, but other factors, such as the healthy vaccine effect, may be important. Immunizations should be part of the SIDS prevention campaigns.


Objectives: This report presents final 2003 data on the 10 leading causes of death in the United States by age, race, sex, and Hispanic origin. Leading causes of infant, neonatal, and postneonatal death are also presented. This report supplements the annual report of final mortality statistics. METHODS: Data in this report are based on information from all death certificates filed in the 50 states and the District of Columbia in 2003. Causes of death classified by the International Classification of Diseases, Tenth Revision (ICD-10) are ranked according to the number of deaths assigned to rankable causes. Results: In
2003, the 10 leading causes of death were (in rank order): Diseases of heart; Malignant neoplasms; Cerebrovascular diseases; Chronic lower respiratory diseases; Accidents (unintentional injuries); Diabetes mellitus; Influenza and pneumonia; Alzheimer's disease; Nephritis, nephrotic syndrome and nephrosis; and Septicemia and accounted for about 78 percent of all deaths occurring in the United States. Differences in the ranking are evident by age, sex, race, and Hispanic origin. Leading causes of infant death for 2003 were (in rank order): Congenital malformations, deformations and chromosomal abnormalities; Disorders related to short gestation and low birth weight, not elsewhere classified; Sudden infant death syndrome; Newborn affected by maternal complications of pregnancy; Newborn affected by complications of placenta, cord and membranes; Accidents (unintentional injuries); Respiratory distress of newborn; Bacterial sepsis of newborn; Neonatal hemorrhage; and Diseases of the circulatory system. Important variation in the leading causes of infant death is noted for the neonatal and postneonatal periods.


Wilson AL, Randall B.
The state of South Dakota's child: 2006--Part II--safe sleep.

Sudden Infant Death Syndrome (SIDS) has dramatically declined nationally and in South Dakota since the beginning of the "Back to Sleep Campaign" in 1994. Nonetheless, in spite of data showing that the majority of babies now are placed on their backs, data from the US and South Dakota show that racial disparities, the safety of infants' sleep environment, and child care are issues requiring attention as strategies are developed to prevent sudden unexpected infant deaths. Data from the Regional Infant and Child Mortality Review Committee that reviews deaths of infants and children in southeastern South Dakota show that among 37 cases, nearly half of all unexpected deaths of infants between 1997 and 2006 occurred in out-of-home child care settings, considerably higher than what would be expected with census data predictions. Fewer (82%) of the out-of-home deaths, versus in-home deaths (100%), were associated with risks of being put to sleep in a non-supine position or in the presence of other sleeping hazards.

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Arkell S, Blair P, Henderson J, Fleming P.
Is the mattress important in helping babies keep warm?--Paradoxical effects of a sleeping surface with negligible thermal resistance.

Background: Heavy wrapping and head covering are risk factors for Sudden Infant Death Syndrome. A new mattress construction, PurFlo, has extremely low thermal resistance, and when used with an infant sleeping bag minimizes the risk of head covering. AIM: To
investigate the thermal balance and metabolic rate of infants sleeping on a conventional mattress or a Purflo mattress in infant sleeping bags. Methods: A longitudinal study of thermal balance of infants during day-time sleep on both mattress types in thermoneutral and cool conditions at ages 3 weeks (n = 24), 3 months (n = 22) and 5 months (n = 18). RESULTS: In thermoneutral conditions auxiliary temperatures in quiet sleep were lower on the conventional mattress than on the PurFlo mattress (p < 0.05, Wilcoxon test). On lowering room temperature to 15-16 degrees C axillary temperatures fell, particularly in the older babies, and at each age were lower on the conventional mattress than the Purflo (differences 0.14-0.72 degrees C, p < 0.05, Wilcoxon test). Conclusion: In both thermoneutral and cool conditions, infant temperatures were higher on the PurFlo than the conventional mattress. The more deformable surface of the PurFlo mattress may lead to more effective insulation by the sleeping bag despite a lack of mattress insulation.

Full-text downloading at: [http://www.tandf.co.uk/](http://www.tandf.co.uk/) (not a U.S. Government site)


Aim: Mitochondrial DNA (mtDNA) mutations have been proposed as a genetic risk factor for sudden infant death syndrome (SIDS). The aim of this study was to further investigate this issue, by sequencing the mitochondrial tRNA genes with flanking regions in SIDS cases and controls. Method: The selected genes were investigated in 24 cases of SIDS and 10 controls, the method used were direct sequencing. In addition, the A10398G mutation in the ND3 gene was investigated in 220 SIDS cases, 26 cases of infectious death and 93 controls, using allele-specific PCR. Results: Mutations, recorded as differences from the revised Cambridge sequence, were found in 32 different sites in the coding regions investigated. There was no difference in mutation frequency between SIDS cases and controls, and no single mutation was found associated with SIDS. Conclusion: The present study does not indicate an association between a specific mitochondrial tRNA gene mutation and SIDS, nor a higher mtDNA tRNA mutation frequency in SIDS cases than in controls.


Aim: Long QT syndrome (LQTS) has been shown to be the cause of death in some cases originally diagnosed as sudden infant death syndrome (SIDS). Such cardiac arrhythmias have also been noted in families with mitochondrial disease, and studies indicate that mitochondrial disease could be involved in SIDS. This makes the mtDNA polymorphism T3394C interesting, as a previous study has shown it to be associated with
electrocardiographic (ECG) changes after exercise in a family with LQTS, where some members harboured a KCNH2 mutation. Subjects: A total of 245 SIDS cases and 176 control cases. Methods: DNA was prepared from blood/tissue samples. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were performed to search for the mtDNA polymorphism and KCNH2 mutation. Differences were confirmed by sequencing. Results: The T3394C polymorphism was found in 3 pure SIDS cases (1.5%), 2 borderline SIDS cases (4.4%), 1 case of explained death (1.6%) and 2 living control cases (1.8%) (p = 0.62). The KCNH2 mutation was not found in cases or controls. Conclusion: The mtDNA polymorphism studied was found in a small number of SIDS cases and the frequency did not differ statistically from control subjects, making an association with increased SIDS risk unlikely.

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