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The U-shaped curve of folic acid and spina bifida prevention: Can there be too much of a good thing?

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Background: Periconceptional maternal folic acid (FA) supplementation and food fortification programs reduce risks for selected congenital malformations in a manner that remains unknown. The US prevalence of NTDs has been reduced by 36% since the introduction of mandatory food fortification programs 20 years ago. These programs were established on the premise that FA was a water-soluble vitamin that had a wide margin of safety. In the course of preventing ~700 NTDs in the US each year, mandatory FA fortification has exposed millions of people to a synthetic form of folate leading to excess non-metabolized FA exposure which potentially has deleterious effects.
Methods: Whole genome sequencing (WGS) was performed on 77 wildtype C57BL/6J mouse trios that were maintained on three different FA diets (FA-high, FA-control and FA-deficient). Males on the various diets for three months were mated to dams on the control diet and the reciprocal experiments were performed on treated female mice.
Results: We identified total of 2,621 DNMs (single nucleotide variants (SNVs)) with the median DNM counts: 39,21,42, respectively. Compared to the FA-control diet, we determined that both the high and the deficient FA exposures significantly increased the germline DNM rate (p=6.9×10-4, 1.1×10-4, respectively). This result was reproducible in human cell culture by random mutation capture assays. We observed that different FA diets significantly altered the DNM enrichment in terms of genomic features, such as CpG island, promoter regions and histone markers. Using whole genome bisulfide sequencing, we determined that either an excessive or deficient FA diet significantly alters the methylation landscape of genes involved in nervous system development, as well as cancer related pathways. We determined that FA-deficiency induces global hypomethylation whereas a high FA diet induces not only genome-wide hypermethylation, but also a significant enrichment of promoter region hypermethylation of DNA repair gene clusters. Finally, metabolomic profiling demonstrated that maternal FA-deficient diets cause alterations in pyrimidine and methyl metabolism in the *in utero* exposed offspring.
Conclusions: We determined that either a deficient or excessive FA diet can increase germline DNMs, increasing the risks for numerous genetic disorders. This observation is clinically relevant only if validated in humans, given that the consequences of excess FA exposure may outweigh the beneficial effects associated with the reduction in birth defect prevalence.

Estimating prevalence of spina bifida in the U.S. using administrative databases

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Background: The current prevalence across the lifespan of spina bifida (SB) in the U.S. is not well known and the frequently cited estimates of this prevalence are dated. The University of Minnesota's Institute on Community Integration team and the Association of University Centers on Disability collaborated with the Centers for Disease Control and Prevention to estimate the current prevalence of SB across different demographic characteristics, such as age, gender, race, and geographic region, and calculate the number of people living with SB in the U.S. We identified and secured access to data sources large enough to estimate SB prevalence nationally and across selected subgroups.
Methods: After evaluating the potential of several data sources, we secured access to three major U.S. databases: Medicaid, Medicaid Fee for Service and Medicare Advantage, and a commercial insurance dataset from the Health Care Cost Institute (HCCI).

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Claims data from 2017-2019 were searched to identify people with ICD diagnosis codes for SB and SB Occulta. Membership files from 2019 were used to set denominators for the prevalence estimates. Medicaid and Medicare data include millions of participants from these government-funded programs. HCCI data cover approximately 30% of all people insured under employer-sponsored plans in the U.S.
Results: We estimated the prevalence of SB and SB Occulta for three major insured populations, extrapolated these estimates to the U.S. general population, and calculated the number of people living with SB in this population. We also estimated the prevalence of SB across age groups, race, gender, and geographic regions.
Conclusions: Large administrative datasets offer a robust and relatively inexpensive way to obtain current estimates of the prevalence of SB and SB Occulta nationally and among subgroups.

Factors associated with transfer distance from birth hospital to repair hospital for first surgical repair among infants with myelomeningocele in California

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Background: The objective of our study was to examine if selected infant, maternal, and healthcare-related factors predicted increased risk of traveling long distances for first surgical repair among infants with spina bifida that received interhospital transfer for spina bifida repair surgery in California.
Methods: A total of 677 eligible cases with complete geocoded data were identified for birth years 2006-2012 using data from the California Perinatal Quality Care Collaborative linked to hospital and vital records. The median distance from home to birth hospital among eligible infants was 9 miles, and from birth hospital to repair hospital was 15 miles. We limited our analysis to infants who lived close to the birth hospital, creating two study groups to examine transfer distance patterns: '*lived close and had a short transfer*' (i.e., lived <9 miles from birth hospital and traveled <15 miles from birth hospital to repair hospital) (n=92), and '*lived close and had a long transfer*' (i.e., lived <9 miles from birth hospital and traveled ≥15 miles from birth hospital to repair hospital) (n=96). Log-binomial regression was used to estimate crude and adjusted risk ratios (cRRs and aRRs, respectively) and 95% confidence intervals (CIs).
Results: We found that low birth weight (aRR=1.44; 95% CI=1.04, 1.99) and preterm birth (aRR=1.41; 95% CI=1.01, 1.97) were positively associated, whereas initiating prenatal care early in the first trimester was inversely associated (aRR=0.64; 95% CI=0.46, 0.89) with transferring a longer distance (≥15 miles) from birth hospital to repair hospital. No significant associations were noted by maternal race-ethnicity, socio-economic indicators, or the level of hospital care at the birth hospital.
Conclusions: Our study identified selected infant factors associated with the distance to access surgical care for infants with myelomeningocele who had to transfer from birth hospital to repair hospital. Distance-based barriers to care should be identified and optimized.

Factors associated with mortality in individuals participating in the National Spina Bifida Patient Registry (NSBPR)

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Background: Although survival has increased with medical advancements, spina bifida continues to carry an increased risk of mortality. The literature notes substantial variation of the rate and cause of mortality across and within age groups, lesion levels, and countries. The aim of this study was to describe the leading causes of death in participants of the NSBPR and identify possible risk factors associated with the most common causes of death.
Methods: A retrospective cohort study was performed of NSBPR participants who died between the years 2009-2021. Chi-square test and Kruskal-Wallis test were performed to determine the association between cause of death and sociodemographic and condition-related factors.
Results: Participants with myelomeningocele (MMC) (n=133) and non-myelomeningocele (NMMC) (n=7) were included in the overall analysis. Causes of death were obtained from patient's family (30%), healthcare provider report (27%), death certificate (16%), electronic medical record (13%) and unknown (13%). Median age at death was 21 years for MMC (range 0-77) and 46 years for NMMC (range 6-78). The top 3 reasons for all-cause mortality were cardiac/respiratory (29%), infection (24%) and unknown (21%). For the MMC sample, 55% were male, 78% were non-Hispanic white, 30% had private insurance, 89% had a history of shunt placement, and historically, 9% were community ambulators. The causes of death in MMC were cardiac/respiratory (29%), infection (24%), neurologic (17%), nephrological (4%), gastrointestinal (2%), and unknown/other (24%). Analysis of the 3 top categories in MMC found that age at death significantly differed by cause of death. Median ages of death in MMC were 21 (cardiac/respiratory), 30.5 (infection) and 13.5 (neurologic) years (p=0.0128). There were no differences by clinical variables.
Conclusions: The leading causes of death in MMC varied and were related to age. Neurologic causes occurred more often in younger participants while infections occurred more often in older participants. Risk factors related to mortality remain largely unclear.

Reducing the severity of spina bifida using exosomes from amniotic fluid-derived stemcells: An explorative study

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Background: Mesenchymal stem cells (MSCs) isolated from placenta and amniotic fluid (AF) display remarkable healing and protective properties. AF and placental MSC therapies have shown potential benefits in the treatment of spina bifida (SB) in ovine and rodent models. MSCs modulate the function of immune cells and tissue-resident progenitor cells through the release of paracrine signals, including exosomes (EXOs), small extracellular vesicles (30-150nm) produced by all cells. EXOs display readily available targeting capabilities and endogenous specific homing markers, which make them an interesting tool to develop effective cell-free therapeutic systems for tissue repair.
Methods: Our research team has been testing the therapeutic potential of AF-MSC EXOs in a genetic SB model, the Fkbp8-/- mouse. To this EXOs were injected intraperitoneally into pregnant Fkbp8+/- dams resulting from heterozygous crosses at E8-12. The effect on SB phenotype was assessed in terms of length of the lesion compared to untreated embryos, while spine structure investigated by skeletal staining with Alcian Blue (unmineralized cartilages) and Alizarin Red S (mineralized cartilages and bones). Intraperitoneal injections of fluorescently labelled MSC-EXOs (109) were used to track their biodistribution in pregnant dams (E5).
Results: A reduction in length of the SB lesion was observed in treated compared with untreated embryos harvested at E18.5, with an ongoing vertebrae closure compared to the open thoracic, lumbar, and sacral vertebrae that are associated to SB. Biodistribution data show that fluorescently labelled MSC-EXOs preferentially accumulate within the uterus.

Conclusions: The insights obtained from these preliminary studies support the potential role of AF-MSC to be used for the development of cell-free strategies to improve the prognosis of patients with SB.

Population estimates of people with spina bifida in the United States in 2020

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Background: Spina bifida is a birth defect that results in deficits of neurological function. Individuals diagnosed with spina bifida often require a lifetime of medical care to manage this condition. Currently, the number of people living with spina bifida in the United States is unclear. The purpose of this study is to provide estimates of the magnitude of this condition, and its distribution by gender and age.
Methods: Total births affected by spina bifida were calculated using rates from the Birth Defects Monitoring Program (BDMP) and state-based birth defects tracking systems supported by the Centers for Disease Control (CDC), over an 80-year period (1940-2020). Spina bifida mortality rates were determined using death certificate data available through the Centers for Disease Control and Prevention, National Center for Health Statistics. Life tables were created for each year of birth between 1940 and 2020 to estimate the total number of people with spina bifida alive in 2020 in the United States.
Results: In 2020, the estimated number of people in the U.S. living with spina bifida (0-80 years of age) was 124,150 (67,662 female; 56,488 male). The majority were adults aged 30 to 80 years (66.6%), compared to children and young adults (33.4%).
Conclusions: Understanding the approximate size and distribution by age and gender may assist health care providers in planning services for this changing population.

Age-specific probability of four major health outcomes in children with spina bifida

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Background: The natural history of spina bifida (SB) has not been well characterized. In particular, the risk of serious health outcomes as children with SB grow has not been presented in a way that facilitates its communication to clinicians and patients. This study was designed to estimate the age-specific probability of four health outcomes in a large registry of individuals with SB.
Methods: We examined the association between age and four health outcomes in individuals with myelomeningocele (MMC) and non-myelomeningocele (NMMC) from the National Spina Bifida Patient Registry. We created 16 age categories, one for each year between the ages of 5 and 19 years and one for those aged ≥ 20 years. We used generalized linear mixed models to calculate the adjusted probability and 95% prediction intervals of each outcome for each age category, adjusting for sex, and race/ethnicity.
Results: Our analytical sample included 7,069 individuals of whom 80% (n=5,627) had MMC and 20% (n=1,442) had NMMC. Respectively for the MMC and NMMC groups, the adjusted coefficients for the correlation between age and the probability of each outcome were -0.933 and -0.657 for bladder incontinence, -.922 and -0.773 for bowel incontinence, 0.942 and 0.382 for skin breakdown, and 0.809 and 0.619 for lack of ambulation.
Conclusions: In individuals with SB, age is inversely associated with the probability of bladder and

bowel incontinence and directly associated with the probability of skin breakdown and lack of ambulation. Given the high correlations, we produced charts with the probabilities of each outcome, year by year, from age 5 to age 19 years. These charts can help clinicians provide information to their patients about the risk of these four health outcomes.

A global update on the status of prevention of folic acid-preventable spina bifida and anencephaly in year 2020: 30-year anniversary of gaining knowledge about folic acid's prevention potential for neural tube defects

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Background: Spina bifida and anencephaly are major neural tube defects largely preventable through maternal periconceptional intake of folic acid. We estimated the global proportion of folic acid preventable spina bifida and anencephaly (FAP SBA) prevented through mandatory folic acid fortification of cereal grains, including wheat flour, maize flour, and rice, at the end of year 2020, a time point marking the 30th anniversary of the publication of landmark British Medical Research Council (MRC) study providing unequivocal knowledge on folic acid's FAP SBA prevention potential.

Methods: The Food Fortification Initiative database was used to identify countries with mandatory fortification policies with folic acid added to cereal grains. We examined status of FAP SBA prevention assuming mandatory folic acid fortification at 200 mcg/day of folic acid fully protects against FAP SBA and reduces their prevalence to a minimum achievable rate of 0.5 cases / 1,000 live births. The country-specific annual number of FAP SBA cases prevented was quantified as the maximum prevention potential possible for any of the fortified grain examined (wheat flour / maize flour / rice) based on the level of total folic acid consumption from fortified grain examined, and the fortification program coverage.

Results: Our analysis showed that 61,677 FAP SBA cases were prevented in the year 2020 through mandatory folic acid fortification of cereal grains in 58 countries, translating to 22% prevention of total possible FAP SBA prevention globally. Many countries in Africa, Asia, and Europe are yet to implement fortification. In 2020, 30 years after MRC study was published, 218,270 preventable FAP SBA cases still occurred globally.

Conclusions: Global prevention efforts for FAP SBA are inadequate even after three decades of knowledge on their prevention. Universal mandatory fortification of staples should be urgently implemented to prevent thousands of FAP SBA and associated elective terminations, stillbirths, and child mortality.

Early neonatal mortality among babies born with spina bifida in Finland, 2000-2014

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Background: Recent advancements in medicine and surgery have resulted in an improved survival among spina bifida-affected individuals; however, mortality remains a significant concern at all ages, and especially during infancy. We examined early neonatal mortality risk, temporal trends, and selected infant and maternal factors associated with early neonatal mortality among all spina bifida-affected live births in Finland.

Methods: We linked multi-registry population-based data from the national registers in Finland for infants born with spina bifida from 2000-2014. Early neonatal mortality was defined as death in 0-6 days after birth. Early neonatal mortality risk and 95% confidence intervals (CI) was estimated using the Poisson approximation of binomial distribution. Poisson regression was used to examine temporal trend in early neonatal mortality from 2000 to 2014 for spina bifida cases and all births in Finland. Exact logistic regression was used to estimate unadjusted odds ratios (uORs) and 95% confidence intervals (CIs).

Results: A total of 181 babies were born alive with spina bifida in Finland during the study period; 61% had isolated spina bifida. Pooling all study years,

7.2% (95% CI=4.2%, 12.4%) of all live-born cases experienced early neonatal death. There was a significant increase in early neonatal mortality among spina bifida births over the study period (p <0.0001). Low gestational age (<37 weeks) (uOR=6.96; 95% CI=1.86, 29.01), cases occurring as a part of a syndrome (uOR=125.67; 95% CI=14.90, >999.999), and advanced maternal age at gestation (≥35 years) (uOR=5.33; 95% CI=1.21, 21.87) were positively associated with early neonatal mortality.

Conclusions: Using national data from Finland, we found high early neonatal mortality with increasing trend over birth period spanning 15 years (2000-2014), and unadjusted positive associations with some infant and maternal factors. Future studies should pool data from Nordic countries to increase study size allowing multivariable analysis.