Non-Anemic Iron Deficiency, Depression, and other Health Issues In State Fair Attendees

Funding Request - $12,500

Contact person: Daniel D. Gallaher, Ph.D., Professor, Department of Food Science and Nutrition, 1334 Eckles Ave., University of Minnesota, St. Paul, MN. Telephone: 612-624-0746, Email: dgallahe@umn.edu

Principal Investigator: Daniel D. Gallaher, Ph.D., Professor, Department of Food Science and Nutrition, 1334 Eckles Ave., University of Minnesota, St. Paul, MN. Telephone: 612-624-0746, Email: dgallahe@umn.edu

Key Personnel:

Sabrina P. Trudo, Ph.D., Co-Investigator, Associate Professor, Department of Food Science and Nutrition University of Minnesota. Has extensive human studies experience, and therefore will assist in preparation of IRB forms, trial design, and appropriate approaches to working with human subjects in the environment of the State Fair.

Joannie Dobbs, Ph.D., Co-Investigator, Assistant Specialist For Food Composition and Health Education, Department of Human Nutrition, Food and Animal Sciences, University of Hawaii at Manoa. Will assist with development of the survey and will analyze survey results and participate in statistical analysis.

Abstract

Depression is a serious disorder that significantly diminishes quality of life and is a leading cause of disability worldwide. It is a common disorder that is estimated to have a 12-month prevalence in the United States of 10%. It is significantly associated with numerous chronic diseases, including arthritis, asthma, cancer, cardiovascular disease, diabetes, and chronic pain conditions. There is evidence suggesting that, in some cases, there is a causal relationship between depression and these physical ailments. People with depression are at high risk for early death, due to both a greater risk of suicide and the chronic diseases they experience. Thus, reducing the prevalence of depression would constitute a significant advancement in public health. Recent evidence suggests that depression may result, in some cases, from a nutritional deficiency, specifically iron deficiency. Iron deficiency is the most common of all nutritional deficiencies. It is estimated that as many as 70% of the world's population has inadequate iron status, and that 30% of the population has iron-deficiency anemia. Iron deficiency is the only nutritional deficiency that is common in both developing and developed countries. It has long been known that iron deficiency in young children can lead to permanent impairments in cognitive function, thus establishing the importance of iron in neurological function. However, recent evidence suggests that iron deficiency is also associated with depression, perhaps long before the routinely monitored clinical parameters indicate iron-deficiency anemia. Indeed, we have preliminary evidence that individuals who have low iron status, but are not sufficiently iron deficient to be anemic (referred to as non-anemic iron deficiency, NAID), show a much greater likelihood of being depressed than those with normal iron status. Thus, the overall goal of our research project is to examine rigorously the relationship between iron status and depression. It is our hypothesis that individuals who have NAID will have a much greater prevalence of depression than those with normal iron status. To test this hypothesis, we will recruit attendees of the Minnesota State Fair to donate a small amount of blood, to be used to assess iron status, and to take a survey that will assess their degree of depression, using a validated survey instrument. The primary measures of iron status will be the less commonly monitored but earlier indicators of iron deficiency: plasma ferritin and plasma transferrin receptor, which are measured by ELISA. Together, these two measures can be used to calculate total body iron, which is now regarded as the most accurate measure of iron status. We will also measure hemoglobin, the more routinely monitored indicator of iron status clinically, to determine whether the individuals are anemic. We will then correlate the degree of depression with total body iron to determine the association. Finding an association between low iron status and depression would suggest that a relatively straightforward and inexpensive treatment exists that could greatly reduce the prevalence of depression, namely improving iron status. If our hypothesis is correct, then a dramatic decrease in this debilitating condition could be achieved for Minnesotans.

Specific Aims

The specific aims of the proposed research are to determine in a large and varied group of State Fair attendees the following:

1. Their iron nutritional status, to be determined by measurement of their plasma ferritin and transferrin receptor concentrations.
2. Their degree of depression, using the PHQ-9 depression screen, a validated instrument for measuring depression, as well as fatigue and other health issues that we suspect are related to low iron status.

Our hypothesis is that iron deficiency that is not severe enough to result in anemia (and therefore is not commonly diagnosed) is strongly associated with depression. Further, it will also be associated with greater fatigue as well as other conditions not normally associated with iron deficiency.

Background and significance

Iron deficiency is the most common nutritional deficiency in the world, affecting an estimated 2 billion people (1). It is the only nutritional deficiency that is common both in developing and developed countries. In the USA, it is estimated that 9-11% of non-pregnant premenopausal women have iron deficiency anemia (2).

Iron deficiency is best known for the fatigue and lassitude that accompanies it. This most commonly occurs when the individual develops iron deficiency anemia (defined as a low hemoglobin concentration or a low hematocrit). However, there is growing evidence in the literature that there may be pathophysiological processes and symptoms of iron deficiency long before an individual becomes anemic. For example, in a study of non-anemic women with unexplained fatigue, iron supplementation for one month reduced fatigue 29% versus a reduction in fatigue of 13% in women given a placebo (3). This situation of subclinical iron deficiency, often referred to as non-anemic iron deficiency (NAID), is quite likely common and is certainly far more common than iron deficiency anemia. NAID is underdiagnosed due to the more sophisticated testing needed to diagnose it, thus making it much harder for people to connect symptoms with iron deficiency. For example, in a study conducted in the Netherlands, the prevalence of NAID was estimated at between 14% in men and 9% in women, using serum ferritin as the measure of iron status (4).

Iron deficiency during childhood development can lead to impairments in cognitive development (5), thus establishing the potential of iron deficiency to have detrimental neuropsychological consequences. One such consequence, depression, is a serious mood disorder that significantly diminishes quality of life and is a leading cause of disability worldwide (6). Although an association between iron deficiency anemia and depression has been reported (7), the relationship between the much more common NAID and depression is unexplored. However, we have recently obtained preliminary evidence that NAID is also associated with depression. In a laboratory class taught by one of us (DDG), we assessed iron status using several different measures, including plasma ferritin. A value of <15 ng/mL for plasma ferritin is indicative of low iron status. We found that 48% of female students with ferritin values of 1-10 ng/mL reported feeling sad or depressed in the last 3 months, whereas 21% of students with ferritin between 11-20 ng/mL reported sadness or depression, and only 4% with serum ferritin between 21-30 ng/mL reported sadness or depression. Of note was that none of these female students were anemic. Thus, our findings suggest that depression may be highly prevalent in NAID.

Who in the community will benefit from the results of our project?

Depression can increase work absenteeism, lead to short-term disability, and decrease productivity. Further, depression can adversely affect the outcome for a number of chronic diseases, thus increasing the cost of

treatment. Thus, untreated depression has a significant negative societal impact. Depression in Minnesota is estimated at 5.9% of the population, which is relatively low compared to other states (8). However, this still represents a significant proportion of the state population to be afflicted with a debilitating condition. A finding that low iron status is associated with depression suggests that depression may be treated in an inexpensive and straightforward manner, by increasing iron intake, either through diet or with supplements.

Partnership

This project is a partnership between two investigators at the University of Minnesota (Gallaher and Trudo) and an investigator at the University of Hawaii (Dobbs). Dr. Gallaher has extensive experience in determining iron status in humans, although only in an academic environment (i.e. the classroom). Dr. Trudo has significant experience conducting human trials. Dr. Dobbs has considerable experience in analysis of survey data and has a considerable understanding of the relationship between NAID and various health conditions. These three investigators bring together considerable and complimentary experience for conducting the proposed study.

Project design and methods

Male and female subjects between the ages of 18 and 85 will be invited to complete a computer-based survey that uses a validated instrument to assess depression, as well as other health issues suspected to occur with NAID, including fatigue. Subsequently, 300 µL of blood will be collected by professional phlebotomists from each subject using minimally invasive capillary blood collectors (i.e., finger sticks, essentially). The surveys and blood samples will be coded to ensure confidentiality. The blood will be analyzed for whole blood hemoglobin, plasma ferritin, and plasma transferrin receptor (TfR) concentration. Plasma ferritin and TfR will be measured by ELISA, and will be used to calculate total body iron (9). Hemoglobin will be measured by a spectrophotometric method. We will then correlate total body iron with the scores from the depression and fatigue survey instruments to determine whether, in subjects that are not anemic (hemoglobin within normal range), total body iron correlates with depression as well as with the other measures we will examine using the survey.

Drs. Gallaher and Trudo will oversee the project at the State Fair. Graduate students will be hired to assist in administering the electronic survey. Professional phlebotomists will be hired to collect blood from the subjects. We plan on having two graduate students and two phlebotomists working at the Fair at any given time. Our goal is to enroll 200 subjects over 2 days.

Next steps

We plan to disseminate our project findings initially by presenting the results at the Experimental Biology meetings, the main nutrition research meeting in the United States. Subsequently, we would aim to publish the findings in a journal that focuses on clinical nutrition.

If our hypothesis is correct, and we find that subjects with low iron status, as measured by total body iron, have a much greater prevalence of depression, we believe there will be a number of agencies who would sponsor further research. These would include NIH, USDA, and the National Cattlemen's Beef Association. Our next step would be to conduct an intervention study, in which we would identify individuals with low iron status who are depressed and intervene to determine whether improving their iron status resolves their depression.

If an iron intervention proves successful in resolving depression, it may then be appropriate to engage community health agencies to determine how to develop a public health message to spread this information to the community at large. This could include both county and state public health agencies.

Timeline

Both the biochemical assay (ferritin, transferrin receptor, hemoglobin) and the survey results will be analyzed within the first 3 months after completion of the sample and data collection. During the next three months we will statistically analyze the data. The next 6 months will be devoted to writing a manuscript for publication.

Biosketches

See attached.

Budget

Item	Estimated cost
Phlebotomists	640
Graduate students	710
Technician for assays	3600
Survey analysis	1500
Transferrin Receptor kits	3450
Ferritin kits	1300
Miscellaneous supplies	1300
TOTAL	12500

References

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