THE RELATIONSHIPS BETWEEN SERUM FERRITIN, GENDER, AND EXERCISE IN CANADIANS OF ICELANDIC DESCENT: IMPLICATIONS FOR NURSING

by

Wally J. Bartfay

A thesis
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in Partial Fulfillment of the Requirements
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ABSTRACT

It has been suggested that increased levels of stored iron may be a risk factor for the development of cardiovascular disease. The relationships between serum ferritin, gender and exercise in male and female Manitobians of Icelandic descent age 21 to 60 years were studied. Mean serum ferritin levels obtained were 187.93 ug/L and 47.84 ug/L for males and females respectively. The mean serum ferritin level for premenopausal females was 33.06 ug/L compared to 71.14 ug/L for postmenopausal females. Statistically significant differences were noted for serum ferritin levels between males and females; males and premenopausal women; males and postmenopausal women, and between premenopausal and postmenopausal females. Males, but not females, who exercised regularly (45 minutes or more per week) had significantly lower levels of serum ferritin compared to their sedentary counterparts. However, in postmenopausal females, exercise was found to be negatively correlated to serum ferritin. Hemoglobin and hematocrit were found to be positively correlated to serum ferritin levels in males and females. Higher intakes of dietary iron were found to be positively correlated with serum ferritin levels in females; whereas, alcohol consumption was found to be positively correlated to serum ferritin in males. These findings suggest that regular exercise in males and postmenopausal women may be beneficial in decreasing the risk of cardiovascular disease through the depleting of iron stores in the body.

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I would like to acknowledge the Paul T. Thorlakson Foundation for partially funding this study. I would also like to acknowledge the support and encouragement of Dr. Johann Axelsson, Dr. Stefan Sigurdsson, and all the members of the Icelandic-Canadian Study, University of Iceland; Mrs. Rhonda Findlater and Mrs. Sonya Anderson for their assistance in the collection and preparation of blood samples; Dr. Shojani, Ms. Gail Turnbull and all the technicians of the Department of Hematology, St. Boniface General Hospital, for their assistance with this research endeavor, and Dr. Linda Kristjanson for her extensive feedback and suggestions on earlier drafts of the Nursing Theory of Health Equity. And finally, I would like to thank my wife Emma for her statistical advice and assistance; the development of mathematical formulas to measure concepts such as health equity and the environment, and for the numerous hours that she sat beside me for support and encouragement throughout the length of this study.

DEDICATION

This thesis is dedicated to all individuals and their significant others, who have ever suffered as a result of cardiovascular disease.

This thesis is also dedicated to all my teachers and mentors who have encouraged me to pursue my dreams. Happy are those who dream and are ready to pay the price to make those dreams come true.

And finally, this thesis is dedicated to my wife Emma.

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CHAPTER 1: INTRODUCTION

1.1 Background

Cardiovascular disease (CVD) is the leading cause of death, disability and hospitalization in Canada. Approximately three million Canadians suffer from some form of heart or blood vessel disease, and CVD accounts for approximately 43 percent (%) of all deaths in Canada (Gelsky, MacDonald & Young, 1991). In 1988 alone, 77,000 Canadians , approximately the population of Kingston, Ontario, died from CVD (Minister of Supply and Services Canada, 1991). In 1986, one in four (26 %) disability pensions paid through the Canada Pension Plan were attributed to CVD (Reeder, Lauzon, Mao, Nair & Petrasovitis, 1991).

Manitoba has the highest incidence of deaths attributed to CVD among the three prairie provinces in Canada (Gelsky, MacDonald & Young, 1991). Findings from the Manitoba Heart Health Survey revealed that 63 % of adult Manitobans had at least one of the three major risk factors associated with the development of CVD (i.e., hypertension, smoking, elevated blood cholesterol) (Gelsky, MacDonald & Young, 1991). The costs associated with CVD are high, whether they are measured in terms of morbidity, mortality, hospitalization, decreased quality of life, human suffering or economic losses. For example, the potential years of life lost to age 70 in Manitoba, for ischemic heart disease and stroke alone, has been estimated to be 7,214 years (Government of Manitoba, 1986). Moreover, diseases of the circulatory system in Manitoba accounted for the majority of both hospital in-patient cases (16,994) and total patient days (257,817) at a cost of $20,499,926 annually (Manitoba Health Services Commission, 1990-1991).

Efforts directed towards prevention, treatment, and rehabilitation of individuals with CVD requires special attention to their physiology and, often, the unique aspects of their pathophysiology (Van Camp & Boyer, 1989). Of special interest to nursing are the nonsurgical and nonpharmacological therapies, including diet, exercise, and health promoting lifestyles.

1.2 Statement of the problem

In 1981, Hopkins and Williams published an extensive list of 246 proposed risk factors associated with the development of coronary heart disease (CHD). A careful review of the most common risk factors (i.e., hypertension, smoking, obesity, hyperlipidaemia) fails to adequately account for the international variation in disease incidence and for the gender differences in disease expression. The disparity in CHD risk between men and premenopausal women is especially striking in developed and affluent countries where heart disease reaches epidemic proportions in men whilst women are largely protected. This protection appears to end with the onset of menopause (Gorden, Kannel, Hjortland, & McNamara, 1978; Hjortland, McNamara, & Kannel, 1976; Kannel, Hjortland, McNamara & Gorden, 1976; Shibata, Matsuzaki, & Hatano, 1979). The results of the Framingham study, an ongoing large scale prospective study of heart disease of the residents of Framingham, Massachusetts (Cantwell, 1975; Dawber, 1980; Gorden et al., 1978; Hjortland et al., 1976; Kannel et al., 1976), indicate that in women the incidence of CHD rises sharply with the onset of either surgical or natural menopause. Furthermore, the results appear to implicate uterine rather than ovarian function as the factor conferring protection against CHD, since there was an increased incidence of CHD reported in women who underwent surgical menopause whether the ovaries

were removed or not (Gorden et al., 1978; Hjortland et al., 1976; Kannel et al., 1976; McCord, 1991). Moreover, postmenopausal women receiving estrogen had a doubled risk of CHD (Gorden et al., 1978; McCord, 1991; Sullivan, 1991; Sullivan, 1989; Sullivan, 1981). It has been suggested that blood loss through menses may be a protective factor against CHD.

In an attempt to account for the noted gender differences, Sullivan (1981) hypothesized that "the greater incidence of heart diseases in men and postmenopausal women compared with the incidence in premenopausal women is due to higher levels of stored iron in these two groups" (p. 1293). The hypothesis is supported by the following observations:

(1) the well-known cardiotoxic effects of excessive iron stores manifested by conditions such as hemochromatosis (a disorder of iron metabolism) and thalassemia (a heterogeneous group of hemolytic anemias resulting from abnormal hemoglobin synthesis) (Ashinsky, 1992; Cross, Halliwell, Borish, Pryor, Ames, Saul, McCord, & Harman, 1987; Hughes, 1978; Olivieri, Koren, Matsui, Liu, Blendis, Cameron, McClelland, & Templeton, 1992; Sullivan, 1991; Sullivan, 1989; Sullivan, 1981; Vigorita & Hutchins, 1979);

(2) accumulation of stored iron in men after adolescence (Cook, Finch, & Smith, 1976; Finch, Cook, Labbe & Culala, 1977; Jonsson, Johannesson, Sigfusson, Magnusson, Thjodleifsson & Magnusson, 1991; Salonen, Nyyssonen, Korpela, Tuomilehto, Seppanen, & Salonen, 1992; Sullivan, 1992; Sullivan, 1981);

(3) accumulation of stored iron in women following menopause to levels comparable to men (Cook et al., 1976; Finch et al., 1977; Jonsson et al., 1991; Sullivan, 1989; Sullivan, 1981);

(4) low incidence of heart diseases in iron deficient and improvised (malnourished) individuals (Davis & Park, 1984; Hamilton & Whitney, 1982; Keys, 1970; Murray, Murray & Murray, 1991; Sullivan, 1991;Sullivan, 1989; Sullivan, 1981), and

(5) the protective effects of antioxidants {substances that inhibit the oxidation of other compounds} and iron chelators such as desferrioxamine [deferoxamine, Desferal] {removes stored iron} (Babbs, 1985; Balla, Jacob, Eaton, Belcher, &Vercellotti, 1991; Bernier, Hearse, & Manning, 1986; Bolli, Patel, Zhu, O'Neil, Hartley, Charlat & Roberts, 1987; Dhaliwal, Kirshenbaum, Randhawa, & Singal, 1991; DeBoer & Clark, 1992; Faber, Vercellotti, Jacob, Pieper & Gross, 1988; Ganguly, 1991; Heinecke, Rosen & Chait, 1984; Kuross & Hebbel, 1988; Lesnefsky, Repine & Horwitz, 1990; McCord, 1991; Pratt, Horesh, Berger, Harken, & Repine, 1990; Salonen, Yla-Herttuala, Yamanoto, Butler, Korpela, Salonen, Nyyssonen, Palinski, & Witztum, 1992; Singal, Gupta, & Randhawa, 1991; Sullivan, 1991; Sullivan, 1989; van der Kraaij, Mostert, van Eijk and Koster, 1988; van Jaarsveld, Kuyl & Alberts, 1992; Williams, Zweier, & Flahety, 1991).

In a recent large scale prospective study (n=1,931) of Eastern Finnish men, Salonen and coworkers (1992) found that men with a serum ferritin greater than or equal to ($\geq$) 200 micrograms per liter (ug/ L) had a 2.2 fold risk of acute myocardial infarction as compared to men with lower serum ferritin values ($p < 0.01$). This landmark study provides the first empirical evidence in support of the conjecture that stored iron promotes CHD and iron depletion protects against CHD (Sullivan, 1992; Sullivan, 1989; Sullivan, 1981).

Although women were not sampled in the study by Salonen and coworkers (1992), the finding that serum ferritin is associated with an increased risk of CHD in men is especially relevant to the hypothesis that low iron stores in menstruating women protect them from CHD (Sullivan, 1981). Additional studies involving both menstruating and menopausal women would be the next logical step to determine the validity of the iron hypothesis (Sullivan, 1992).

There is also evidence to suggest that physical exertion may enhance iron excretion (Blum, Sherman, & Boileau, 1986; Lauffer, 1991; Taylor, Rogers, Goodman, Baynes, Bothwell, Benzwoda, Kramer, & Hattingh, 1987; Salonen et al., 1992). For example, Blum and coworkers (1986) reported significant declines in serum ferritin levels in women enrolled in aerobics/ fitness classes after a period of only six weeks. Lauffer (1991) contends that the iron hypothesis is consistent with the graded reductions in mortality observed as a function of fitness level. The role of exercise-induced reductions in iron levels needs to be addressed in future studies (Lauffer, 1991).

This study extends the existing areas of research related to stored iron by examining the relationships between serum ferritin, gender, and exercise in Canadians of Icelandic decent. This study is a component of the International Collaborative Icelandic-Canadian Study headed by Dr. Johann Axelsson of the University of Iceland, Reykjavik, Iceland and Dr. Barbara Naimark of the University of Manitoba, Winnipeg, Manitoba, Canada.

1.3 Research question

What are the relationships between serum ferritin, gender and exercise in Canadians of Icelandic decent?

1.4 Hypotheses

(1) Premenopausal women will have lower levels of stored iron as measured by serum ferritin levels, as compared to postmenopausal women.

(2) Premenopausal women will have lower levels of stored iron as measured by serum ferritin levels, as compared to men.

(3) Postmenopausal women will have similar levels of stored iron as measured by serum ferritin levels, as compared to men .

(4) Premenopausal women who exercise regularly will have lower levels of stored iron as measured by serum ferritin levels, as compared to premenopausal women who do not exercise regularly.

(5) Postmenopausal women who exercise regularly will have lower levels of stored iron as measured by serum ferritin levels, as compared to postmenopausal women who do not exercise regularly.

(6) Postmenopausal women who exercise regularly will have similar levels of stored iron as measured by serum ferritin levels, as compared to premenopausal women who do not exercise regularly.

(7) Men who exercise regularly will have lower levels of stored iron as measured by serum ferritin, as compared to men who do not exercise regularly.

1.5 Definition of major terms

(1) **Premenopausal women:** Consists of all nonpregnant females of Icelandic descent who had their last menstrual period less than 12 months ago. Premenopausal women are also referred to as **menstruating** women for the purposes of this study and this includes all women irregardless of whether or not their period was regular or irregular in nature during this noted time period.

(2) **Postmenopausal women**: Consists of all females of Icelandic descent who had their last menstrual period 12 or more months ago. Postmenopausal women are also referred to as **menopausal** women for the purposes of this study.

(3) **Serum ferritin**: A measure of the amount of stored iron in the body determined by a sample of venous blood (fasting for 24 hours) and measured by radioimmunoassay (RAI). For the purposes of this study, normal values for males may range from 10 to 175 micrograms per liter (ug/L) and 10 to 95 ug/L for females (standard values utilized by St. Boniface General Hospital, Winnipeg, Manitoba, Canada).

(4) **Regular exercise**: Is defined as aerobic activity engaged in for 45 minutes or more per week as reported by the subjects on the Lifestyles questionnaire (see Appendix A). This was determined by multiplying the responses obtained on question 1 and question 3 of the section entitled Exercise and physical fitness of this noted questionnaire.

(5) **Regular blood donors**: Consists of all subjects who have had donated blood five {5} or more times as determined by the question 2 of the blood transfusion and donation history section of the lifestyles questionnaire.

(6) **Alcohol**: Refers to the amount of ethanol consumed (in ounces per week) as determined by questions 10, 11 and 12 of the Medications and supplements section of the lifestyles questionnaire. Specially, one ounce of pure alcohol was equivalent to the following: (a) Thirty ounces of beer or one bottle {question 10}; (b) eight ounces of wine or 1 glass {question 11}, and (c) two ounces of liquor (spirits) or 1 glass {question 12}.

(7) **Heme iron:** Dietary iron comprised of hemoglobin or myoglobin that is readily absorbed in the small intestine and is obtained exclusively from meat sources {i.e., pork, beef, fish, poultry} (Editorial, 1981; Fleck, 1981; Monsen et al., 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984).

(8) **Nonheme iron:** Consists of inorganic forms of dietary iron that are not readily absorbed in the small intestine and they are of both plant and animal foods (Editorial, 1981; Fleck, 1981; Kreutler, 1980; Monsen et al., 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984). This form of dietary iron is also known as vegetal iron (Fleck, 1981).

(9) **Health equity:** A dynamic state that results from a summation of the available health resources and the actual or potential health liabilities present in a specific moment in time. Health equity is measured by serum ferritin levels.

(10) **Health resources:** A sum of all the internal and external positive assets that can be utilized to resist and counteract the effects of health liabilities on health equity (e.g., regular exercise).

(11) **Health liabilities:** These items tax existing health resources and negatively affect health equity (e.g., sedentary lifestyle).

1.6 Summary

It has been hypothesized that stored iron promotes coronary heart disease (CHD) and iron depletion protects against CHD (Sullivan, 1992; Sullivan, 1989; Sullivan, 1981). In a recent prospective landmark study of Eastern Finnish men, Salonen and coworkers (1992) found that men with a serum ferritin of $\geq$200 ug /L had a 2.2 fold risk of acute myocardial infarction as compared to men with lower serum ferritin values. Additional

studies involving both menstruating and menopausal women would be the next logical step to determine the validity of the iron hypothesis (Sullivan, 1992). There is also evidence to suggest that physical exertion may enhance iron excretion (Blum, Sherman, & Boileau, 1986; Lauffer, 1991; Taylor, Rogers, Goodman, Baynes, Bothwell, Benzwoda, Kramer, & Hattingh, 1987; Salonen et al., 1992). This study extends the existing areas of research related to stored iron by examining the relationships between serum ferritin, gender, and exercise in Canadians of Icelandic descent.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Canadians of Icelandic descent

Background

Iceland is a small volcanic island located in the North Atlantic Ocean (Carwardine, 1986; Hjalmarsson, 1988; Kidson, 1971; McCririck, 1976; Oberbeck, Schwarzbach, Englander, Eldjarn, Gislason, Dreyer-Eimbcke, von Linden & Schwabe, 1974). Iceland is approximately 103,100 square kilometers in area, about 300 kilometers north to south, and 500 kilometers west to east (McCrick, 1976; Nordel & Kristinsson, 1987). Immigration to Iceland began about 870 A.D. (Nordel & Kristinsson, 1987). Currently, there are approximately 250,000 inhabitants, two-thirds of whom live in the capital city of Reykjavik and the surrounding area on the southwestern corner of the island (Naimark, 1991).

The nation is small and unusually homogeneous genetically and enjoys a high standard of education and health care (Arngrimsson, 1989; Carwardine, 1986; Petursdottir, 1984). Approximately one quarter of the gross national product is based on fishing and the fish-processing industry (Oberbeck et al., 1974). Iceland is the most sparsely populated country in Europe, with a national average of only two individuals per square kilometer (Carwardine, 1986). Present day Icelanders descend from a stock of Scandinavian and Celtic peoples (Arngrimsson, 1989; Hjalmarsson, 1988; Kidson, 1971; McCririck, 1976; Nordal & Kristinsson, 1987).

Emigration to North America

Emigration to North American began at the end of the late eighteenth century and early nineteenth century. The earliest modern Icelandic settlement was established in Utah in 1855, but it was not until the 1870's that continuous emigration took place (Nordal & Kristinsson, 1987).

Approximately 18,000 Icelanders, about one fifth of the total population, emigrated to North America between 1870 and 1914 (Axelson, Palsson, Petursdottir, Sigfusson & Way, 1981; Petursdottir, 1984). Comparatively, Nordal and Kristinsson (1987, p. 63) report that between 10,000-12,000 people emigrated from Iceland to Canada and the United States during this same time period. "Census returns in the United States and Canada in 1930 and 1931 respectively showed 7,413 people of Icelandic descent in the United States and 19,382 in Canada (Nordal & Kristinsson, 1987, p. 63).

Although settlements arose in Saskatchewan, Alberta, and British Columbia, Manitoba boasts the largest Icelandic settlement in Canada. In 1873, the first Icelandic immigrants came to Canada, and in 1875 the first permanent Icelandic settlement in Canada was established in Manitoba on the western shore of Lake Winnipeg (Axelsson et al., 1981; Nordal & Kristinsson, 1987; Richtik, 1986). The settlement was called Nyja Island (New Iceland) and the first town was named Gimli. In 1878, the Icelanders who settled this area, declared this area as an independent republic, "with its own constitution, laws and government, and Icelandic as the only official language; it lasted almost a decade before the Canadian government abolished it in 1887" (Anderson, 1986, p. 95). Icelandic-Canadians still refer to this area as New Iceland, and this area has now taken on the symbolic quality of spiritual home for Icelanders in North America (Brydon, 1991, p. 2).

Population distribution

According to Nordal and Kristinsson (1987, pp. 63-64), approximately 82 % of the people of Icelandic descent listed Icelandic as their mother tongue on the 1931 Canadian census, while the corresponding estimates were 51 % in 1951 and 28 % in 1971. Currently, there are 3,055

individuals nationally who report their mother tongue as Icelandic (see Table 1), of whom 1,715 reside in the province of Manitoba (Minister of Industry, Science and Technology, 1992).

Table 1:
Detailed account of Icelandic mother tongue (single response) for Canada, Provinces and Territories

	Totals
Canada	**3,055**
Newfoundland	**5**
Prince Edward Island	**0**
Nova Scotia	**15**
New Brunswick	**0**
Quebec	**20**
Ontario	**250**
Manitoba	**1,715**
Saskatchewan	**260**
Alberta	**200**
British Columbia	**585**
Yukon Territory	**0**
Northwest Territories	**5**

****Source: Adapted from Minister of Industry, Science and Technology (1992).**

According to the 1986 Census (Statistics Canada, 1989), 14,470 individuals noted that they were of Icelandic descent of whom 6,980 resided in the province of Manitoba (see Table 2). "Icelandic populations provide unique opportunities for epidemiological and anthropological research, because of their genetic homogeneity and the availability of detailed genealogical information concerning them" (Axelsson et al., 1981, p. 201).

Table 2:
Population declared to be of Icelandic origin for Canada, Provinces and Territories

	Totals
Canada	**14,470**
Newfoundland	**10**
Prince Edward Island	**0**
Nova Scotia	**105**
New Brunswick	**30**
Quebec	**95**
Ontario	**1,270**
Manitoba	**6,980**
Saskatchewan	**1,425**
Alberta	**1,650**
British Columbia	**2,850**
Yukon	**20**
Northwest Territories	**35**

****Source**: **Adapted from Statistics Canada (1989).**

Moreover, due to the unusual genetic homogeneity of this population, "inferences which may be made from quantitative findings are often more clear-cut than whose which would be warranted by studies on more heterogeneous populations" (Axelsson, Oskarsson, Petursdottir, Way, Sigfusson & Karlsson, 1984, p. 64).

2.2 Risk factors for CVD

Background

Large scale epidemiological, clinical and laboratory studies have identified certain risk factors associated with the development of CVD. These risk factors have been broadly classified as either controllable or uncontrollable. Controllable risk factors are amenable to changes in lifestyle (i.e., smoking, diet high in saturated fat). By contrast, uncontrollable risk

factors are not amenable to changes in lifestyle (i.e., male sex, genetic predisposition). Table 3 provides an overview of the 10 most common risk factors associated with the development of CVD. Information is given about the nature of the risk factors, classification, examples of lifestyle modifications where appropriate, and the literary sources reviewed.

Table 3:
The 10 most common risk factors associated with the development of CVD

Risk factor	Classification	Lifestyle modification	Sources reviewed
Smoking	Controllable	Stop smoking	Andreoli et al., (1983); Bruess, Richardson & Laing (1989); Canobbio (1990); Holm & Penckofer (1990); Hopkins & Williams (1981); Howard et al., (1991); Kannel (1983).
Diet (e.g., high in saturated fat & cholesterol)	Controllable	Proper nutrition/diet	Andreoli et al., (1983); Bruess, Richardson & Laing (1989); Canobbio (1990); Hopkins & Williams (1981); Howard et al., (1991); Kannel (1983); Merk & Company (1989); Seiden (1989).

Table 3 continued...

Risk factor	Classification	Lifestyle modification	Sources reviewed
Hypertension	Controllable	Proper nutrition/diet, low sodium diet, exercise, & medications.	Andreoli et al., (1983); Bruess, Richardson & Laing (1989); Holmes & Penckofer (1990); Hopkins & Williams (1981); Howard et al., (1991); Kannel (1983).
Diabetes & glucose intolerance	Controllable	Proper nutrition/diet, weight control, exercise & medications.	Andreoli et al., (1983); Bruess, Richardson & Laing (1989); Canobbio (1990); Hopkins & Williams (1981); Kannel (1983).
Sedentary lifestyle (physical inactivity)	Controllable	Exercise	Andreoli et al., (1983); Bruess, Richardson, & Laing (1989); Canobbio (1990); Holm & Penckofer (1990); Howard et al., (1991); Kannel (1983).
Psychosocial (type A personality)	Controllable	Stress management, relaxation techniques	Andreoli et al., (1983); Canobbio (1990); Hopkins & Williams (1981); Jenkins (1988); Kannel (1983).
Obesity (> 30 % above ideal body weight)	Controllable	Proper nutrition/diet, exercise.	Andreoli et al., (1983); Canobbio (1990); Holm & Penckofer (1990); Hopkins & Williams (1981); Kannel (1983).

Table 3 continued...

Risk factor	Classification	Lifestyle modification	Sources reviewed
Male sex	Uncontrollable	Not modifiable	Andreoli et al., (1983); Canobbio (1990); Hopkins & Williams (1981); Kannel (1983).
Advancing age	Uncontrollable	Not modifiable	Andreoli et al., (1983); Canobbio (1990); Holm & Penckofer (1990); Hopkins & Williams (1981); Kannel (1983).
Genetic predisposition {heredity} (e.g., parent who had myocardial infarction).	Uncontrollable	Not modifiable	Andreoli et al., (1983); Canobbio (1990); Hopkins & Williams (1981); Kannel (1983); Shear et al., (1985).

Findings from the Manitoba Heart Health Survey revealed that 63 % of adult Manitobans had at least one of the three major risk factors associated with the development of CVD (hypertension, smoking, elevated serum cholesterol) (Gelskey et al., 1991). Moreover, approximately half of the respondents surveyed were considered sedentary, six percent had diabetes, and two in five were obese (body mass index $\geq$ 27).

Iron as a possible risk factor for CVD

As many as 246 suspected risk factors have been identified with the development of CVD (Hopkins & Williams, 1981). A review of the most common risk factors (i.e., hypertension, obesity, smoking) fails to sufficiently account for the international variation in CVD incidence, and for gender differences in disease onset. The disparity between CVD risk between males and females in especially striking in industrialized western

countries that reach epidemic proportions in males whilst women are largely protected until the onset of menopause (Gorden et al., 1978; Hjortland et al., 1976; Kannel et al., 1976; Shibata, Matsuzaki & Hatano, 1979). The basis for this noted gender difference and the loss of protection with menopause remains unknown. In an attempt to account for these findings, Sullivan (1981) hypothesized that the higher incidence of CVD in males and postmenopausal females, compared to the low incidence in premenopausal women, is attributed to higher levels of stored iron in males and postmenopausal females.

Sullivan (1981) argues that several observations make it unlikely that oestrogen (estrogen) is responsible for the gender differences in CVD or the effects of menopause. The Framingham study, for example, reported that the risk of CVD in females increased significantly after natural menopause, simple hysterectomy, or hysterectomy with bilateral oophorectomy (Gorden et al., 1978; Hjortland et al., 1976; McCord, 1991; Sullivan, 1981). "It is now evident that an increase in coronary heart disease incidence is demonstrable after both surgical and natural menopause and that this increase is not restricted to younger women with premature menopause" (Gorden et al., 1978, p. 157). Moreover, after a simple hysterectomy a female's risk of myocardial infarction increases dramatically, despite continued ovarian function and estrogen production (Sullivan, 1991). Hence, regular menstrual blood loss that lowers iron stores may be the protective factor rather than endogenous estrogen levels (McCord, 1991).

Sullivan (1981) argues that anemia is unlikely to be the explanation for the gender difference in risk and the effect of menopause since changes in hematocrit as a function of age and gender do not follow CVD risk patterns. Postmenopausal women have a significant increase in the

incidence of CVD without a concomitant increase in hematocrit (Sullivan, 1991). "There is, however, a 300 % difference in serum ferritin between the sexes, and this difference occurs at about the age of the menopause" (Sullivan, 1981, p. 1294).

Van der Schouw and colleagues (1990) reported that the mean ferritin levels were significantly higher immediately in patients with myocardial infarction as compared to population controls. Interestingly, Sullivan (1989) reports that research has shown that the onset of myocardial infarctions has a prominent morning peak with a threefold increase at 09: 00 AM as compared with later periods (e.g., 11: 00 PM). "This circadian variation is identical to that previously observed for serum iron. Serum iron levels are two to three times higher in the morning (between 8 AM and 10 AM) than at night" (Sullivan, 1989, p. 1184).

> "The amount of bound iron in the plasma is reported to exhibit a circadian variation which can be as much as 60 ug/dl [deciliter] over a 24 hour period. The lowest values were found two hours following retirement for sleep; the highest values were found 5-7 hours later" (Harper, Rodwell & Mayes, 1977, p. 533).

Cella and Watson (1989) report that this noted diurnal variation is unaffected by meals, with the exception of iron-deficient individuals.

The landmark study by Salonen and colleagues (1992) provides the first support for the conjecture that serum ferritin is a strong risk factor for acute myocardial infarction in Eastern Finnish men (n=1,931). The researchers reported that eastern Finnish men with serum ferritin levels

greater than or equal to (≥) 200 ug/L had a 2.2 fold risk of myocardial infarction than men with serum ferritin levels less than 200 ug/L ($p < 0.01$). The researchers also reported that the intake of alcohol {grams per week) was weakly associated with serum ferritin (Pearson's $r = 0.024$), and of all the dietary sources of iron, meat had the strongest correlation with serum ferritin concentration (Pearson's $r = 0.179$). Moreover, for each milligram (mg) of daily dietary iron consumed, there was an increment of five percent in the risk of acute myocardial infarction.

2.3 Iron: An overview

Functions of iron

Iron was first recognized as a constituent of blood in the seventeenth century (Fleck, 1981; Stare & McWilliams, 1984). All cells of the body contain iron (Kreutler, 1980). Iron is needed to manufacture enzymes that control cellular oxidation (Bodinski, 1987; Editorial, 1976; Fleck, 1981) and it is unsurpassed in its versatility as a biological catalyst (Emery, 1978). Iron plays a principle role in erythropoiesis and it is necessary for hemoglobin synthesis (Cella & Watson, 1989; Spence & Mason, 1987). The major function of iron is oxygen transport via hemoglobin in red blood cells and myoglobin in muscles (Kreutler, 1980). "Virtually all iron exists in combination with protein in transport, storage, enzymes, or respiratory compounds" (Stare & McWilliams, 1984, p. 165).

Distribution

Only 300 milligrams of iron are present at birth, the remainder being accumulated over the lifespan (Hughes, 1978). The estimated total iron content of the body of the healthy adult has been estimated between three and four grams (Munro & Linder, 1978; Spence & Mason, 1987; Stare & McWilliams, 1984) of which approximately 65 % resides in hemoglobin and

3 % in myoglobin (Cella & Watson, 1989). According to Spence and Mason (1987), approximately 15 to 30 % of the iron is stored in the liver, spleen, bone marrow, and elsewhere, mainly as ferritin and hemosiderin. Approximately 70 % of the iron in the body is considered functional iron, since it is present in hemoglobin, myoglobin and tissue enzymes {i.e., cytochrome oxidase and catalase} (Stare & McWilliams, 1984). The remaining 30 % of body iron is designated as storage iron or nonessential iron, present in bone marrow and various organs {i.e., liver, spleen} (Stare & McWilliams, 1984). Since the body has no physiologic mechanism for excreting excess iron (Bodinski, 1987; Halliwell & Gutteridge, 1985; Harper, Rodwell & Mayes, 1977; Kreutler, 1980), the level of both functional and storage iron is regulated through absorption (Stare & McWilliams, 1984).

2.4 Absorption, transport and storage of iron

Nonheme and heme iron

Except for blood transfusions, the only way that iron can enter the body is orally (Cella & Watson, 1989). "Three factors determine the iron absorbed from the diet: the amount of iron ingested, its bioavailability and the iron status of the individual" (Hercberg & Galan, 1992, p. 149). There are two forms of iron present in foods, heme (or haem) and nonheme. Heme iron is found in hemoglobin and muscle myoglobin, and is obtained exclusively from meat sources {i.e., beef, pork, fish, poultry} (Bodinski, 1987; Kreutler, 1980). In general, meat consists of approximately 40 % heme iron and approximately 60 % nonheme iron (Stare & McWilliams, 1984).

Nonheme iron is present in both animal {i.e., fish} and plant sources {i.e., grains, vegetables} (Bodinski, 1987; Kreutler, 1980). Nonheme iron is

usually of low bioavailability; however, the presence of certain factors (i.e., ascorbic acid, meat) can enhance absorption.

Although the exact nature of the mechanism regulating iron absorption is still being debated, it now appears that dietary iron linked to a carrier substance becomes attached to the surface of the cells lining the upper intestine (Fleck, 1981; Stare & McWilliams, 1984). "The precise mechanisms of the regulation of iron absorption are still not clear at the molecular level" (Editorial, 1985). Both heme and nonheme sources of dietary iron enter the mucosal cells lining the upper portions of the small intestine. According to Kreutler (1980), heme iron is absorbed first as part of the porphyrin component of hemoglobin.

Iron is then released to join the inorganic pool of iron in the mucosa, bound to the protein ferritin, on which the body can draw iron from as required. "Ferritin functions in the storage and delivery of iron for intracellular use. In addition, it functions in the detoxification of elemental iron, which is toxic in a noncomplexed form (Torti, Kwak, Miller, Miller, Ringold, Myambo, Young & Torti, 1988, p. 12638). The complex of apoferritin (an iron binding protein) and iron, termed ferritin, is held in the epithelial cells until binding sites for iron are available on molecules of transferrin (Harper, Rodwell & Mayes, 1977; Stare & McWilliams, 1984). "The molecule acts as a holding bin of sorts and never actually leaves the mucosal cell. Ferritin is lost when the mucosal cells are sloughed off into the intestinal lumen" (Kreutler, 1980, pp. 338-339).

Transferrin

Iron bound to ferritin in the mucosal cells are picked up by the protein transferrin. One molecule of transferrin can complex two atoms of iron (Stare & McWilliams, 1984). "Currently it is believed that transferrin serves

both as the transporter of iron in the plasma and its carrier through the membrane {via endocytosis}" (Editorial, 1989, p. 54). The portion of iron picked up by transferrin is driven by the body's needs and iron stores available. For example, the requirements for iron are considerably increased during periods of growth, infection, and during pregnancy and lactation (Hercberg & Galan, 1992; Stare & McWilliams, 1984). "Total requirements are greater than 1000 mg [milligrams] for the duration of pregnancy, but they are more concentrated during the second and third trimesters of gestation" (Hercberg & Galan, 1992, p. 147).

Transferrin delivers iron to (a) the bone marrow via the circulatory system (Kreutler, 1980; Stare & McWilliams, 1984); (b) to cells to make myoglobin or respiratory enzymes (Stare & McWilliams, 1984), and (c) to storage sights (i.e., liver, spleen) (Kreutler, 1980; Stare & McWilliams, 1984). The bone marrow picks up iron as required from the blood to synthesize hemoglobin which it incorporates into newly formed red blood cells that exist for approximately 120 days (Williams & Caliendo, 1984). "When the body destroys old red blood cells, it conserves the iron by storing it in the liver and bone marrow or by reusing it immediately for the synthesis of new red blood cells" (Williams & Caliendo,1984, p. 367). Storage forms of iron exist as ferritin and hemosiderin (Fleck, 1981; Kreutler, 1980; Stare & McWilliams, 1984).

When transferrin is saturated to approximately a third of its total iron-binding capacity (TIBC) {0.3 mg/ deciliter of plasma}, "no more iron is absorbed from the mucosal cells except under conditions of excessive intakes in which iron absorption is no longer under control" (Stare & McWilliams, 1984, p. 169). Kreutler (1980, p. 344) notes that "the regulation of iron absorption is not absolute, and in fact fails at very high levels of iron intake."

According to Stare and McWilliams (1984, p. 182), an excess absorption as small as 3 mg/ day will result in 1 mg of storage iron daily, which could accumulate to a substantial amount of stored iron over a period of years.

Dietary iron uptake

Oxidized iron (ferric iron) has an electrical charge or valence of +3, while the reduced iron (ferrous iron) has an electrical charge of +2 (Stare & McWilliams, 1984). Iron is mainly absorbed in the ferrous state (Bodinski, 1987; Halliwell & Gutteridge, 1985; Harper, Rodwell & Mayes, 1977). In foods, iron is generally found with a +3 charge; however, dietary iron is absorbed better when it has a +2 charge (Hamilton & Whitney, 1982; Kreutler, 1980). Consequently, factors that affect the reduction of iron also affect its absorption. For example, hydrochloric acid within the stomach and ascorbic acid (vitamin C) facilitates reduction of the +3 (ferric) ion to a +2 (ferrous) ion. Reduced or ferrous iron is absorbed more readily than the ferric or oxidized (trivalent) form (Stare & McWilliams, 1984).

Hercberg and Galan (1992, p. 145) report that in healthy, well-nourished individuals, nutritional balance generally exists in which the amount of dietary iron absorbed is sufficient to (1) compensate for daily iron losses; (2) to permit metabolic iron utilization, and (3) to maintain adequate body iron stores. The body's iron status can be unbalanced by a plethora of factors (i.e., poor absorption, low dietary iron intake, infection), and this will lead to the mobilization of iron stores. Three stages of iron deficiency are widely reported in the literature: (1) There is a depletion of iron stores {decrease in serum ferritin}; (2) iron stores are exhausted and an inadequacy of iron transport to the bone marrow occurs {transferrin saturation is reduced}, and (3) anemia {characterized by low hemoglobin} develops (de Wijn, de Jongste, Mosterd & Willebrand, 1971; Expert Scientific Working

Group, 1985; Fleck, 1981; Hercberg & Galan, 1992; O'Toole, Iwane, Douglas, Applegate & Hiller, 1989; Plowman & McSwegin, 1981; Risser, Risser & Goldberg, 1990; Stare & McWilliams, 1984). Hence, iron-deficient individuals absorb a higher percentage of the available dietary iron than do those who are well nourished (Fleck, 1981; Williams & Caliendo, 1984).

A healthy adult normally absorbs between 10 to 15 % of the dietary iron intake (Bodinski, 1987; Hercberg & Galan, 1992). The majority of iron absorption takes place in the upper portions of the small intestines (duodenum and jejunum), and a small amount is also absorbed by the stomach (Bodinski, 1987). The rate of iron absorption is related to the state of body iron stores, the lower the stores of iron the greater the iron absorption (Bodinski, 1987; Fleck, 1981). If body stores of iron are adequate, approximately 25 % of the ingested heme iron will be absorbed (Kreutler, 1980). Hercberb and Galan (1992) note that approximately "25-30 % of haem iron is absorbed, compared with 1-7 % for non-haem iron" (pp. 150-151). Hamilton & Whitney (1982) estimate the absorption of iron from meat (heme iron source) to be 20 %, compared with only 5 % from bread (nonheme iron source).

Iron travels in the blood stream bound to the beta-globulin transferrin that is manufactured by the liver (Cella & Watson, 1987). Ferritin is a water-soluble macromolecule consisting of an outer shell of protein within which up to 4500 atoms of iron can be stored as ferric oxyhydroxide (Munro & Linder, 1978). "Ferritin exists as a protein shell consisting of 24 subunits with variable combinations of two types of subunits, the H (heart) subunit and the L (liver) subunit" (Bio-Rad Laboratories, 1991, p. 2). Iron is also

stored as hemosiderin, an intracellular iron-protein complex (Spence & Mason, 1987).

2.5 Bioavailability of iron in meals

"Food composition tables reflect total iron content and do not distinguish between heme and nonheme iron or otherwise indicate the amount of absorbable iron" (Kreutler, 1980, p. 341). Hence, the amount of dietary iron present in a food source is not an adequate indicator of its potential for absorption. For example, "spinach, which was formerly considered a good source of iron, is no longer as highly recommended because it contains oxalates that inhibit iron absorption" (Bodinski, 1987, p. 145).

> "Some of the complications in determining the nutritional adequacy of iron in the diet are variations in iron absorption among individuals, including meal-to-meal fluctuations; rate of gastric motility; differences in personal iron stores; and lack of knowledge about the iron availability of specific foods and meals" (Fleck, 1981, pp. 221-222).

The total bioavailability of iron in a meal results from the combination of all dietary factors that promote or inhibit the absorption of the common nonheme pool (Hercberg & Galan, 1992, p. 151). "The nonheme iron pool consists of iron from other foods such as vegetables, grains, fruits, eggs, and dairy products as well as from the nonheme iron of meats, poultry, and fish and soluble iron supplements" (Monsen, Hallberg, Layrisse, Hegsted, Cook, Mertz and Finch, 1978, p. 135).

The absorption of dietary iron depends on whether a food source is eaten alone or in combination with other foods (Editorial, 1986; Stare and

McWilliams, 1984). For example, the consumption of meat in conjunction with vegetables increases the absorption of iron from vegetable sources two or threefold (Stare & McWilliams, 1984, p. 170). "An undefined meat factor present in meat, poultry, and fish also enhances absorption of nonheme iron" (Williams & Caliendo, 1984, p. 365). Salonen and coworkers (1992, p. 806) reported that "of all foodstuffs, the consumption of meat had the strongest correlation with serum ferritin concentrations (Pearson's r = 0.179)."

Vitamin C

The absorption of iron is greatly enhanced in the presence of ascorbic acid {vitamin C} (Bloomfield, Fricker & Fitch, 1992; Editorial, 1987; Fleck, 1981; Labuza & Erdman, 1984; May, Williams & Linder, 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984). The overall absorption of nonheme iron can be greatly increased if fruit or vegetables containing vitamin C are present with the meal. Vitamin C promotes the absorption of iron by reducing ferric salts to ferrous salts (Bodinski, 1987). Foods containing 25 milligrams or more of vitamin C can double the amount of dietary iron absorbed (Cook & Monsen, 1977).

Alcohol

Alcohol is both a food and a drug (Lieber, 1988). Alcohol consumed with meals can also enhance the absorption of iron (Harju, 1989; Lieber, 1988; Stare & McWilliams, 1984;Williams & Caliendo, 1984). "Alcoholics who consume large amounts of wine daily are susceptible to iron overload because alcohol increases absorption of iron and some wines contain a significant amount of iron" (Williams & Caliendo, 1984, p. 370).

Method of preparation

The method by which meals are prepared can also affect the iron content of foods. "Steamed vegetables have more iron than boiled vegetables; those cooked for a short time in a small amount of water have more than those cooked for a longer period and in a large amount of water; and those cooked in their skins have more iron than peeled ones" (Stare & McWilliams, 1984, p. 179).

Kreutler (1980) notes that when cast iron cooking vessels were utilized by the majority of individuals in the late nineteenth century, iron deficiency was rare. Moreover, the mid-twentieth century shift to aluminum, stainless steel, and enamel vessels may well have increased the risk of iron-deficiency anemia. For example, the iron content of 100 grams of spaghetti sauce is approximately three milligrams when prepared in glass cookware (Bodinski, 1987; Hamilton &Whitney, 1982). However, when the same amount of spaghetti sauce is cooked in an unenameled iron skillet, the iron content increases to approximately 87 milligrams (Bodinski, 1987; Hamilton & Whitney, 1982). "Even in the short time it takes to scramble eggs, their iron content can be tripled by cooking them in an iron pan" (Hamilton & Whitney, 1982, p. 326). This finding is supported by Bobinski (1987, p. 143) who noted that scrambled eggs show a 40% increase in iron content when prepared in an iron skillet.

Inhibitors of dietary iron

A diet high in fiber (bulk) is known to inhibit iron absorption (Bindra & Gibson, 1986; Bodinski, 1987; Jenkins, Hill & Cummings, 1975; Kreutler, 1980; Stare & McWilliams). Moreover, phosvitins (present in eggs), oxylates, phylates (present in cereals) are also known to decrease iron absorption (Bodinski, 1987; Kreutler, 1980; Stare & McWilliams, 1984).

Tea is also a powerful inhibitor of nonheme iron absorption because of its tannate content (Bindra & Gibson, 1986; Hercberg & Galen, 1992; Labuza & Erdman, 1984; Williams & Caliendo, 1984). Calcium and phosphate salts and ethylenedia-minetetraacetic acid [EDTA] {an antioxidant and food preservative} also appears to decrease the absorption of iron (Fleck, 1981; Monsen et al., 1978). A high alkaline intake (e.g., antacids) also decreases the absorption of iron (Bodinski, 1987; Stare & McWilliams, 1984). Milk and other dairy products are also considered as poor sources of dietary iron (Bloomfield, Fricker & Fitch, 1992; Carmichael, Christopher, Hegenauer & Saltman, 1975; Stare & McWilliams, 1984). Surprisingly, "iron from supplements is poorly absorbed, even though they may contain as many as 50 milligrams per dose" (Hamilton & Whitney, 1982, p. 325). By contrast, "iron from animal sources that exist in the iron-protoporphyrin complex heme is readily absorbed and unaffected by the factors which decrease iron absorption" (Hughes, 1978, p. 356).

Bodinksi (1987, p. 144) notes that low gastric acidity as a result of achlorhydria (often present in the elderly) reduces iron absorption. "Utilization of ferric iron is reduced up to 50 % in persons with a decreased secretion of hydrochloric acid in the stomach, known as achlorhydria" (Stare & McWilliams, 1984, p. 170).

2.6 Iron losses

The average daily loss of iron is approximately 0.9 to 1 milligrams in males and 0.8 to 1.7 milligrams in females (Harju, 1989; Hercberg & Galan, 1992; Spence & Mason, 1987). Hercberg and Galan (1992, p. 147) estimate average total iron losses (basal losses + menstrual iron losses) in menstruating women at approximately 2.2 milligrams per day and 1.4 milligrams per day in menopausal women. "In adult women, the average

loss of blood during a menstrual period is 35-70 ml, which represents a monthly loss of 16-32 mg of iron, or an additional average loss of 0.5-1 mg/day" (Harper, Rodwell & Mayes, 1977, p.531). Bodinski (1987) reports that a menstruating women loses on average 30 mg of iron per menstrual period.

Iron loss occurs principally from the desquamation of cells, of which approximately two-thirds are from the gastrointestinal tract (Hercberg & Galan, 1992). Minute losses may also occur through the clipping of nails, the cutting of hair, the shedding of skin cells (Fleck, 1981; Hamilton & Whitney, 1982; Stare & McWilliams, 1984), and through feces, urine or perspiration (Fleck, 1981; Spence & Mason, 1987; Stare & McWilliams, 1984; Williams & Caliendo, 1984). "Iron losses in sweat are now considered negligible, even in a tropical context" (Hercberg & Galan, 1992, p. 145).

Oral contraceptives

Iron losses are also reduced by approximately 50% in women taking oral contraceptives (Hercberg & Galan, 1992). Frassinelli-Gunderson, Margen and Brown (1985) compared the iron status of 46 women taking oral contraceptives for two or more continuous years with 71 controls. The mean serum ferritin value for the women taking oral contraceptives was 39.5 $\pm$ 21.5 ug/L compared to 25.4 $\pm$ 15.96 ug/L for the controls. Hence, "young women who regularly take oral contraceptives may have levels of stored iron usually seen in older, perimenopausal women" (Sullivan, 1989, p. 1185).

Blood donors and pathological losses

It has been established that blood donors and those who undergo phlebotomy will have decreased stores of iron (Ashinsky, 1992; Birgefard, Hogman, Killander, & Wide, 1978; Cook et al., 1977; McCord, 1991; Selby,

1991; Sullivan, 1991). Sullivan (1981) reports that the donation of one unit of blood per year will reduce serum ferritin by approximately half in males. Blood donors lose 250 milligrams of iron with every 0.5 liter of blood donated (Bodinski, 1987). Stare and McWilliams (1984) note that the blood volume and the number of red blood cells will return to normal levels quickly; however, the return of hemoglobin to previous levels can occur only at the expense of stored iron. "To replace the amount of iron lost would require the absorption of an additional 0.7 mg of iron a day for a year" (Stare & McWilliams, 1984, p. 168). Pathological iron losses may also occur in individuals with gastrointestinal disorders that result in bleeding {i.e., gastric and duodenal ulcers, ulcerative colitis}, parasitic infections {e.g., hookworm}, and in those who consume certain medications {i.e., aspirin, anticoagulants, corticosteroids} (Fleck, 1981; Hercberg & Galan, 1992).

2.7 Hereditary and nutritional iron overload

Since the body lacks a mechanism for the excretion of excessive amounts of iron, the mineral can accumulate in the soft tissues of the body {i.e., liver, heart} (Editorial, 1980). This accumulation may result in necrosis and it can also distort the structure of the cells of the tissues (Kreutler, 1980). Phillips, Becker, Keller and Hartman (1992), report that individuals with sickle cell anemia often develop iron overload as a result of multiple transfusions of red blood cells. Moreover, congestive heart failure is also common in these individuals. For example, case studies on patients over the age of 45 years who have undergone multiple blood transfusions, revealed serum ferritin levels greater than 6,000 ug/L (Phillips, Becker, Keller & Hartman, 1992). Congestive heart failure appeared to be the cause of death in all three patients.

Hemochromatosis

Systemic iron overload in the absence of iron-loading anemia or blood transfusions has been described in Caucasians and sub-Saharan Africans (Gordeuk, 1992, p. 169). In Caucasians, iron overload results from a genetic disorder termed hereditary hemochromatosis. This disorder is characterized by an excessive rate of iron absorption by the small intestine (Ashinsky, 1992; Crawford & Halliday, 1991; Editorial, 1978; Gordeuk, 1992; Kreutler, 1980; Zilva & Pannall, 1975). For example, Anderson, Birgegard, Nyman and Hemmingsson (1991) reported that the mean serum ferritin value in five patients at diagnosis was 755 ug/L (with a range of 648 to 900 ug/L) compared to 85 ug/L (with a range of 19 to 232) in eight normal controls.

Hemochromatosis has been linked to tissue fibrosis and organ failure as a result of iron overload. Excessive iron deposition occurs in the liver (causing fibrosis), the pancreas, heart, pituitary and the joints (Crawford & Halliday, 1991; Harju, 1989; Kreutler, 1980). Cardiac involvement in hemochromatosis includes the development of congestive heart failure (CHF) and /or cardiac arrhythmias (Rosenqvist & Hultcrantz, 1989). "Iron deposition in the heart in patients with hemochromatosis often occurs in association with congestive heart failure and electrocardiographic abnormalities including arrhythmias and conduction disturbances" (Vigorta & Hutchins, 1979, p. 418).

This condition has only been described in populations derived from Europe (Gordeuk, 1992). "There is considerable variation in estimated prevalence between and within countries, ranging from 0.5/1000 in Finland to 11.7/1000 among World War II veterans in Australia" (Gordeuk, 1992, p. 171). The gene frequency in the Caucasian population is approximately one

in 20 with a disease expression of approximately one in 400 (Rosenqvist & Hultcrantz, 1989). Clinical expression, is more common in males and appears to typically occur during the middle to late adult years (Gordeuk, 1992). "Hemochromatosis is found 5 to 10 times more often in men than in women, because women lose blood through menstruation and pregnancy" (Ashinsky, 1992, p. 138). Treatment typically consists of phlebotomy (Crosby, 1991).

Iron overload among sub-Saharan Africans is thought to be caused solely by increased dietary iron derived from the ingestion of home brewed beer fermented in cast iron pots (Editorial, 1980; Gordeuk, 1992; Halliwell & Gutteridge, 1985; Kreutler, 1980; Stare & McWilliams, 1984; Zilva & Pannall, 1975). Absorption is facilitated by the acid content of the beer and the condition is commonly referred to as siderosis or dietary iron overload (Gordeuk, 1992; Kreutler, 1980). Iron overload has been reported in at least 15 African countries and it "is virtually the only part of the world where iron overload due to increased dietary iron has been recognized" (Gordeuk, 1992, p. 175). The condition is more prevalent in males and the prevalence and severity increases with advancing age (Gordeuk, 1992). "Eventually, scarring of the liver develops {cirrhosis}, dark pigmentation of the skin occurs, diabetes develops because pancreatic cells that produce insulin are destroyed, and finally heart failure may develop" (Williams & Caliendo, 1984, p. 370).

Thalassaemias

"Iron overload can be produced by greater than normal absorption of iron from the alimentary canal, by parenteral injection or by a combination of both processes" (Editorial, 1985). The thalassaemias are relatively common hyperplastic refractory anemias that are characterized by increased

iron absorption which is somehow stimulated by high degrees of ineffective erythropoiesis (Gordeuk, 1992, p. 170). The disease was named from a Greek word for sea since several individuals with thalassaemia are typically of Mediterranean ancestry (Halliwell & Gutteridge, 1985).

Treatment consists of frequent blood transfusions, and iron overload "develops because the iron derived from the transfused blood cannot be excreted in significant amounts and accumulates in vital organs such as the heart, liver and pancreas" (Editorial, 1979, p. 138). Iron chelating drugs such as desferrioxamine (Desferal) have been utilized to decreased iron stores in patients with thalassemia (Editorial, 1979; Olivieri, Koren, Matsui, Liu, Blendis, Cameron, McClelland & Templeton, 1992). "Administration of chelating agents, such as desferoxamine (Desferal), mesylate, has been advocated, but these agents remove only 10 to 20 mg of iron a day" (Ashinksy, 1992, p. 140). A further discussion of iron chelation drugs will be provided in the following section (2.8).

2.8 Iron and free radicals

Currently, there has been growing support for the contention that low molecular weight transition metal complexes, particularly of iron, are powerful oxidation catalysts which play a role in all forms of oxygen-free-radical-mediated toxicity (Lauffer, 1991; Faber, Vercellotti, Jacob, Pieper & Gross, 1988).

> "Oxygen free radicals are capable of reversibly or irreversibly damaging compounds of all biochemical classes, including nucleic acids, protein and free amino acid, lipids and lipoproteins, carbohydrates, and connective tissue macromolecules. These species may have an impact on such cell activities

> as membrane function, metabolism, and gene expression" (Cross et al., 1987, p. 526).

Oxidation refers to the loss of electrons by an atom or molecule, and reduction refers to the gain of electrons (Halliwell & Gutteridge, 1985). Free radicals are highly reactive species that contain one or more unpaired electrons (Halliwell & Gutteridge, 1985; Masterton, Slowinski & Stanitski, 1981; Pryor, 1976).

> "A compound can become a free radical either by gaining an electron or by losing an electron. When such an electron transfer reaction takes place with a non-radical, that nonradical becomes a radical, thereby initiating a chain reaction." (Chakravarti, Kirshenbaum & Singal, 1991, p. 99).

According to Halliwell and Gutteridge (1985), all the metals located in the first row of the d-block of the periodic table contain unpaired electrons and can thus qualify as radicals (except zinc because it has a fixed valency of two).

Recently, oxygen radicals have been implicated in the pathogenesis of several diseases such as CVD and cancer (Cross, Halliwell, Borish, Pryor, Ames, Saul, McCord & Harman, 1987). Campbell (1993, p. 2) notes that transition ions, particularly ferrous iron, catalyze the formation of oxygen-free radicals which are potent oxidizing agents. Neilands and Nakamura (1985, p. 193) contend that excessive amounts of iron may be toxic due to its propensity to convert superoxide and peroxide to hydroxyl radicals

(powerful oxidizing agents). Salonen and coworkers (1992) note that iron can induce lipid peroxidation (a chain reaction providing a continuous supply of free radicals) in vitro and in vivo in humans, and it has also been reported to promote ischemic myocardial injury. Ferritin, cytochromes, and other iron containing enzymes have been proposed as potential sources of iron for inducing these reactions (Babbs, 1985; Carlin & Djursater, 1984). The combination of reactions that iron can catalyze are now commonly referred to as iron-catalyzed Haber-Weiss reactions, or as superoxide-driven Fenton chemistry (McCord, 1991, p. 1112).

Arterial injury by ischemia

Aggressive cytotoxic oxygen metabolites (i.e., superoxide anion, hydroxyl radical, hydrogen peroxide) have been implicated in arterial injury by ischemia followed by reoxygenation (Bolli, Patel, Zhu, O'Neil, Hartley, Charlat & Roberts, 1987; Das, Engleman, Liu, Maity, Rousou, Flack, Laksmipati, Jones, Prasad & Deaton, 1992; Deboer & Clark, 1992; Gey, Brubacher & Stahelin, 1987; Heinecke, Rosen & Chait, 1984; Lesnefsky, Repine & Horwitz, 1990; McCord, 1991; Prasad, Liu, Rousou, Engleman, Jones, George & Das, 1992). Since "lipid peroxidation is known to be catalyzed by iron, enhanced lipid peroxidation has been proposed as an initial step by which excess iron causes cellular injury" (Houglum, Filip, Witztum & Chojkier, 1990, p. 1991). Lauffer (1993) contends that during an ischemic episode, irreversible damage may occur in individuals with high intracellular iron, whereas individuals with lower levels of iron may not develop permanent damage. In post-ischemic tissue, superoxide radicals appear in excessive concentrations leading to the subsequent generation of the very reactive hydroxyl radical via the superoxide-driven, iron-catalyzed Haber-Weiss reactions (Babbs, 1985, p. 779).

> "Importantly, the superoxide radical is capable of reducing ferritin-bound iron to the ferrous state, whereupon it is released. It is this iron, liberated by the pathological production of superoxide, that is now free to catalyze Haber-Weiss chemistry and to wreck additional cellular havoc" (McCord, 1991, p. 1112).

In the case of coronary artery disease (CAD), either low molecular weight forms of iron or the iron-containing enzyme lipooxygenase are likely catalysts in low density lipoprotein {LDL} oxidation, the committed step in atherogenesis (Lauffer, 1991, p. 104). Moreover, lipid peroxidation is also known to be transition metal-dependent (Heinecke, Rosen & Chait, 1984). "Oxidized low density lipoprotein {LDL}, formed in vivo from presently unknown reactions, may play a role in atherogenesis. In vitro, transition metals such as iron and copper will facilitate LDL oxidation" (Balla, Jacob, Eaton, Belcher & Vercellotti, 1991, p. 1700).

Antioxidant defense and iron chelators

Within cells, antioxidant defense is provided by specific enzymes such as superoxide dismutase, glutathione peroxidase and catalase (Chakravarti, Kirshenbaum & Singal, 1991; Cross et al., 1987; Dhaliwal, Kirshenbaum, Randhawa & Singal, 1991; Fridovich, 1976). In extracellular fluids, other antioxidants, such as transferrin-lactoferrin, ceruloplasmin, albumin, haptoglobin-hemopexin, uric acid (urate), glucose and vitamin E, are known to be operative (Cross et al., 1987). For example, transferrin-lactoferrin binds iron and stops or decreases its participation in lipid peroxidation and iron-catalyzed Haber-Weiss reactions (Cross, 1987).

Sullivan (1991b) argues that iron depletion and iron deficiency can protect against potentially fatal oxygen-radical injury. Since iron has been implicated in promoting oxidative damage, metal-chelating agents, such as desferriozamine (deferoxamine or Desferal), have been proposed as antioxidants (Bolli et al., 1987; Bernier, Hearse & Manning, 1986; Deboer & Clark, 1992; Faber et al., 1988; Lesnefsky, Repine & Horwitz, 1990; McCord, 1991; Patt, Horesh, Berger, Harken, Repine & Colorado, 1990; van der Kraaij, Mostert, van Eijk & Koster, 1988; van Jaarsveld, Kuyl & Alberts, 1992; Williams, Zweier & Flaherty, 1991). "Chelation of iron can also prevent or reduce acute ischemic damage in non-atherosclerotic animal models, presumably by preventing the formation of oxygen-free radicals and lipid peroxidation" (Campbell, 1993). Sullivan (1989) reports that "deferoxamine improves ventricular function in both the failing hearts of patients with thalassemia and the hearts of normal animals after experimental ischemic episodes" (p. 1180).

Chelation therapy has been seen to ameliorate organ disfunction (i.e., liver, heart) in patients with hemochromatosis and transfusional iron excess. For example, Freeman, Giles, Berdoukas, Talley and Murray (1989) reported on the effects of desferrioxamine on the iron overloaded heart in 23 asymptomatic patients with thalassaemia major and transfusional-dependent anemia. The patients were studied prospectively over a period of four years. Prior to therapy, abnormalities of left ventricular function in 18 of the 23 patients (78 %) were observed. Following treatment, 11 of the 18 patients had normal left ventricular function restored, five continued to have abnormal function, and two patients died. Results suggest that left ventricular induced iron overload in unchelated individuals can be reversed with long term treatment with desferrioxamine.

2.9 Dietary iron and CVD

"During World War II, Northern Europe suffered a shortage of meat and dairy products. At the same time, the region's heart attack death rate declined dramatically" (Davis & Park, 1984, p. 76). Akinkugbe (1990) reports that the incidence of CVD is slowly rising in the developing world as malnutrition is steadily overcome. Hence, CVD appears to be an inevitable concomitant of affluence and prosperity, whilst poverty is protective of CVD (Sullivan, 1981).

Murray and colleagues (1991) report that chronic iron and copper (Cu) deficiency may protect against the atherogenic effects of high-fat diets. "Milk-drinking nomads seem uniquely free of symptomatic coronary artery disease despite an intake of fat which may reach 70 % of total energy intake...iron deficiency, and to a lesser extent Cu deficiency, inhibited lipid auto-oxidation" (Murray, Murray & Murray, 1991, p. 1479a). Similarly, Sullivan (1981) contends that "a reasonable interpretation of the data on the worldwide distributions of iron deficiency and of heart disease is that low rates of heart disease are often associated with iron deficiency" (p. 1294).

Reddy and Sanders (1990) compared the hematological profiles of premenopausal Indian vegetarians (n=23), Caucasian vegetarians (n=18) and Caucasian omnivores (n=22) aged 25 to 40 years. The researchers reported that iron intake was similar in all groups, however, heme iron constituted one-quarter of the dietary iron intake for the omnivores. Serum ferritin values were found to be markedly lower in both vegetarian groups as compared to the omnivore group.

Although the rates of heart disease, cancer and diabetes were lower in the past for Alaskin Natives, as compared to Caucasians in the United States, there rates have been rising (Nobmann, Byers, Lanier, Hankin and

Jackson; 1992). Nobmann and coworkers (1992) assessed the seasonal dietary intakes of 351 Alaska Native adults in 11 communities. Findings revealed that Alaska natives consumed more iron (25 %), protein (39 %), fat (21 %), carbohydrate (13 %), vitamin A (53 %), and vitamin C (31 %), but less calcium (19 %) than did the general United States population. Interestingly, Alaska Natives also consumed six times more fish (heme iron source), but less fruit and vegetables (non-heme iron sources).

Although the incidence of heart disease was not reported, Ihanainen, Salonen, Seppanen and Salonen (1989) investigated the food consumption and nutrient intake of 1157 eastern Finnish men aged 54 years utilizing a four day dietary record. Results indicated a mean dietary intake of 18 mg of iron per day with a range of 4.8 to 64.5 mg. The researchers reported that a low consumption of vegetables and potatoes, typical of Finnish men, was observed in this study. "Meat consumption consisted of sausages (39 %), beef (37 %) and pork (21 %). The mean consumption of coffee (586 g/d) was higher than the mean consumption of tea (99 g/d) -also a typical Finnish feature" (Ihanainen et al., 1989, p. 599).

2.10 Published values for serum ferritin

The serum ferritin level is a valuable parameter for the assessment of stored iron in the body (Cook, Lipschitz, Miles & Finch, 1974; Lipschitz, Cook & Finch, 1974). Serum ferritin measurement appears to be the most sensitive indicator for assessing iron status in a population (Hercberg & Galan, 1992). Moreover, it is regarded as the most reliable single clinical parameter for determination of iron status (Bloomfield, Fricker & Fitch, 1992). "Intraindividual variability for serum ferritin is of the order of 6-10 % for within-day variation and is lower than 15 % for between-days variation" (Hercberg & Galan, 1992, p. 154). However, serum ferritin tests

may on occasion give incorrect results. "Inflammation may cause a falsely elevated value...an illness with fever can elevate a low value into the normal range for a few weeks" (Risser, Risser & Goldberg, 1990, p. 97).

Not only are differences between age and gender reported in the literature for serum ferritin, there are also differences in the range of values reported. The mean serum ferritin concentration reported in the study by Salonen and coworkers (1992) on eastern Finnish men (n= 1,931) was 166 ug/ L. Comparatively, Jonsson and colleagues (1991) reported a mean serum ferritin level of 199 ug/ L for males and 91.5 ug/ L for females in an adult Icelandic population (n=2588) aged 25-74 years (see Table 4).

Table 4:
Mean serum ferritin levels (ug/ L)
in an adult Icelandic population

	Urban	Rural	Overall	p value
Male	**171**	**227**	**199**	**< 0.05**
Female	**83**	**100**	**91.5**	**< 0.05**

****Source: Adapted from Jonsson et al. (1991).**

Serum ferritin levels increased per year on the average of 2.2 ug/L for males, and 3.9 ug/L in postmenopausal women, but decreased 0.8 ug/L per year in premenopausal women. Although the results of a dietary survey were not provided, the investigators did report that no significant differences between dietary compositions were revealed between urban and rural subjects.

Cook and coworkers (1976) reported a median serum ferritin value of 94 ug/ L for males and 25 ug/ L for females aged 18-45 years in a population residing in Washington State (n=1564, $p < 0.01$) (see Table 5). There was also a progressive increase in both adult males and

postmenopausal females of one to two ug/L per year (Cook et al., 1976, p. 454).

Table 5:
Medium values of serum ferritin (ug/ L)
in a Washington State population

	12-18 years	18-45 years	Over 45 years
Males	**23**	**94**	**124**
Females	**21**	**25**	**89**

** Source: Adapted from Cook et al. (1976).

In a randomized sample stratified for age and gender from three Portuguese communities (n= 353), Vincente, Porto and deSousa (1990) sought to establish serum ferritin reference values dependent on sex and age. A linear regression model relating the log of serum ferritin for each particular age point was employed by the investigators. A summary of the geometric means obtained for males (n= 157) and females (n= 193) are provided in Table 6. Geometric means are used to average percents or indices and to determine the average rate of increase from one period to another (Mason, Lind & Marchal, 1988, p. 64). Vincente and colleagues (1990) found that serum ferritin values tended to increase with age in females over 40 years and in males under forty. The cessation of regular menstrual blood loss was cited as a possible reason for the increase in older females; in the case of younger males, the increase may have been attributed to the expansion of iron stores through absorption of dietary iron after maximal growth.

Table 6:
Reference values for serum ferritin (ug/L) depending on age and gender in three Portuguese communities

Age in years	Males	Females
20	59	32
30	108	32
40	155	38
50	155	47
60	155	60

** Source: Adapted from Vicente, Porto & deSousa (1990).

Walters, Miller & Worwood (1973) reported a mean of 103 ug/ L in healthy male subjects (n=12) aged 19 to 46 with a range of 36 to 224 ug/ L. By contrast, a mean of 35.6 ug/ L was reported for healthy females subjects (n=10) with a range of 2 to 83 ug/ L.

Milman, Anderson and Strandberg-Pedersen (1986) investigated serum ferritin values in healthy male and female subjects and geriatric patients without a history of disease associated with abnormal serum ferritin values. The results of this study are presented in Table 7.

Table 7:
Serum ferritin values (ug/L) for healthy male and female subjects and geriatric patients

Age in years	18-45	60-79	80-93
Number of males	125	67	61
Number of females	115	75	64
Geometric means for males	67	73	77
Geometric means for females	23	62	57
Range for males	20-227	18-432	17-348
Range for females	5-104	7-410	9-383

**Source: Adapted from Milman, Anderson and Strandberg-Pedersen (1986).

Comparatively, Addison, Beamish, Hales, Hodkins, Jocobs and Llewellin (1972), reported a mean of 52 ug/L in healthy male controls (n=33) and 28.8 ug/L for their female counterparts (n=18). The range was 12 to 128 ug/L for males and 10 to 56 ug/L in females.

A study on healthy male workers (n=75) and female hospital workers (n= 44) reported means of 69.2 ug/L and 34.8 ug/L respectedly (Jacobs, Miller, Worwood, Beamish & Wardrop, 1972). The range was 6 to 186 ug/L for males and 3 to 162 ug/L for females.

Fricker, Le Moel and Apfelbaum (1990) investigated the relationship between iron stores and obesity in 20 obese and 20 nonobese menstruating women. The obese group had significantly higher serum ferritin concentrations (48 +/- 44.3 ug/L) is comparison to the nonobese group (25.8 +/- 19.5 ug/L, $p < 0.05$). Although the women were matched for age and contraception, the dietary iron intake was significantly higher in the obese group ($p < 0.05$). The results suggests that obese women are at lower risk of depleting iron stores, possible because of an increased intake of dietary iron.

2.11 The effects of blood donation on serum ferritin values

According to Bodinski (1987), and May, Williams and Linder (1978), blood donors lose 250 milligrams (mg) of iron with every 500 milliliters (ml.) of blood donated. Similarly, Ashinsky (1992) reports that each 500 ml. of blood contains between 200 to 250 mg of iron.

Milman and Sondergaard (1984) compared the serum ferritin values for first-time male blood donors (n=21) to multiple male blood donors (n = 1,327). The researchers reported a geometric mean of 52 ug/L with a range of 15 to 114 ug/L in first-time blood donors. By contrast, a geometric mean of 36 ug/L with a range of 4 to 247 ug/L was found in the multiple

blood donor group. Hence, blood donation appears to deplete iron stores as measured by serum ferritin.

Milman and Kirchhoff (1991a) investigated the effect of blood donations on the iron status of 1,359 nonpregnant Danish women, of whom 809 were premenopausal, 550 were postmenopausal, and 180 were blood donors. Blood donors were found to have lower serum ferritin values than non donors in all age groups regardless of menstrual status ($p < 0.0001$ in all groups). Premenopausal donors had a medium serum ferritin of 31 ug/L compared to 39 ug/L for the non-donors. Postmenopausal donors had a medium serum ferritin value of 47 ug/L compared to 72 ug/L in the non-donor group. Blood donors using oral contraceptives were also found to have higher serum ferritin values (medium 33 ug/L) as compared to nonusers (medium 22 ug/L).

Milman and Kirchhoff (1991b) assessed the iron stores in 1,433 Danish males, of whom 27 % (n=389) were blood donors and 73 % (n=1,044) were non-donors ($p < 0.0001$). The medium serum ferritin value was 95 ug/L for the blood donors versus 136 ug/L for the non-donors.

2.12 Exercise and the incidence of CVD

One of the first studies to examine the effects of inactivity on heart disease was conducted by Morris and Raffle (1954). These investigators compared the incidence of CAD between London bus drivers and conductors. The more physically active conductors had a 30 % lower rate of CAD than the sedentary bus drivers.

"The advent of automation, remote control, and robotics and the increased use of other labor-saving devices have led to a reduction in physical activity and the greatest epidemic that mankind has ever

experienced - coronary artery disease {CAD}" (Sharkey, 1990, p. 179). For example, the incidence of cardiovascular disease among North American Natives has increased significantly over the years (Nobmann, Byers, Lanier, Hankin & Jackson, 1992; Young, 1990). Rode and Shephard (1984) note that the traditional lifestyle of the Canadian Inuit consisted of an active lifestyle where individuals would typically walk through deep snow, carry young children and engage in vigorous hunting expeditions. This traditionally active lifestyle has been currently replaced a more sedentary one where snowmobiles replace walking, hunting is mainly recreational and video and television watching has become the norm (Rode & Shepard, 1984). This change from an active lifestyle to a more sedentary one may be a contributing factor to the increased incidence of cardiovascular disease observed in North American Natives.

> "Most studies link physical activity -not fitness- to a lower risk of heart disease. The amount of activity is more related to reduced risk than is the level of fitness...thus it may be possible to achieve many of the cardioprotective benefits of exercise via participation in moderate activities, such as walking" (Sharkey, 1990, p. 188).

"Somewhere on the scale between marathoners and couch potatoes are reasonably active individuals who enjoy surprisingly good health. Some do little more than walk back and forth to work and play a little tennis on the weekends" (Monahan, 1987, p. 181). Sharkey (1990) reports that as little as 20 minutes of daily walking reduces the risk of CAD by approximately 30 percent.

2.13 The effects of exercise on iron

The reduction of cardiovascular disease mortality due to exercise has long been thought to derive from improvements in well established risk factors such as systolic blood pressure, lipid profiles, and a general improvement in cardiocirculatory performance (Frontera & Adams, 1986; Lauffer, 1991; McNaughton & Davies, 1987; Quirion, De Careful, Laurencelle, Method, Vogelaere & Dulac, 1987; Sharkey, 1990). Lauffer (1991) notes that the mechanisms by which exercise protects against CVD remains largely a mystery, and that exercise-induced reductions in iron levels could be responsible for some of the beneficial effects. Furthermore, "the iron hypothesis is consistent with the graded reductions in mortality observed as a function of fitness level, and it is the first unified mechanism which can explain the reductions in both heart disease and cancer" (Lauffer, 1991, p. 103).

Dilutional pseudoanemia

Several investigators have reported that iron deficiency is more prevalent among highly trained athletes as compared to sedentary individuals (Blum, Sherman & Boileau, 1986; Parr, Bachman & Moss, 1984). Interestingly, a high level of hemoglobin has also been suggested as a possible risk factor associated with the development of coronary heart disease (Campbell, 1993; Elwood, 1977). Eicher (1986) reports that athletes normally have slightly lower hemoglobin concentrations than their sedentary counterparts. Athletes, particularly endurance athletes, have lower levels of hemoglobin as compared to sedentary individuals as a result of the body's normal adaptation to exercise to increase plasma volume (Eicher, 1986; O'Toole, Iwane, Douglas, Applegate, & Douglas, 1989; Selby & Eicher, 1986). Increased exercise leads to expanded plasma volume, this

pseudoanemia is an adaptation to the hemoconcentration of endurance exercise (Slavin, 1991, p. 88). This phenomenon is referred to as dilutional pseudoanemia or as athletes anemia as requires no treatment.

Possible causes

Pseudoanemia has been attributed to footstrike hemolysis in runners (Eicher, 1986; Selby, 1991; Steenkamp, Fuller, Graves, Noakes & Jacobs, 1986; Weight, Bryne & Jacobs, 1991), gastrointestinal blood loss in runners and various contact sports enthusiasts {i.e., boxing, karate} (Fisher, McMahon, Ryan, Larson & Brand, 1986; Keeffe, Lowe, Gross & Wayne, 1984; McCabe, Peura, Kadakia, Bocek & Johnson, 1986; McMahon, Ryan, Larson, & Fisher, 1984; Riess, 1979; Risser, Risser & Goldberg, 1990; Selby, 1991), and intravascular hemolysis in endurance swimmers (Selby & Eicher, 1986).

The degree of dilutional anemia correlates with the amount of exercise engaged in (Eichner, 1986). "A new jogger will increase his or her plasma volume by 5 %, a military recruit by 10 %, and an elite distance runner by 20 %. However, hemodilution reverses rapidly over a few days if training ceases" (Selby, 1991, p. 98). Interestingly, O'Toole and colleagues (1989) report that the incidence of dilutional anemia appears to be higher in men than in women. The reason for this noted gender difference remains unknown.

Menstrual problems in female athletes

Menstrual problems {i.e., amenorrhea, oligomenorrhea} have also been widely reported in females who engage in stenuous exercise (Bullen, Skrinar, Beitins, von Mering, Turnbull & McArthur, 1985; Litt, 1986; Loucks & Horvath, 1985; Shangold, 1986). Reports estimate that approximately 20 to 30 % of post-menarche female athletes who train

competitively suffer from this condition (Webb & Proctor, 1983, p. 201). For example, in a study on female college runners, Webb and Proctor (1983, p. 205) reported that the "incidence of menstrual function change during heavy training/ competition was quite prevalent in the sample with 125 of 143 athletes (87 %) reporting changes. The most commonly reported characteristic was the absence of menses (70 %)."

Low body fat and weight were thought to be the causes of these menstrual problems (Lutter, 1982); however, normal menstrual function has been observed in athletes with only four percent body fat (Litt, 1986). Moreover, forced periods of inactivity in previously amenorrheic athletes have resulted in a return of menses without a subsequent increase in either body fat or weight (Litt, 1986).

Deuster and colleagues (1991) contend that the distribution of trace minerals (i.e., iron, copper, zinc) appears to be influenced by several hormones including luteinizing hormone, follicle-stimulating hormone, prolactin and estrogen. Zilva and Pannall (1975), for example, note that "androgens tend to increase plasma iron concentrations and oestrogens to lower it" (p. 392). Similarly, it has been reported that the performance of female athletes varies with the phases of the menstrual cycle where hormonal levels are known to fluctuate (Lamont, 1986). Although not conclusive, exercise might result in changes in hormonal levels; notably decreased estrogen {oestrogen} (Lloyd, Triantafyllou, Baker, Houts, Whiteside, Kalenak & Stumpf, 1986; Munnings, 1988). Since menstrual problems (i.e., amenorrhea) should result in greater levels of stored iron due to decreases in blood loss, other mechanisms must be responsible for the continued depletion of iron stores in female athletes (e.g., diet).

Cohen, Potosnak, Frank and Baker (1985), for example, evaluated the nutritional and hematological status of professional ballet dancers from the American Ballet Theatre. The dancers had a low percentage of body fat. The percent body fat for the men (n = 10) was 7.82 +/- 1.39 and 12.86 +/- 1.83 for the women (n = 12). "Of particular importance is the emphasis in the ballet world on thinness, especially among ballerinas" (Cohen et al., 1985, p. 44). Each dancer was also asked to complete a six day dietary record. Female dancers tended to avoid heme sources of iron (i.e., red meat, fish. Although female dancers tended to avoid milk, they did consume cheese on occasion. The women tended to predominantly consume nonheme sources of dietary iron such as salads, vegetables, fruit and fruit juices. Comparatively, male dancers consumed greater amounts of heme sources of iron (i.e., red meat, fish, poultry), and to some extent greater amounts of milk. Males also ate less salads, fruit and vegetables than did the females. All the dancers ate breads, cereals and eggs regularly. Moreover, the dancers tended to consume large amounts of multiple megavitamins and iron supplements. Interestingly, no special time was allotted for lunch, and half of the dancers deferred their major meal of the day until 11: 00 PM, after their performance (Cohen et al., 1985, p. 48). Actual values for the serum ferritin levels were not reported; however, the investigators did report the following: "Serum ferritin was below normal in eight women and three men...low ferritin levels were present among the women whether they menstruated or not, and therefore could not have been due to menstrual blood loss" (Cohen et al., 1985, p. 49). These findings may have been attributed to their busy work schedule (10:30 AM to 11:00 PM) and/or influenced by their dietary habits and intakes of iron.

Serum ferritin values in athletes

"There is no general agreement about normal serum ferritin level in athletes" (Pattini & Schena, 1990, pp. 351-352). However, estimates of 30 to 40 ug/L have been reported as normal iron stores in athletes (Dickson, Wilkinson & Noakes, 1982; Dufeaux, Hoederath, Steitberg, Hollmann & Assmann, 1981). However, the accuracy of iron status assessment in athletes has been questioned because of the possible confounding effects of inflammation following exercise (Clement & Sawchulk, 1984; Dickson, Wilkson & Noakes, 1982; Finch, Huebers, 1982). For example, Dickson and colleagues (1982) reported prerace serum ferritin levels in ultraendurance runners to be approximately 35 % above a true baseline value.

A study to determine the effects of strength training on the parameters of red cell oxygen transport and iron status was conducted by Schobersberger, Tschann, Hasibeder, Steidl, Herold, Nachbauer and Koller (1990). Twelve healthy males participated in a six week strength training program that consisted of two hour sessions four times weekly. Following the six week program, the serum ferritin decreased significantly by 35 % ($p < 0.01$). The investigators contend that mechanical stress of red cells resulted from the activation of large muscle masses that led to increased intravascular hemolysis.

Diehl, Lohman, Smith and Kertzer (1986) reported the effects of physical training and competition on female field hockey players. Iron reserves, as measured by serum ferritin, appeared to be progressively depleted with each successive season of play. Following a single season of play, the mean serum ferritin values were between 23 to 25 ug/L. The

investigators reported that after three seasons of play, serum ferritin values were frequently between 10 to 20 ug/L.

More recently, similar findings were reported by Roberts and Smith (1990) who noted a decrease in serum ferritin levels from season to season in elite Canadian speed and synchronized swimmers and speed skaters. The midseason serum ferritin team values for year one and year two are summarized in Table 9.

Table 8:
Midseason serum ferritin team values (ug/L)
for year one and year two

	Number	Year 1	Year 2
Female synchronized swimmers	**9**	**48+/-10**	**24+/-6**
Male speed swimmers	**7**	**66+/13**	**56+/-7**
Female speed skaters	**6**	**57+/-14**	**51+/-7**
Male speed skaters	**6**	**94+/-27**	**72+/-19**

****Source: Adapted from Roberts & Smith (1990).**

The researchers reported a significant decrease in serum ferritin for both the synchronized swimmers and for the male speed skaters ($p < 0.05$). Although the study population was small, the results suggest a decrease tendency in the levels of serum ferritin for each successive season of play.

Singh, Deuster, Day and Moser-Veillon (1990) evaluated the mineral status of 14 highly trained female runners with 11 untrained females, as determined by three day dietary records, and from blood and urine samples. Although the mean dietary intakes of iron did not differ in the two groups, the serum ferritin concentration of the highly trained group was 18 +/- 4 ug/L versus 30 +/- 6 ug/L in the untrained group.

O'Toole and coworkers (1989), examined the iron status of 50 ultraendurance athletes participating in the 1988 Hawaii Ironman Triathlon

World Championship. The mean serum ferritin levels for men (n=31) was 95.2 ug/L. Comparatively, the mean serum ferritin levels for women less than 45 years of age (n=15) was 29 ug/L, and 57.5 ug/L for women 45 years of age or older. There was a significant difference in serum ferritin levels between younger and older women ($p < 0.005$), between men and younger women ($p < 0.001$), but no significant difference between men and older women.

Blum, Sherman and Boileau (1986) reported on the effects of a fitness type exercise regimen on the iron stores of adult women. Twenty-four previously untrained females (aged 22 to 51 years) were recruited from a faculty/ staff fitness type aerobic exercise class. Fitness classes consisted of (a) a five to 10 minute warm-up were participants engaged in slow jogging, stretching, and muscle endurance exercises (i.e., push-ups), (b) 20 minutes of aerobic calisthenics (i.e., skipping, jumping), and (c) and five to 10 minute cool down period consisting of slow jogging and stretching. Exercise classes lasted 35 minutes and were scheduled four days per week, for a total of 13 weeks. A second group of 11 women (aged 20 to 39 years) not engaging in regular exercise served as the sedentary control group. Three day dietary records were collected on two separate occasions. Blood samples were collected at the beginning of the study, at six weeks and at 13 weeks for both the exercise group and the sedentary group. The mean serum ferritin values for these two groups are reported in Table 9.

Table 9:
Mean serum ferritin values (ug/L) for exercise and sedentary group at weeks 0, 6 and 13

	Week 0	Week 6	Week 13
Exercise group	**30.7 +/-4.1**	**24.6 +/-4.1**	**24.9 +/-3.6**
Sedentary group	**26.1 +/- 4.7**	**27.3 +/- 5**	**28.2 +/-4.6**

****Adapted from Blum, Sherman and Boileau (1986).**

"Ferritin concentrations were lower at wk [week] 6 and 13 ($p < 0.01$ and $p < 0.05$) than initially. No changes in these measures were detected among the 11 sedentary control subjects" (Blum, Sherman & Boileau, 1986, p. 456). Dietary analysis revealed no significant differences in dietary intake between exercise and sedentary groups for either records one or two (12 mg daily, exercise and sedentary combined).

2.14 Summary

In sum, the review of the literature suggests that gender, menstrual status, blood donation history, and exercise appears to affect iron status as measured by serum ferritin. Premenopausal women, blood donors, and individuals who are physically active tend to have lower iron stores; whereas males, non-donors, postmenopausal women, and individuals who are less physically active tend to have higher iron stores. There is evidence to suggest that physical exertion may enhance iron excretion (Blum, Sherman, & Boileau, 1986; Lauffer, 1991; Taylor, Rogers, Goodman, Baynes, Bothwell, Benzwoda, Kramer, & Hattingh, 1987; Salonen et al., 1992).

It has been hypothesized that stored iron promotes coronary heart disease (CHD) and iron depletion protects against CHD (Sullivan, 1992; Sullivan, 1989; Sullivan, 1981). In a recent prospective landmark study of Eastern Finnish men, Salonen and coworkers (1992) found that men with a

serum ferritin of $\geq$ 200 ug /L had a 2.2 fold risk of acute myocardial infarction as compared to men with lower serum ferritin values. It has been suggested that prospective studies involving menstruating and menopausal women are needed to determine gender differences related to the iron hypothesis (Sullivan, 1992).

CHAPTER 3: CONCEPTUAL FRAMEWORK

3.1 Introduction

This chapter conveys the various concepts, definitions and assumptions of the Nursing Theory of Health Equity that has been utilized to guide this study (Bartfay & Bartfay, 1993). This theory of nursing can be utilized for a variety of theoretical, educational, practice and research endeavors. Moreover, the theory compliments existing conceptual models and theories in describing, explaining, predicting and controlling phenomena of interest to the discipline of nursing.

3.2 Key concepts and definitions

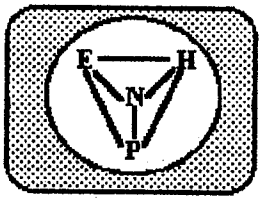
Nursing

The metaparadigm of each discipline provides the foundation for establishing it's unique perspective and orientation (Fawcett, 1984). The central concepts of the discipline of nursing are person {P}, health {H}, environment {E}, and nursing {N} (Bush, 1979; Fawcett, 1980; Flaskerud & Haltoran, 1980; Hanchett & Clarke, 1988; Thibodeau, 1983). Through a syntheses of the four metaparadigm concepts of nursing, the discipline of nursing begins to crystallize and take shape. Nursing may be described as a noun (e.g., profession, art, science), a verb (e.g., to care, help, assist), and as an adjective (e.g,. holistic, accountable). The nurse as a noun, for example, is often portrayed as a single individual who carries out assessments and interventions at the micro (e.g., single client) or macro (e.g., family) level. The work and concern of nurses as collectivities (i.e., Canadian Nurses Association, Manitoba Association of Registered Nurses) has not been adequately addressed.

Nursing is here defined for the purposes of this study as the qualitative and quantitative study and application of knowledge related to

health experiences and events between persons (individuals and aggregates), the environment (internal and external), and the members of the profession over time along the life continuum. Nursing is conceptualized as a three dimensional tetrahedron with the four metaparadigm concepts interconnected and interrelated (see Diagram 1).

Diagram 1: Four metaparadigm concepts of nursing



**Note: Environment =E; Health =H; Nursing =N, and Persons =P.

The solid circle encompassing the four metaparadigm concepts are representative of nursing's unique body of knowledge. The thickness of the circle surrounding the four metaparadigm concepts of nursing is directly correlated with the passage of time. That is to say, as nursing's body of knowledge grows with the passage of time, so will the thickness of the solid circle encompassing the four metaparadigm concepts.

Health

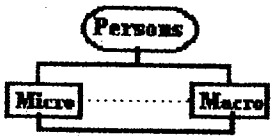
Despite a plethora of attempts to define, measure, and operationalize the concept of health (see Baranowski, 1981; Patrick, Bush & Chen, 1973; Randall, 1981; Reynolds, 1988; Salmon, 1984; Shaver, 1985; World Health Organization, 1947), there remains no universally accepted and utilized definition of health. Definitions including terms such as homeostasis, optimal functioning, absence of disease or patterns of the whole are often cited, but do not capture the essence of the concept of health.

Illich's (1976) contends that each culture gives shape to an unique conformation of attitudes towards what health is. For example, dyschronic spirochetosis is so prevalent among North Amazonian Indians, that they accept its endemicity to such an extent that its victims are regarded as healthy (Logan & Hunt, 1978). Interestingly, individuals who do not have this disfiguring disease are regarded as pathological and unable to arrange a contract of marriage. Other definitions of health also fail to adequately address the time element required to internalize cultural meanings and values associated with health. For the purposes of this study, health is defined as a mental construct dependent on the unique perspectives and beliefs of a given culture (Icelandic-Canadian) developed over time as a result of unique life experiences and events.

Persons

Nurses are concerned with the health experiences and events of both micro (individual) and macro (aggregates of two or more) entities. There is evidence in the literature to suggest that interventions carried-out at the micro level (i.e., individual) can have direct influence on the macro level (i.e., community) and vice versa (Elder, Hovell, Lasater, Wells, Carleton, 1985; Maccoby, Farquhar, Wood & Alexander, 1977; Perry, Crocket, & Pirie, 1987; Puska, 1984). These potential influences are depicted as a dotted line between micro and macro levels in Diagram 2.

Diagram 2: Influence between micro and macro levels



For example, a nurse informs an individual (micro) with an elevated serum ferritin to limit the consumption of alcohol with meals since it will enhance iron absorption. The individual (micro), along with members of his family (macro), decrease their consumption of alcohol as a consequence of the nursing intervention carried-out at the micro level.

For the purposes of this study, persons are also referred to as subjects who consented to partake in this investigation. The subjects are pure bred Canadians of Icelandic descent aged 20 to 60 years (i.e., there was no inter-marriage with non-Icelanders). Although data collection took place at the micro level (individual), results are presented in macro forms (group data) to facilitate the identification of general trends and relationships between dependent (serum ferritin) and independent variables (i.e., exercise, gender).

Environment

The environment has a profound influence on the health and well being of individuals. The environment (En) consists of a summation (Σ) of all the internal factors (If) and external factors (Ef) that have the potential to facilitate or inhibit a variety of life experiences and events such as human health and development over time. The following formula depicts this relationship:

$$En = \sum_{Tn=1}^{X} If(Tn) + Ef(Tn) \qquad X = 1, 2, 3, \ldots$$

Internal factors (If) are located within individuals. Biochemical processes (e.g., iron absorption in the presence of vitamin C), genetic makeup (e.g., family history of heart disease), personality (e.g., type A personality), or a variety of cognitive (e.g., knowledge related to CVD risk factors) and affective attributes (e.g., motivation to exercise) exemplify this

category. External factors (Ef) are located outside of individuals. They involve such things as the availability of physical fitness centers at work and in the community, and various organized sporting events (e.g., hockey tournaments). For the purposes of this investigation, both internal (genetic makeup, lifestyles) and external factors (urban residence) were assumed to be constant since no planned intervention or manipulation to directly affect the environment has taken place (e.g., teaching program to change attitudes towards exercise in the community).

Time is both subjective and objective in nature. Time is a continuous measurable duration or quantity (i.e., seconds, days, years) that occurs in a relatively irreversible order with the existing technology on hand. Moreover, time also refers to an occasion associated with certain life experiences (e.g., marriage) or events (e.g., birth, menopause) that possess certain defining characteristics or conditions.

To determine and study the effects of time on nursing, health, person(s), and the environment, a baseline measure or starting point has to be established and operationalized. This is represented in the formula as Tn = 1. A variety of units may be utilized to describe this baseline measure (i.e., minutes, days, years). The symbol X represents an end point of time. Consequently, time is operationalized mathematically as the duration or period from 1 to X. For example, time was operationalized for the four day food record (see Appendix B) as the period or duration from 1 (described in days) to X4 (day four) inclusive. Cross-sectional design studies are used to describe the status of phenomena and/ or the relationships between phenomena at a fixed point in time (Brink & Wood, 1989; Burns & Grove, 1987; Treece & Treece, 1982). The required fixed point in time for this cross-sectional design study has been operationalized as a two month period

starting from December, 1992 (Tn = 1) to January, 1993 (X). This period corresponds specifically to the data collection period of the study.

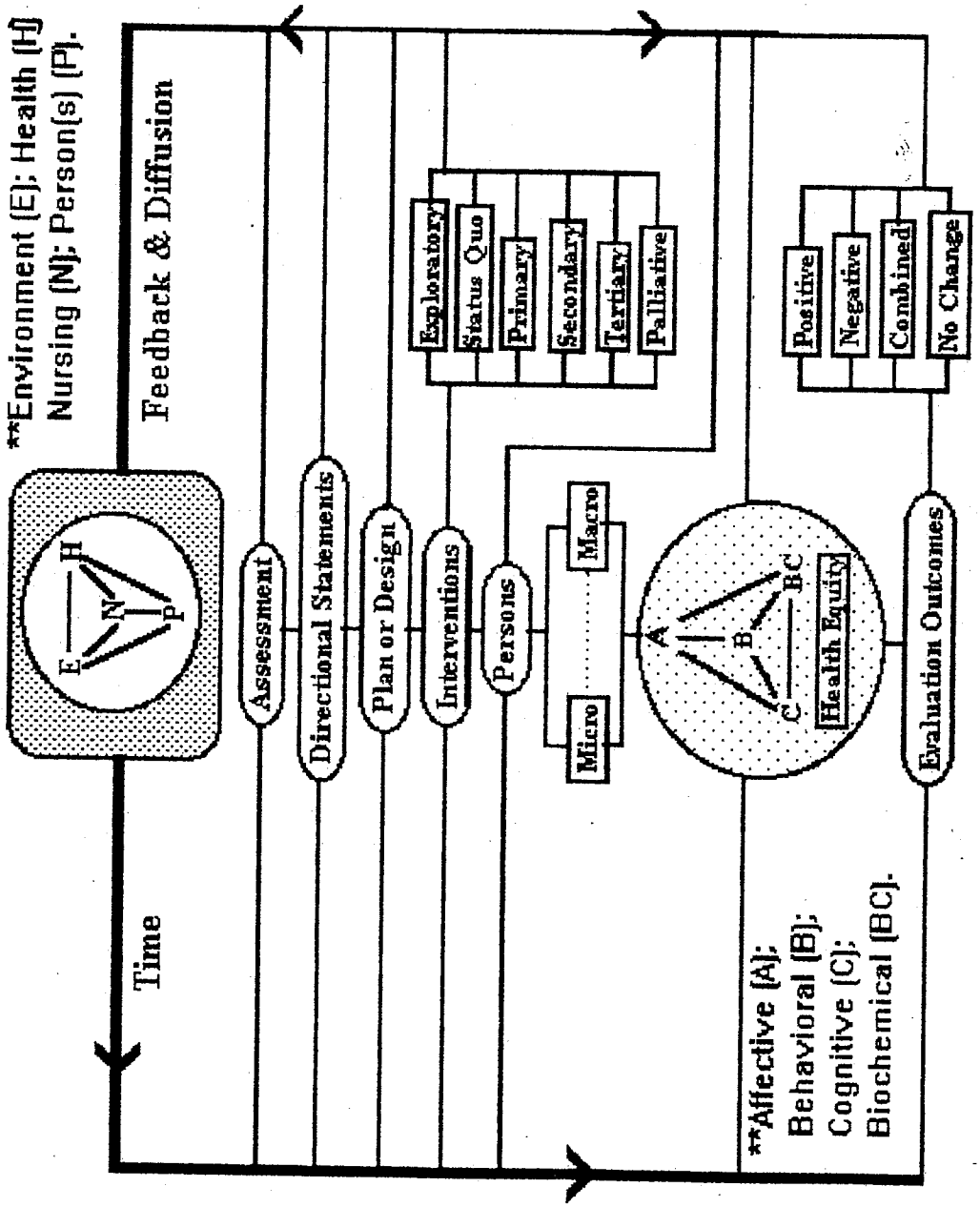
3.3 Theoretical assumptions and foundations

The Nursing Theory of Health Equity is based on components of the nursing process, the problem solving method, and the research method. The following four components appear to be central to all models, theories, and forms of nursing practice and research: (1) some form of data collection or assessment occurs; (2) the data is categorized and inferences are made about the nature of the data collected; (3) some form of intervention or interaction takes place, and (4) an evaluation of the outcome takes place after a period of time. Diagram 3 (p. 60) provides a schematic overview of how the various concepts of the meta-theory are interrelated and connected. The theory does not assume a linear progression of movement between the various terms and concepts depicted in the conceptual diagram with the exception of time alone. For example, a nurse may conduct an initial assessment (e.g., X1) and then go back at a latter time (e.g., X3) to gather additional data.

3.4 Assessment

Assessment is defined as an ongoing process of data collection, validation of findings and intuitive feelings under the rubrics of the four metaparadigm concepts of nursing. This process provides the foundation for a plethora of theoretical, educational, practice and research endeavors. Assessment may be an individual or collective process. The types of data collected may be objective (e.g., lab values for serum ferritin), subjective (e.g., client statements about exercise habits), historical (e.g., documents related to Icelandic settlement in Manitoba), or predictive (e.g., population

Diagram 3: Conceptual diagram



estimates for Icelandic-Canadians). The quality of the assessment carried-out is affected by the availability of resources, technology, timing and the experience of the data collector(s). Various guides and tools have been developed to facilitate the assessment process (i.e. Bates, 1991; Bodinski, 1987; Morton, 1991; Reutler, 1984). The assessment phase of this study consisted of the review of the corresponding literature (chapter two) and the statement of the problem (chapter one).

3.5 Directional statements

Directional statements are arrived at by making inferences about the data collected under the rubrics of the four metaparadigm concepts of nursing. Directional statements identify common themes derived at by an analysis of the data collected during the assessment phase. They can be stated as actual or potential nursing diagnosis (see Gorden, 1982) or as problem statements and hypothesis (see Brink & Wood, 1983; Burns & Grove, 1987; Polit & Hungler, 1991) depending on the intended use of the data. For the purposes of this study, both the research question and the research hypotheses comprise the directional statement component of the theory.

3.6 Plan or design

The plan or design component of the theory provides the blueprint for carrying-out various interventions or strategies that seek to address the identified directional statements in an ethical and moral manner. The plan or design may be formal (e.g. written) or informal in nature (e.g. word of mouth) depending on the specified needs of the individual(s) concerned. This component of the theory is addressed in chapter four (methodology).

3.7 Intervention

The intervention component of the theory refers to the execution of the plan or design (chapter four). Interventions can occur at the micro (e.g., individual) or macro (e.g., community) level. The quality of the interventions carried-out are effected by the experience and expertise of the nurse(s) (Benner & Tanner, 1987; Benner, 1982), resources, technology, and timing. The theory consists of the following six types of mutually exclusive interventions that seek to maintain, stabilize and/or increase health equity during specific moments in time. Status quo, exploratory, primary, secondary, tertiary and palliative interventions seek to affect health equity positively by increasing and/or maintaining the available health resources and by eliminating or minimizing the impact of health liabilities.

Status quo

Status quo interventions occur when no planned intervention takes place to directly affect health equity during a specific moment of time. Although no planned interventions take place, changes to health equity may occur with the passage of time because of it's dynamic nature. For example, it may not be appropriate to carry-out discharge teaching related to the dietary iron and the importance of regular exercise when the individual is not ready as evidenced by extreme anxiety.

Exploratory

Exploratory interventions involve research and inquiry where little or nothing is known about the phenomenon of interest and it's affect on health equity. It provides a starting point for the acquisition and application of knowledge related to health experiences and events. This study is exploratory in nature because there has been no documented investigations

to determine the relationships between serum ferritin, gender and exercise in Canadians of Icelandic descent.

Primary

Primary interventions occur when there is a potential threat or decrease in the health equity status. Primary interventions seek to prevent potential problems from becoming actual problems by directly increasing health equity. This is achieved by increasing the available health resources and/or by decreasing potential health liabilities. For example, you might be interested in positively affecting health equity (He) by increasing the knowledge (Hr) of Manitobians related to risk factors associated with the development of CVD. A pretest (X1) could be administered to arrive at an estimate of health equity where 100 percent would be a hypothetical maximum for health equity. The health resources (Hr) may be perceived of as the correct number of items obtained on the cardiovascular knowledge test. Conversely, the number of incorrect items obtained on the cardiovascular knowledge test would represent health liabilities (Hl). An educational primary intervention takes place (X2) and a posttest is conducted (X3) to determine changes to health equity (He) over the specified period of time (1 to X3).

Secondary

Secondary interventions occur when there is an actual decrease in health equity. These interventions seek to detect, manipulate or treat actual problems to decrease their impact or possible after effects by stabilizing or increasing health equity. This is achieved by either increasing the available health resources and/or by decreasing actual health liabilities. For example, excessive intakes of dietary iron (Hl) and sedentary lifestyles (Hl) may contribute to the development of cardiovascular disease that can negatively

affect health equity. Secondary interventions can be undertaken to increase the available health resources (i.e., positive attitudes towards exercise, knowledge related to dietary iron and food preparation) and/or by decreasing the noted health liabilities (i.e., excessive consumption of dietary iron) to positively affect health equity.

Tertiary

Tertiary interventions attempt to restore and stabilize the impact of actual problems and their consequences on health equity during specific moments in time. This is achieved by attempting to increase or maintain the available health resources present during specific moments in time. For example, a victim of a left-sided cerebral vascular accident may require physical therapy to regain the use of the right arm.

Palliative

Palliative interventions do not attempt to eliminate health liabilities, but seek to minimize their impact and consequences on health equity over time. For example, it is not always possible to positively affect health equity as in the case of chronic organ dysfunction associated with hereditary hemochromatosis. However, an attempt can be made to maintain a desired state of heath equity (i.e., relatively pain free and comfortable) by maintaining and/or increasing the available health resources (i.e., support mechanisms, use of iron chelators).

3.8 Health equity

Health equity (He) is a dynamic state that results from a summation (Σ) of the available health resources (Hr) and the actual or potential health liabilities (Hl) present in a specific moment in time. It may be conceptualized as a great wall of defence (He) that seeks to keep out the intruders (Hl) by attempting to maintain and/ or increase the strength and

height of the wall (Hr). The following formula depicts the concept of health equity:

$$He = \sum_{Tn=1}^{X} Hr(Tn) + Hl(Tn) \qquad X = 1, 2, 3, \ldots$$

Health resources (Hr) represent a sum of all the internal and external positive assets that can be utilized to resist and counteract the effects of health liabilities (Hl). Positive attitudes, knowledge, regular exercise and the availability of health professionals in a community are examples of health resources. Health liabilities (Hl) tax existing health resources and negatively effect health equity. Excessive consumption of alcohol, lack of knowledge, negative attitudes towards exercise, fluid and electrolyte imbalances and genetic predisposition to heart disease are examples of health liabilities. The symbols Tn = 1 and X shown in the formula are identical in meaning to those described previously under the heading of environment.

For the purposes of this study, potential health resources include (a) regular exercise, (b) being premenopausal, (c) limited consumption of alcohol, and (d) limited consumption of dietary iron (especially heme iron). Potential health liabilities include (a) lack of regular exercise, (b) being menopausal, (c) male gender, (d) copious consumption of alcohol, and (e) copious consumption of dietary iron (especially heme iron). Health equity is determined by the actual serum ferritin values obtained for the various study cohorts (i.e., males, premenopausal and postmenopausal). Moreover, it is assumed that normal values of serum ferritin for both males (10 to 175 ug/L) and females (10 to 95 ug/L) represent higher levels of health equity. Conversely, it is assumed that higher levels of serum ferritin for both males

(> 175 ug/L) and females (> 95 ug/L) correspond to lower levels of health equity.

3.9 Determinants of health equity

The determinants of health equity refer to a plethora of factors that can negatively and positively affect health equity for both micro and macro entities. They consist of both overt and covert processes that are all interrelated and interconnected. An intervention carried-out on one determinant of health equity (e.g., knowledge) has the potential of influencing additional determinants (e.g., behavioral). For example, an undesirable change to the behavioral determinant (i.e., increased consumption of alcohol with meals) may influence the biochemical determinant (i.e., increased absorption of dietary iron) and result in the development of CHD over time.

These factors can be categorized under the rubrics of one of the following four determinants: (1) Affective; (2) cognitive; (3) behavioral, and (4) biochemical. The determinants of health equity (e.g., biochemical) and their actual and potential effects on each other can be thought of as specific points comprising the tetrahedron as depicted in Diagram 3.

Diagram 4: Determinants of health equity

**Note: Affective = A; Behavioral = B; Cognitive = C, and Biochemical = BC.

The determinants of health equity may be conceptualized as a three dimensional tetrahedral (pyramid) surrounded by a permeable plastic bubble. The permeable plastic bubble is representative of the concept of

health equity. The thickness of the plastic bubble determines the level of health equity. For the purposes of this study, a thicker plastic bubble would be present if serum ferritin levels are within normal ranges for both males (10 to 175 ug/L) and females (10 to 95 ug/L). Conversely, a thinner plastic bubble would be present if serum ferritin levels exceed normal values for both males (> 175 ug/L) and females (> 95 ug/L).

Affective determinant

The affective determinant of health equity is a subjective process or event that includes interests, feelings, motivation, attitudes, beliefs, emotions and apprehensions. Moreover, the affective determinant serves as the stimulus or mechanism that guides various ethical and moral behaviors that are developed as a result of various life processes and events over time.

Behavioral determinant

The behavioral determinant of health equity consists of both conscious (e.g., choice of food items) and unconscious (e.g., sleep walking) acts or practices. These acts and practices are observable over time. For the purposes of this study, behavioral determinants represent specific forms of lifestyle behaviors such as engaging in regular exercise or not.

Cognitive determinant

The cognitive determinant of health equity consists of knowledge, comprehension, analysis, synthesis, evaluation and application of information acquired with the onset of time. Moreover, it involves both objective and subjective mental processes such as thinking, remembering, and perceiving that may enhance (i.e., through educational primary interventions) or deteriorate with the passage of time.

Biochemical determinant

The biochemical determinant of health equity consists of events, processes, reactions and interactions between and among organic (i.e., meat source) and inorganic matter (i.e., nonheme iron, vitamin C) in all its forms and phenomena overtime. Moreover, the biochemical determinants are subject to the laws of nature and the universe (e.g., Boyle's law).

3.10 Evaluation outcomes

The theory assumes that every educational, theoretical, research or practice endeavor undertaken will always result in four actual or suspected outcomes. This phenomenon is here defined as the **Law of Interactions** and stipulates that interventions, despite their nature or type, will result in one of the following four outcomes: (1) positive; (2) negative; (3) combined, or (4) no change. Evaluation outcomes will be discussed in chapter six (discussion) following a review of the results obtained in chapter five.

Positive

Positive outcomes consist of desirable outcomes that positively affect health equity either intentionally or unintentionally. Positive outcomes can either increase health resources and/or decrease the number of health liabilities present. For example, decreasing serum ferritin levels will positively affect health equity. Confirmation of a potential health resource (i.e., regular exercise to decrease serum ferritin levels) would also be regarded as a positive outcome since it positively affects health equity.

Negative

Negative outcomes consists of undesirable outcomes that negatively affect health equity. Negative outcomes tax existing health resources and/or increase the amount of health liabilities present. Confirmation of a potential

health liability (i.e., sedentary lifestyle increases serum ferritin levels) would be regarded as a negative outcome since it negatively affects health equity.

Combined

Combined outcomes consists of both negative and positive outcomes that affect health equity in varying degrees. For example, whole blood is administered to a victim of an automobile accident and the individual's life is saved. However, this intervention also results in the development of cardiac arrhythmias associated with elevated levels of iron. Results may indicate, for example, that the findings obtained for a particular study are not statistically significant. However, the results may be clinically significant.

No change

No change outcomes consists of outcomes that cannot be classified as either positive, negative, or combined during the actual time of evaluation. For example, a community wide health promotion campaign related to decreasing the risk factors associated with heart disease may take decades to observe a decrease in mortality and morbidity rates.

3.11 Feedback and diffusion

The feedback and diffusion component of the theory involves the dispersion and sharing of the results, outcomes or assertions over time. It is a continuous process that can be either formal (e.g., written) or informal (e.g., word of mouth) in nature, and it is based on the evaluation outcomes achieved or suspected. Formal presentations and the publication of the research findings are planned to fulfill this component of the theory.

3.12 Summary

This chapter has provided an overview of the major assumptions, definitions and concepts of the Nursing Theory of Health Equity (Bartfay & Bartfay, 1993). The potential health resources identified for investigation

include (a) regular exercise, (b) being premenopausal, (c) limited consumption of alcohol, and (d) limited consumption of dietary iron (especially heme iron). Potential health liabilities identified include (a) lack of regular exercise, (b) being menopausal, (c) male gender, (d) copious consumption of alcohol, and (e) copious consumption of dietary iron (especially heme iron). Health equity will be determined by the actual serum ferritin values obtained for the various study cohorts (i.e., males, premenopausal, postmenopausal). Moreover, it is assumed that normal values of serum ferritin for both males (10 to 175 ug/L) and females (10 to 95 ug/L) represent higher levels of health equity. Whereas, higher levels of serum ferritin for both males (> 175 ug/L) and females (> 95 ug/L) would correspond to lower levels of health equity.

CHAPTER 4: METHODOLOGY

4.1 Design

A cross-sectional design study was employed to determine the relationships between serum ferritin levels, gender and exercise in Canadians of Icelandic decent. Cross-sectional design studies are used to describe the status of phenomena and/ or the relationships between phenomena at a fixed point in time (Brink & Wood, 1989; Burns & Grove, 1987; Treece & Treece, 1982). Furthermore, cross-sectional studies are "based on observations of different age or developmental groups at a single point in time for the purposes of inferring trends over time (Polit & Hungler, 1991, p. 643).

4.2 Sample

Subjects partaking in the echocardiographic component of the Icelandic-Canadian Study, by Dr. Barbara Naimark at St. Boniface General Hospital, were approached and invited to partake in the serum ferritin component of the study. In addition, subjects partaking in the bicycle ergometry component of the Icelandic-Canadian Study, at the Max Bell Centre of the University of Manitoba (headed by Dr. Johann Axelsson of the University of Iceland), were also approached and asked to partake in the serum ferritin component of the study. The final study sample consisted of 55 males and 55 nonpregnant females aged 21 to 60 years of age who were of pure Icelandic descent (i.e., there was no inter-marriage with non-Icelanders).

4.3 Ethical considerations

The study protocol was reviewed and accepted by the Human Ethics Committee, Faculty of Medicine, the University of Manitoba. Informed voluntary written consent was obtained from all participants in the study

(see Appendix D). All subjects were provided with a letter explaining the nature and purpose of the study, the potential risks and benefits, procedures, and the name of the investigator and contact phone numbers should questions or concerns arise (see Appendix E). Subjects were informed that they could withdraw from the study at any point without prejudice or without jeopardizing the care that they would receive at St. Boniface General Hospital or at the University of Manitoba. Opportunities for questions were provided during each phase of data collection (i.e., lifestyles questionnaire, dietary record, drawing of blood samples).

The data collected was kept in a locked filing cabinet to assure confidentiality and anonymity. Subjects were informed that only the investigator, members of the thesis committee, and members of the Canadian Icelandic Study research team would have access to the data. Participants wishing to obtain their individual results (e.g., serum ferritin levels) were informed that they could contact the researcher to obtain this information. In addition, individuals with abnormal findings (e.g., elevated serum ferritin levels) were contacted by phone and /or letter, and encouraged to inform their physician of the results.

4.4 Data collection

Four independent variables were examined to determine their relationship to the dependent variable stored iron measured by serum ferritin levels. Independent variables included: (1) age; (2) sex; (3) menstrual status, and (4) exercise status. Data collection involved the following: (1) A lifestyles questionnaire administered by the researcher (see Appendix A); (2) a four day dietary record completed by the participants (see Appendix B), and (3) fasting venous blood samples for serum ferritin

(5 ml.) analysis and also for hematocrit and hemoglobin (5 ml.) levels.

Lifestyles questionnaire

The first part of data collection involved the administration of a lifestyles questionnaire (see Appendix A). The questions and answer choices were read out-loud by the investigator, and the answer choices were recorded accordingly. The questionnaire was retrospective in nature and consisted of the following seven sections:

(1) Personal medical history (three questions);

(2) medications and supplements (15 questions);

(3) iron status (five questions);

(4) diet and food preparation (eight questions);

(5) exercise and physical fitness (five questions);

(6) blood transfusion and donation history (three questions), and

(7) menstrual and birthing history (11 questions).

Dietary exchanges of iron

Subjects were asked to keep a four day prospective dietary record (see Appendix B) to assess their dietary intake of iron. A sample dietary record (see Appendix C) was given to all participants to reinforce the verbal explanation and facilitate the recording process.

Dietary intake of iron was estimated for both the four day food record, and also for the diet and food preparation section of the lifestyles questionnaire. The total dietary intake of iron for each subject was determined by assigning values to the consumed items and by totalling the amounts listed. The mean dietary intake of iron per day was then calculated by dividing the totals by the corresponding number of days represented (e.g., by four for the four day food record). Table 10 provides a sample recording

for a typical breakfast along with the corresponding values for the dietary intakes of iron.

Table 10:
Sample of dietary intake
of iron consumed for breakfast

Food item(s) consumed	Assigned values per item	No. of items	Totals
2 eggs prepared in stainless steel pan	+1	2	+2
1 slice of ham	+2	1	+2
2 pieces of toast	+1	2	+2
1 cup of tea	-1	1	-1
1 glass of orange juice	+2	1	+2
Total dietary intake of iron			+7

Items considered as good dietary sources of iron (i.e., beef, pork, fish, poultry) and that are easily absorbed (heme iron) were assigned a value of two {2} (Bodinski, 1987; Cook & Monsen, 1976; Editorial, 1981; Fleck, 1981; Guthrie, 1979; Hamilton & Whitney, 1982; Kreutler, 1980; Labuza & Erdman, 1984; Monsen & Cook, 1976; Monsen, Hallberg, Layrisse, Hegsted, Cook, Mertz & Finch, 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984). Items that also enhance iron absorption (i.e., alcohol, ascorbic acid or vitamin C) were also assigned a value of two {2} (Bodinski, 1987; Fleck, 1981; Hamilton & Whitney, 1982; Kreutler, 1980; Labuza & Erdman, 1984; Lieber, 1988; Monsen & Cook, 1976; Monsen et al., 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984).

The preparation of food items in cast iron pans, skillets or pots were assigned of value of one {1} since they are known to increase the iron content of foods (Bobinski, 1987; Hamilton & Whitney, 1982; Kreutler, 1980). Items considered as poor dietary sources of iron (i.e., eggs, milk,

cheese, fruit, vegetables, cereals, legumes) that are not readily absorbed (nonheme iron) were also assigned a value of one {1} (Carmichael, Christopher, Hegenauer & Saltman, 1975; Cook & Monsen, 1976; Editorial, 1981; Fleck, 1981; Guthrie, 1979; Hamilton & Whitney, 1982; Jenkins, Hill & Cummings, 1975; Kreutler, 1980; Labuza & Erdman, 1984; Mackler & Herbert, 1985; Monsen & Cook, 1976; Monsen et al., 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984). Items that were known to inhibit the absorption of iron (i.e., tannic acid in tea, antacids, calcium and phosphate salts) were assigned a value of negative one {-1} (Bodinski, 1987; Fleck, 1981; Labuza & Erdman, 1984; Hamilton & Whitney, 1982; Kreutler, 1980; Mindell, 1979; Monsen & Cook, 1976; Monsen et al., 1978; Stare & McWilliams, 1984; Williams & Caliendo, 1984).

Consumption of alcohol

Alcohol was defined as the amount of ethanol consumed (in ounces) as determined by questions 10, 11 and 12 of the medications and supplements section of the lifestyles questionnaire (see Appendix A). Specifically, one ounce of pure alcohol was equivalent to the following: (a) Thirty ounces of beer or one bottle {question 10}; (b) eight ounces of wine or 1 glass {question 11}, and (c) two ounces of liquor (spirits) or 1 glass {question 12}.

Serum Ferritin

Serum ferritin levels are used to measure the iron storage status of individuals (Birgegard et al., 1978; Cella & Watson, 1989; Cook & Monsen, 1975; Cook et al., 1976; Cook, Lipschitz, Miles, & Finch, 1974; Hamilton et al., 1986). Unlike many blood tests, the serum ferritin test is not affected by moderate hemolysis of the sample (Hamilton, Cahill, Rose, & Douglas, 1986). Samples drawn are also stable for seven days when stored at two to

eight degrees Celsius (Bio-Rad Laboratories, 1991, p. 5). For the purposes of this study, normal values for males were defined as 10 to 175 micrograms per liter (ug/L) and 10 to 95 ug/L for females (standard values utilized by St. Boniface General Hospital, Winnipeg, Manitoba, Canada).

Participants were informed that bruising or mild localized discomfort could be experienced at the venipuncture sight. Subjects were asked to fast for a least 12 hours before the venipuncture. Blood samples were obtained at the Max Bell Centre at the University of Manitoba between 07:00 A.M. and 11:00 A.M. Five milliliters of venous blood was obtained for serum ferritin analysis {camouflage red top tube}, and an additional five milliliters was also obtained for hemoglobin and hematocrit analysis {heparinized lavender tube} utilizing a Vacutainer ® system. Venous blood was drawn from the antecubital vein of a selected arm upon release of a rubber tourniquet. Blood samples for hemoglobin and hematocrit were refrigerated utilizing a standard household table top refrigerator at minus 5 degrees Celsius until transport. Samples obtained for serum ferritin were spun at 3,500 revolutions per minute (RPM) for 20 minutes utilizing a table top centrifuge. The plasma was then separated-out and kept at room temperature in small plastic capped containers (3 ml). Samples were transported after 11:00 A.M. by car to St. Boniface General Hospital for laboratory analysis.

General principles of the assay

Serum ferritin levels can be accurately measured utilizing radioimmunoassay (RAI) (Brewer, Pesce & Ashworth, 1974; Cella & Watson, 1989; Chard, 1989; Cook et al., 1974; Hamilton et al., 1986; Mason & Holy, 1986). The RAI is an ultramicromethod that consists of the following three basic components: (1) A binding protein; (2) a radioactive

labelled compound (i.e., 125 Iodine [125-I] labelled human serum albumin), and (3) the same, labelled compound (Brewer, Pesce & Ashworth, 1974; Chard, 1987; Parker, 1976; Mason & Holy, 1986; Parker, 1976; Regenmortel, Briand, Muller & Plaue, 1988; Simmons & Ewing, 1974; Yalow, 1974). A stoichiometric amount of labelled (tagged) compound is added to the binding protein. The unlabelled (untagged) compound is then added and the amount of unlabelled compound is determined by the amount of compound displaced.

Assay procedure utilized

The Quantimune ® Ferritin immunoradiometric {IRMA} assay was employed to determine serum ferritin levels for this study (Bio-Rad Laboratories, 1991). This two site assay "uses highly purified 125 I-labeled antibody to ferritin as the tracer, and ferritin antibodies immobilized on polyacrylamide beads as the solid phase" (Bio-Rad Laboratories, 1991, p. 2). The ferritin standard consisted of human liver ferritin in a solution of phosphate buffer and bovine serum albumin. The supplied kit reagents come ready to use with this assay system. The following eight assay steps were carried-out in accordance with the instruction manual provided by Bio-Rad Laboratories, (1991, p. 5):

(1) The reaction tubes for each standard (0, 5, 10, 25, 100, 250, 1000 and 2500 ug/L concentrations), control, sample, and total counts tube were labeled.

(2) Fifty microliters (ul) of each standard, control and sample were pipetted to their appropriate tubes. If the reduction system required a maximum binding tube, this tube could be prepared using 200 ul of the 2500 ug standard as the sample.

(3) The Tracer/ Immunobead ®Reagent was thoroughly mixed and 200 ul were added to all of the tubes including the total counts tube.

(4) The tubes were then mixed by shaking each rack (vortexing is not necessary), and then set aside until step 8.

(5) The tubes were then incubated at room temperature (21 to 30 degrees Celsius) for 30 minutes.

(6) Following the incubation period, three milliliters (ml) of normal saline (0.9 %) were added to all of the tubes. The tubes were then centrifuged (1500 x g).

(7) The contents of each tube was then decanted using a FoamRac™ or similar device to hold the tubes. The supernatant was decanted promptly and completely. Thorough decanting is critical in this assay. The last drops of supernatant from the tubes were blotted on a paper towel or plastic-backed absorbent paper.

(8) The tubes were then counted for one minute utilizing a LKB Wallar 1272 Clinigamma (automatic gamma counter).

4.5 Assessment of exercise status

Regular exercise

Regular exercise was defined as aerobic activity (i.e., walking, swimming) engaged in for 45 minutes or more per week as reported by the subjects on the questionnaire. This was determined by multiplying the responses obtained on questions one and three (1 and 3) of the section entitled exercise and physical fitness of the lifestyles questionnaire (see Appendix A). The figure obtained represented the average amount of time engaged in aerobic exercise per week for each subject interviewed.

Measures of physical fitness

The subjects overall fitness level was determined by (a) question five of the exercise and physical fitness section of the lifestyles questionnaire, and (b) bicycle ergometry testing, performed at the Max Bell Centre, University of Manitoba, by the Icelandic-Canadian team.

Subjects performed submaximal bicycle ergometry on a stationary Monark ® bicycle in the sitting position. Subjects warmed up for five minutes, and then pedalled at 60 revolutions per minute at one to two kilograms (kg) of resistance until they reached 70 % to 80 % of their maximum-predicted-age-adjusted heart rates (220 - age x 0.7 - 0.8).

Mechanical aspects of ergometry

The physical functions of work, force and power which are described below relate to the mechanical aspects of ergometry (the measurement of work). The term ergometry stems from the Greek ergon (work) and metron (measurement) (American College of Sports Medicine, 1986; Astrand, 1970; Fox, Bowers & Foss, 1988).

The unit for work (or energy) is derived from the equation : Work is equal to the force times distance {W = F x L} (Fox, Bowers & Foss, 1988; Wasserman, Hansen, Sue & Whipp, 1987). The American College of Sports Medicine (1987, p. 158) notes that the metabolic equivalent of work is the total energy expended (E) in performing mechanical work. Work is "a physical quantification of the force operating upon a mass that causes it to change its location" (Wasserman, Hansen, Sue & Whipp, 1987, p. 241).

Under conditions where force is applied and no movement results (i.e., isometric contraction), no work is performed. Force {F} is equal to the mass {m} times acceleration {a} [F= m x a] (American College of Sports Medicine, 1986). The commonly used unit for force is kilopond {kp} (1 kp

is the force acting on the mass of 1 kilogram at normal acceleration of gravity; 100 kpm / minute = 723 foot-ponds/ minute = 16.35 watts) (Astrand, 1970, p. 13).

"If the distance traveled is related to time then power can be expressed as kp-m/ min. Power can also be expressed as watts and kg-m /min." (Fox, Bowers & Foss, 1988, p. 76). Power is used to express work done in a specified unit of time (Fox, Bowers & Foss, 1988).

Determining workload

According to Astrand and Rodahl (1977, p. 453), workload may be determined by either (1) measurement of the oxygen uptake during the actual work operation, or (2) by indirect estimation of the oxygen uptake on the basis of the work pulse recorded during the performance of the work. Load is defined as "the burden placed upon the worker; the rate at which work is being done at any time" (Astrand & Rodahl, 1977, p. 450). Sharkey (1990, p. 303) notes that workload per minute (power in kilogram meters per minute -kgm/min) can be calculated by using the following:

Pedal revolutions per minute (rpm) = 60 for Monark® bicycle.
Force = the resistance to pedalling (from 1 kilogram to 7 kilograms).
Distance = 6 meters on the Monark® bicycle.

Consequently, the workload for one, two and three kilograms of resistance (force), for examples, can be determined as follows:

60 rpm x 1 kg x 6 = 360 kgm/ min.
60 rpm x 2 kg x 6 = 720 kgm/ min.
60 rpm x 2 kg x 6 = 1, 080 kgm / min.

Bicycle ergometry

Three principle methods of producing standard workloads have been utilized in laboratory experiments: (1) Running on a treadmill; (2) working on a bicycle ergometer, and (3) using a step test (Astrand & Rodahl, 1977; Wilson, 1975). Bicycle ergometry is a noninvasive procedure that involves the monitoring of the cardiac electrical and mechanical response to continuous , progressively strenuous, dynamic (or isotonic) exercise upon a stationary bicycle. Bicycle ergometry can be performed in either the supine or upright position (Leff, 1986). Astand and Rodahl (1977) argue that the preferable instrument for routine tests or studies of physical work capacity, is the bicycle ergometer since the energy output in watts (1 watt = 6.12 kpm times minute to the negative 1 power) or the oxygen uptake can be predicted with greater accuracy than for any other type of exercise.

The bicycle gearing and the wheel circumference have been designed so that one complete turn of the pedals moves a point on the rim 6 meters (Astrand, 1970; Fox, Bowers & Foss, 1988). The wheel of the stationary bicycle is braked mechanically by a belt running around the rim (the rim is 1.6 meters in circumference) (Fox, Bowers & Foss, 1988). Resistance is offered through mechanical loading of the flywheel (Fox, Bowers, & Foss, 1988). Two types of bicycle ergometers are in general use:
(1) Mechanically-braked devices that use an adjustable brake to provide resistance to pedalling, and (2) electrically-braked devices that use a magnetic field to produce resistance to pedalling efforts (Wasserman, Hansen, Sue & Whipp, 1987).

Advantages

(1) The bicycle ergometer operated with a mechanical brake is inexpensive (e.g., Monark® bicycle ergometry) (Astand & Rodahl, 1977; Wilson, 1975).

(2) It is portable and is not dependent on the availability of electrical power (Astand & Rodahl, 1977; Wilson, 1975).

(3) It is easy to obtain blood pressure readings and electrocardiogram recordings since the upper body remains relatively still (American College of Sports Medicine, 1986; Astrand & Rodahl, 1977; Hamilton, 1986; Wilson, 1975).

(4) Within limits, the workload is independent of the subject's body weight (Astrand & Rodahl, 1986; Hamilton, 1986; Wilson, 1975).

(5) Bicycling has proved to be a suitable work form since at a given load, "it demands about the same energy output, whether the subject be young or old, trained or out of condition, elite bicyclist or unfamiliar with the sport" (Astrand, 1970, p. 9).

(6) The task is relatively easy to learn (Wilson, 1975).

(7) The aerobic work capacity of the subject can be accurately and repeatedly determined (Wilson, 1975).

Disadvantages

(1) During maximal work when the subject is tired and unable to maintain a constant tempo, the load increases for each pedal revolution (Astrand & Rodahl, 1977).

(2) A constant rate of pedaling is required to maintain power and frequent calibration is necessary (Hamilton, 1986; Wilson, 1975).

(3) Since the test involves muscles less commonly used, there is a greater chance of fatigue (Hamilton, 1986).

(4) Frequent periodic recalibration is required (Wilson, 1975).

(5) The test may require strong subject motivation (Wilson, 1975).

Maximal versus submaximal testing

There are two commonly used categories of ergometric testing: the maximal test and the submaximal test. The maximal test (a) brings the subject to a level of intensity where fatigue or symptoms of distress (e.g. chest pain) prohibit further exercise; (b) maximum oxygen consumption is achieved, and (c) no further increase in heart rate occurs (American College of Sports Medicine, 1986, p. 16). By contrast, the submaximal test stresses the individual to a predetermined end-point (Wilson, 1975). This end-point is usually a predetermined heart rate (i.e., 70 to 80 % of maximal age predicted heart rate for age and sex) (American College of Sports Medicine, 1986; Wasserman, Hansen, Sue & Whipp, 1987).

4.6 Summary

The study utilized a cross-sectional design to determine the relationships between serum ferritin, gender and exercise. Independent variables included: (1) age; (2) sex; (3) menstrual status, and (4) exercise status. The dependent variable was the level of stored iron as measured by serum ferritin levels. Participants consisted of Canadians of pure Icelandic descent residing in Winnipeg, Manitoba.

Subjects participating in the echocardiographic component of the Icelandic-Canadian Study, by Dr. Barbara Naimark at St. Boniface General Hospital, were approached and invited to partake in the serum ferritin component of the study. In addition, subjects partaking in the bicycle ergometry component of the Icelandic-Canadian Study, at the Max Bell Centre of the University of Manitoba (headed by Dr. Johann Axelsson of the University of Iceland), were also approached and asked to partake in the

serum ferritin component of the study. The final study sample consisted of 55 males and 55 nonpregnant females aged 21 to 60 years of age. Data collection involved a lifestyles questionnaire, a four day dietary record, and fasting venous blood samples for serum ferritin, hemoglobin and hematocrit analysis.

CHAPTER 5: RESULTS

5.1 Summary statistics

Statistical Analysis System (SAS) software was utilized to analyze the data (SAS Institute, 1985). Fifty-five males and 55 females (22 menopausal and 33 menstruating) participated in the study. Mean age of the males was 44 with a range of 25 to 60 years. Mean age of the females was 43 with a range of 21 to 59 years.

Mean serum ferritin level obtained for males was 187.93 ug/L with a range of 17 to 478 ug/L {normal range = 10 to 175 ug/L}. Mean serum ferritin value for females was 47.83 ug/L with a range of 5 to 240 ug/L {normal range = 10 to 95 ug/L). The mean serum ferritin level for menstruating women was 33.06 ug/L compared to 71.14 ug/L in menopausal women (see Table 11 for summary).

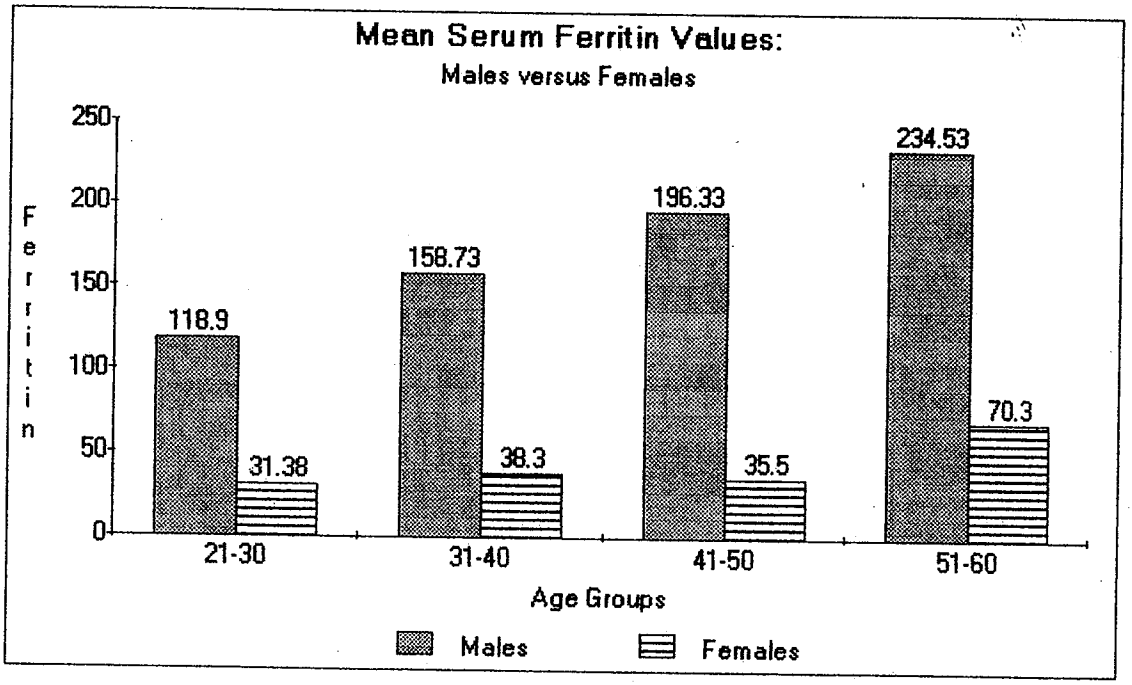
Table 11:
Mean serum ferritin levels (ug/L) obtained for males, females, menstruating and menopausal

	Means serum ferritin levels	Total subjects (n=110)
All males	**187.93**	**n=55**
All females	**47.84**	**n=55**
Menstruating	**33.06**	**n=33**
Menopausal	**71.14**	**n=22**

Statistically significant differences are noted for serum ferritin levels between males and all females; males and premenopausal women; males and postmenopausal women, and between premenopausal and postmenopausal women ($p < 0.05$).

An additional analysis of the mean serum ferritin values obtained was undertaken by dividing the males and females into the following age cohorts (years of age): (a) 21 to 30; (b) 31 to 40; (c) 41 to 50, and (d) 51 to 60 (see Figure 1).

Figure 1:
Mean serum ferritin levels (ug/L) for males and females with age groups



In males, although no significant differences were found between the age cohorts shown in Table 12, multiple pairwise comparison (Montgomery, 1991) between the age cohorts revealed a significant difference in serum ferritin levels between males aged 20 to 30 years and those aged 50 to 60 years {see Table 13}.

Table 12:
Mean serum ferritin levels (ug/L) for males with age groups (in years)

Age groups	21-30	31-40	41-50	51-60	p value
Serum ferritin	118.9	158.73	196.33	234.53	
	n=10	n=11	n=15	n=19	0.09

Table 13:
Multiple pairwise comparison between age groups (years) for males with serum ferritin levels (ug/L)

Age groups	20-30	31-40	41-50	51-60
20-30	---	NS	NS	**
31-40	NS	---	NS	NS
41-50	NS	NS	---	NS
51-60	**	NS	NS	---

Note: ** = Significant at 0.05 level; NS= Not significant at 0.05 level

In females, at least one age cohort was found to be statistically significant with serum ferritin levels at the 5 % level (see Table 14). Multiple pairwise comparison between the age cohorts for females was

Table 14:
Mean serum ferritin levels (ug/L) for females with age groups (in years)

Age groups	21-30	31-40	41-50	51-60	p value
Serum ferritin	31.38	38.3	35.5	70.3	
	n=8	n=10	n=18	n=19	0.03

conducted to determine which of the means differed (Montgomery, 1991) {see Table 15}. Statistically significant differences in serum ferritin levels are noted between females aged 20 to 30 years and those aged 51 to 60 years; between those aged 31 to 40 years and those aged 51 to 60 years, and between those aged 41 to 50 years and those aged 51 to 60 years.

Table 15:
Multiple pairwise comparison between age groups (years) for females with serum ferritin levels (ug/L)

Age groups	20-30	31-40	41-50	51-60
20 -30	---	NS	NS	**
31-40	NS	---	NS	**
41-50	NS	NS	---	**
51-60	**	**	**	---

Note: ** = Significant at 0.05 level; NS= Not significant at 0.05 level

Hemoglobin and hematocrit

Hemoglobin is the main intracellular protein of the red blood cell and its primary function is to transport oxygen to the cells and carry carbon dioxide away from the cells (Cella & Watson, 1989). The mean hemoglobin value obtained for males was 152.6 g/L with a range of 133 to 179 g/L (normal range = 140 to 180 g/L). The mean hemoglobin value obtained for females was 136.8 g/L with a range of 117 to 162 g/L (normal range = 120 to 160 g/L).

The hematocrit {packed red cell volume} measures the proportion (I) of red blood cells in a volume {L) of whole blood expressed as a percentage, and it is normally three times the hemoglobin level (Cella & Watson, 1989). The mean hematocrit value obtained for males was 0.44 I/L with a range of 0.38 to 0.52 I/L (normal range = 0.42 to 0.52 I/L). Females had a mean hematocrit of 0.4 I/L with a range of 0.34 to 0.47 I/L (normal range = 0.37 to 0.47 I/L).

5.2 Correlational analysis

Pearson's product-moment correlation coefficients (r) may be utilized to determine the magnitude and direction of two variables {e.g., exercise

time and serum ferritin} (Agresti & Finlay, 1986; Burns & Grove, 1987; Mason, Lind & Marchal, 1988; Polit & Hungler, 1987). Pearson's r is both a descriptive and inferential statistic (Polit & Hungler, 1991). As a descriptive statistic, Pearson's r summarizes the direction and magnitude of a relationship between two variables. As an inferential statistic, it can be used to test hypotheses concerning population correlations. A +1 value indicates a perfect positive relationship; whereas, a -1 value indicates a perfect negative relationship (Burns & Grove, 1987). "Traditionally, an r of 0.1 to 0.3 is considered a weak relationship, 0.3 to 0.5 a moderate relationship and above 5 a strong relationship" (Burns & Grove, 1987, p. 510).

Table 16 provides a summary of the correlation coefficients for independent variables with the dependent variable serum ferritin for males, premenopausal and postmenopausal females. For males, weak positive correlations with serum ferritin are observed for age, body mass index, dietary intake of iron for both the lifestyles questionnaire and the four day food record, and history of being told they were anemic, but they do not reach the 5 % level of significance. Positive correlations with serum ferritin are observed for hemoglobin, hematocrit and alcohol consumption at the 5 % significance level. Exercise time is inversely related to serum ferritin at the 5 % significance level. Weak negative correlations are observed for self-reported physical fitness level, workload, and blood donation history, but they do not reach a level of significance.

For premenopausal women, exercise time, workload, body mass index, blood donation history, and the consumption of alcohol are positively correlated with serum ferritin, but do not reach the 5 % level of significance. Hemoglobin, hematocrit, and dietary intake of iron for both the four day

food record and the lifestyles questionnaire are positively correlated with serum ferritin at the 5 % significance level.

Table 16:
Pearson's correlation coefficients (r) for independent variables with dependent variable serum ferritin for males, premenopausal and postmenopausal

Independent variables	Males (r)	Premenopausal (r)	Postmenopausal (r)
Age	0.25	-0.12	0.24
Hemoglobin	0.36**	0.45**	0.19
Hematocrit	0.35**	0.42**	0.07
Exercise time	-0.4**	0.19	-0.23**
Self-reported physical fitness level	-0.21	-0.14	-0.01
Workload	-0.1	0.1	-0.22
Body mass index	0.06	0.22	0.27
Blood donation	-0.05	0.39	-0.05
Alcohol	0.26**	0.21	0.11
Dietary intake of iron (lifestyles questionnaire)	0.14	0.46**	0.04
Dietary intake of iron (4 day food record)	0.24	0.48**	0.4
Ever told anemic	0.09	-0.56	-0.4

Note: ** = significant at 0.05 level

Age, self-reported physical fitness level and history of anemia are negatively correlated with serum ferritin, but they do not reach the 5 % significance level.

For postmenopausal women, age, hemoglobin, hematocrit, body mass index, alcohol consumption, and dietary intakes of iron (lifestyles questionnaire & four day food record) are positively correlated with serum

ferritin, but do not reach the 5 % significance level. Weak negative correlations with serum ferritin are observed for self-reported physical fitness level, workload, blood donation history, and anemia but are not significant at the 5 % level. Exercise time is negatively correlated to serum ferritin at the 5 % level of significance.

5.3 Dietary intake of iron

Lifestyles questionnaire

Mean dietary intake of iron per day for males on the lifestyles questionnaire is 13.56 food sources per day with a range of 4 to 23. An additional analysis of mean serum ferritin levels obtained with low (0 to 8); medium (9 to 16) and high (17 to 24) levels of dietary iron per day are reported in Table 17. No significant differences are observed between low, medium and high dietary intake levels of iron per day with serum ferritin levels ($p = 0.74$).

Table 17:
Mean dietary intake of iron (per day) based on the lifestyles questionnaire for males with mean serum ferritin levels (ug/L)

Dietary intake of iron per day	0-8 (Low)	9-16 (Medium)	17-24 (High)	p value
Serum ferritin	163	191	200.57	
	n=5	n=36	n=14	0.74

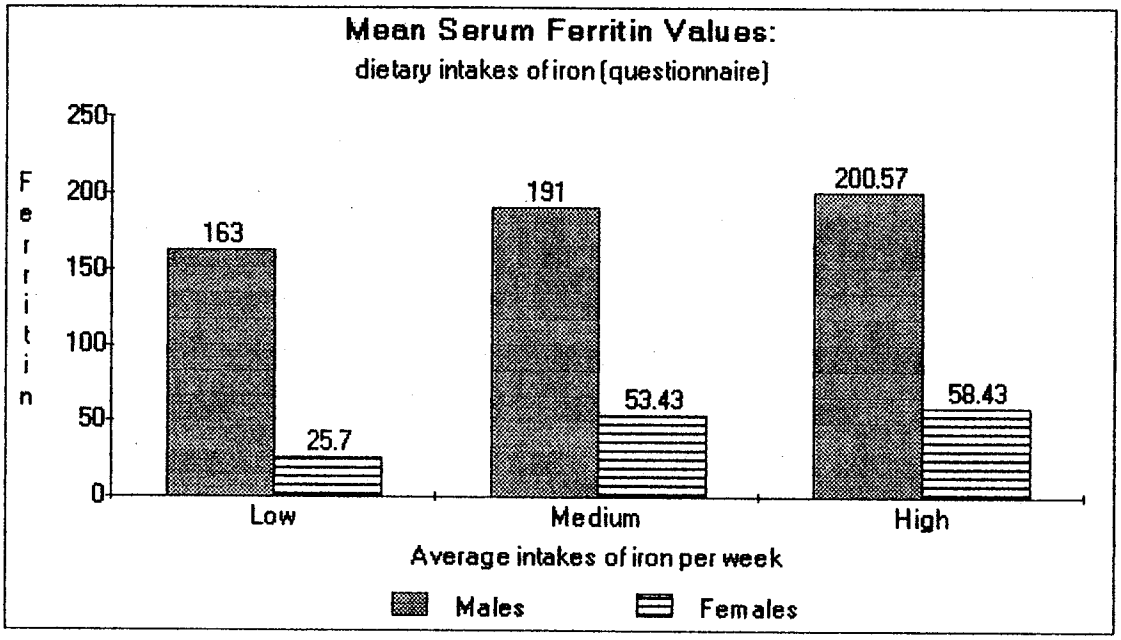
Mean dietary intake of iron based on the lifestyles questionnaire for females is 13.21 food sources per day with a range of 4 to 23. No significant differences between low, medium and high dietary intake levels of iron per day with serum ferritin levels are observed (see Table 18).

Table 18:
Mean dietary intakes of iron (per day) based on the lifestyles questionnaire for females with mean serum ferritin levels (ug/L)

Dietary intake of iron per day	0-8 (Low)	9-16 (Medium)	17-24 (High)	p value
Serum ferritin	25.7 n=10	53.43 n=27	58.43 n=14	0.17

Figure 2 shows the mean serum ferritin levels obtained with low, medium and high intake levels of dietary iron per day (lifestyles questionnaire) for males and females ($p < 0.05$).

Figure 2:
Mean dietary intakes of iron (per day) based on the lifestyles questionnaire for males and females with mean serum ferritin levels (ug/L)



Four day food record

Mean dietary intake of iron based on the four day food record for males is 16.65 food sources per day with a range of 6 to 28. An additional

Table 19:
Mean dietary intakes of iron (per day) based on the four day food record for males with mean serum ferritin levels (ug/L)

Dietary intake of iron per day	0-10 (Low)	11-20 (Medium)	21-30 (High)	p value
Serum ferritin	125	192.07	299.71	
	n=3	n=27	n=7	0.06

analysis of mean serum ferritin levels obtained with low (0 to 10); medium (11 to 20) and high (21 to 30) dietary intake levels of iron per day are reported in Table 19. Although no significant differences with serum ferritin levels were observed between low, medium and high dietary intake levels of iron per day, multiple pairwise comparison (Montgomery, 1991) between the dietary intake groups revealed significant differences between low and high dietary intake groups, and between medium and high dietary intake groups { see Table 20}.

Table 20:
Multiple pairwise comparison between low, medium and high dietary intakes of iron per day (4 day food record) for males with serum ferritin levels (ug/L)

Dietary intake of iron per day	0-10 (Low)	11-20 (Medium)	21-30 (High)
0-10 (Low)	---	NS	**
11-20 (Medium)	NS	---	**
21-30 (High)	**	**	---

Note: ** = Significant at 0.05 level; NS = not significant at the 0.05 level

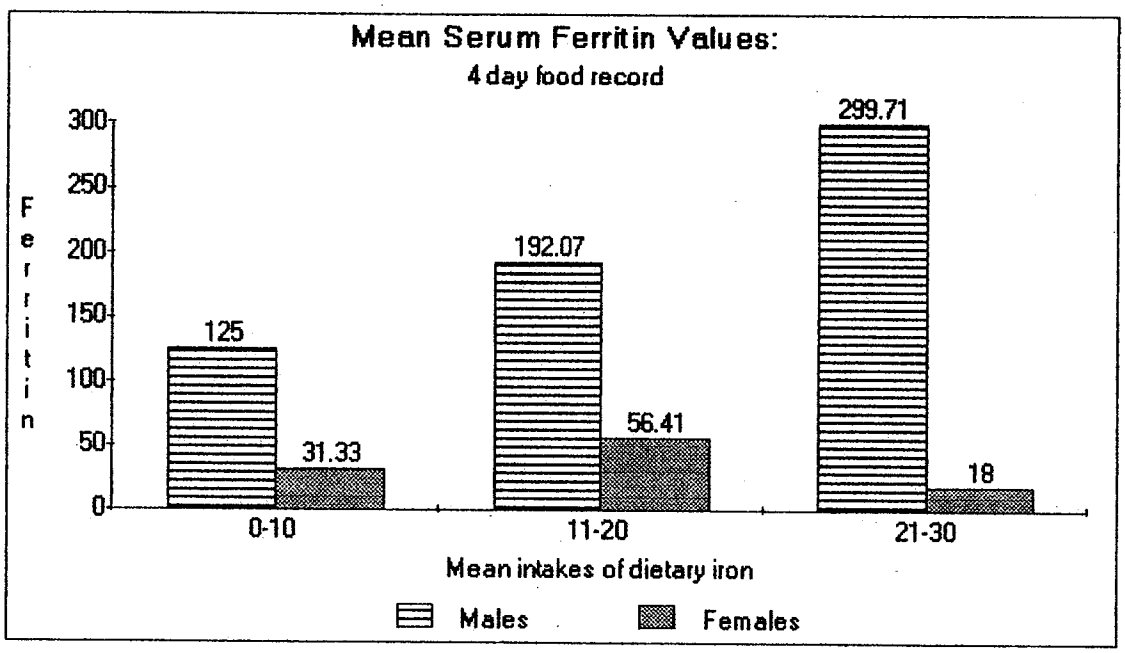
Mean dietary intake of iron based on the four day food record for females is 13.54 food sources per day with a range of 6 to 22. Table 21

Table 21:
Mean dietary intakes of iron (per day) based on the four day food record for females with mean serum ferritin levels (ug/L)

Dietary intake of iron per day	0-10 (Low)	11-20 (Medium)	21-30 (High)	p value
Serum ferritin	31.33	56.41	18	
	n=6	n=34	n=1	N/A

Note: A comparison between the three groups is not appropriate (N/A) because one group has only one observation and the other group has 34 observations.

Figure 3:
Mean dietary intakes of iron (per day) based on the four day food record for males and females with mean serum ferritin levels (ug/L)



shows the mean serum ferritin levels obtained for low, medium and high dietary intake levels of iron per day.

Figure 3 shows the mean serum ferritin levels obtained with low, medium and high intakes of dietary iron per day (four day food record) for males and females ($p < 0.05$). Significant correlations between the two

measures of dietary iron per day (4 day food record & lifestyles questionnaire) are observed for both males ($r = 0.44$, $p < 0.05$) and females ($r = 0.31$, $p < 0.05$).

5.4 Blood donations

Table 22 shows the mean serum ferritin levels obtained for regular blood donars (donated 5 or more times) and nondonars (donated less than 5 times) for males, premenopausal and postmenopausal women. Although the mean serum ferritin levels are higher in nondonar groups than donar groups for males, premenopausal and postmenopausal women, they do not reach the 5 % level of significance.

Table 22:
Mean serum ferritin levels (ug/L)
for regular blood donars and nondonars
for males, premenopausal and postmenopausal

	Regular donars	Nondonars	p values
Males	**184.9**	**197**	**0.74**
Premenopausal	**25.1**	**35.2**	**0.39**
Postmenopausal	**68.9**	**75**	**0.81**

5.5 Consumption of alcohol

Table 23 shows the mean serum ferritin levels obtained with the consumption of : (a) zero to five; (b) 6 to 10; (c) 11 to 15, and (d) 16 to 20 ounces of alcohol per week. A statistically significant difference between the alcohol group means and serum ferritin is observed ($p < 0.05$). Multiple pairwise comparison between the groups was conducted to determine which of the means differed (Montgomery, 1991) {see Table 24}. A statistically significant difference between the zero to 5 ounce group and 16 to 20 ounce group is present.

Table 23:
Mean serum ferritin levels (ug/L) for males with consumption of alcohol (ounces per week)

Ounces per week	0-5	6-10	11-15	16-20	p value
Serum ferritin	160.78	195.95	211.57	338	0.01

Table 24:
Multiple pairwise comparison for consumption of alcohol (ounces per week) for males with serum ferritin (ug/L)

Ounces per week	0 to 5	6 to 10	11 to 15	16 to 20
0 to 5	---	NS	NS	**
6 to 10	NS	---	NS	NS
11 to 15	NS	NS	---	NS
15 to 20	**	NS	NS	---

Note: ** = significant at 0.05 level; NS = not significant at 0.05 level

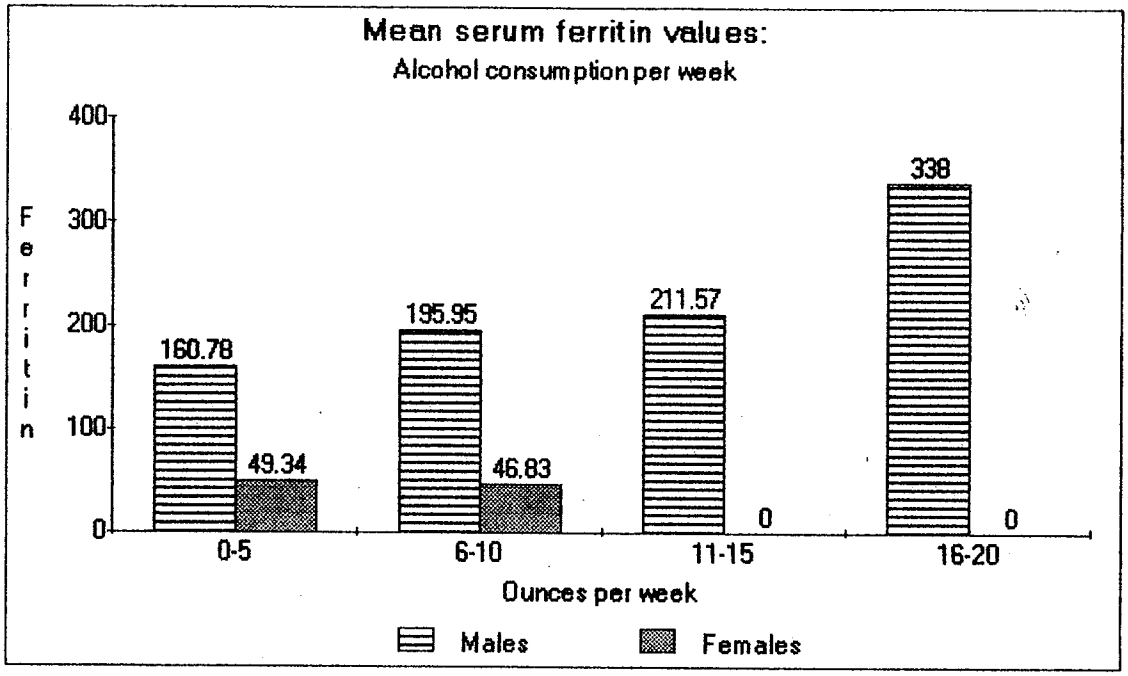
Table 25 shows the mean serum ferritin levels obtained for females with the consumption of: (a) zero to five; (b) 6 to 10; (c) 11 to 15, and (d) 16 to 20 ounces of alcohol per week. The difference between the alcohol group means and serum ferritin is not significant at the 5 % level.

Table 25:
Mean serum ferritin levels (ug/L) for females with consumption of alcohol (ounces per week)

Ounces per week	0-5	6-10	11-15	16-20	p value
Serum ferritin	49.34	49.33	Nil	Nil	0.84

Figure 4 shows the mean serum ferritin levels obtained for males and females with the consumption of: (a) zero to 5; (b) 6 to 10; (c) 11 to 15, and (d) 16 to 20 ounces of alcohol per week. The mean consumption of alcohol per week is 6.44 ounces and 2.73 ounces for males and females respectively ($p < 0.05$).

Figure 4:
Mean serum ferritin levels (ug/L) for males and females with consumption of alcohol (ounces per week)



5.6 Workload (watts)

Table 26 provides a summary of the mean serum ferritin levels obtained for the following workload (watts) ranges: (a) zero to 50; (b) 51 to 100; (c) 101 to 150, and (d) 151 to 200 for males, premenopausal and postmenopausal females. None of the workload groups were found to be significantly related to serum ferritin at the 5 % level. Mean workloads (watts) are 128.85 and 94 for males and all females respectively, this gender difference is not significant at the 5 % level with serum ferritin.

Table 26:
Mean serum ferritin levels (ug/L) with workloads (watts) for males, menstruating and menopausal

Workloads	0-50	51-100	101-150	151-200	p values
Males	Nil	243.78	205.97	121	0.37
Menstruating	Nil	30.14	34.63	Nil	0.71
Menopausal	103	70.82	75.33	Nil	0.78

5.7 Exercise time

Table 27 shows the mean serum ferritin levels obtained for males with the following exercise times (minutes per week): (a) Zero to 40 ; (b) 41- 80; (c) 81-120, and (d) 121-160. Although serum ferritin decreased with exercise time, it did not reach the 5 % level of significance.

Table 27:
Mean serum ferritin values (ug/L) obtained for males with exercise time (minutes per week)

Exercise times	0-40	41-80	81-120	121-160	p value
Serum ferritin	243.62	184.22	157	130	0.07

However, multiple pairwise comparison between the group means for serum ferritin revealed a significant difference between the zero to 40 exercise time group and the 121 to 160 exercise time group {see Table 28}.

Table 28:
Multiple pairwise comparison of mean serum ferritin levels (ug/L) with exercise time (minutes per week) for males.

Exercise times	0 to 40	41 to 80	81 to 120	121 to 160
0 to 40	---	NS	NS	**
41 to 80	NS	---	NS	NS
81 to 120	NS	NS	---	NS
121 to 160	**	NS	NS	---

Note: ** = significant at the 0.05 level; NS = not significant at the 0.05 level.

Table 29 shows the mean serum ferritin levels obtained for premenopausal females with the following exercise times (minutes per week): (a) Zero to 40 ; (b) 41- 80; (c) 81-120, and (d) 121-160. The

difference between the exercise group times and serum ferritin is not significant at the 5 % level.

Table 29:
Mean serum ferritin values (ug/L) obtained for premenopausal females with exercise time (minutes per week)

Exercise times	0-40	41-80	81-120	121-160	p value
Menstruating	31.69	24	28	44.75	0.44

Table 30 shows the mean serum ferritin levels obtained for postmenopausal females with the following exercise times (minutes per week): (a) Zero to 40; (b) 41- 80; (c) 81-120, and (d) 121-160. The difference between the exercise group times and serum ferritin is not significant at the 5 % level.

Table 30:
Mean serum ferritin values (ug/L) obtained for postmenopausal females with exercise time (minutes per week)

Exercise times	0-40	41-80	81-120	121-160	p value
Menopausal	84.29	74	73.63	52	0.67

5.8 Regression analysis

The following criteria was used to select the best regression model for males, premenopausal and postmenopausal females: (1) Mean square error plots; (2) R square plots; (3) C(p) plots, and (4) forward and backward stepwise procedures. Independent variables considered were identical to those listed in Table 16 with the dependent variable serum ferritin.

The final variables selected for males were age, hemoglobin, hematocrit, exercise time and dietary exchanges of iron (lifestyles questionnaire) {see Table 31}.

Table 31:
Regression model for males
with dependent variable serum ferritin (ug/L)

Independent variables	Estimate parameter	P value for model	R square value for model
Age	2.05	0.0074	0.27
Hemoglobin	7.95		
Hematocrit	-1740.14		
Exercise time	-0.71		
Dietary intake of iron (questionnaire)	3.86		

The final variables chosen for premenopausal females were age, exercise time, self-reported physical fitness level, dietary intake of iron (lifestyles questionnaire), alcohol consumption, and history of anemia {see Table 32}.

Table 32:
Regression model for premenopausal females
with dependent variable serum ferritin (ug/L)

Independent variables	Estimate parameter	P value for model	R square value for model
Age	-0.49	0.0009	0.59
Exercise time	0.19		
Self-reported physical fitness level	-10.89		
Dietary intake of iron (questionnaire)	2.38		
Alcohol consumption	0.16		
Ever told anemic	-20.35		

The final variables selected for postmenopausal women were age, dietary intakes of iron (lifestyles questionnaire and 4 day food record), exercise time, history of anemia, consumption of alcohol, and body mass index {see Table 33}.

Table 33:
Regression model for postmenopausal females with dependent variable serum ferritin (ug/L)

Independent variables	Estimate parameter	P value for model	R square value for model
Age	1.74	.08	.61
Dietary intake of iron (questionnaire)	-5.49		
Dietary intake of iron (4 day food record)	3.62		
Exercise time	-0.38		
Ever told anemic	-58.63		
Alcohol consumption	-9.56		
Body mass index	5.05		

5.9 Hypotheses testing

In hypothesis testing, one compares a sample statistic (i.e., mean) with the same statistic from a second sample (Burns & Grove, 1987). The t-test (Student's t) was used to test the significance of the difference between groups means (Agresti & Finlay, 1986; Burns & Grove, 1987; Mason, Lind, & Marchal, 1988; Polit & Hungler, 1991). The level of significance for all procedures was set at the 0.05 level.

Hypothesis 1

Hypothesis one stated that premenopausal women would have **lower** levels of stored iron as measured by serum ferritin levels compared to postmenopausal women. This hypothesis is supported [t statistic 3.1068, $p = 0.004$].

Hypothesis 2

Hypothesis two stated that premenopausal women would have **lower** levels of stored iron as measured by serum ferritin levels compared to men. This hypothesis is supported [t-statistic 8.8021, $p = 0.0001$].

Hypothesis 3

Hypothesis three stated that postmenopausal women would have **similar** levels of stored iron as measured by serum ferritin levels compared to men. The available evidence did not support this hypothesis [t-statistic 5.7022, $p = 0.0001$].

Hypothesis 4

Hypothesis four stated that premenopausal women who exercised regularly (45 minutes or more per week) would have **lower** levels of stored iron as measured by serum ferritin levels compared to premenopausal women who did not exercise regularly (less than 45 minutes per week). This hypothesis was not supported [t-statistic 0.2972, $p = 0.77$]. A second t-test was then undertaken for the same hypothesis with regular exercise now defined as 80 minutes or more per week. Once again, the available evidence did not support hypothesis four [t-statistic 1.2744, $p = 0.22$].

Hypothesis 5

Hypothesis five stated that postmenopausal women who exercised regularly (45 minutes or more per week) would have **lower** levels of stored iron as measured by serum ferritin levels compared to postmenopausal

women who did not exercise regularly (less than 45 minutes per week). This hypothesis was not supported [t-statistic 0.5378, $p = 0.6$]. A second t-test was then performed with regular exercise defined as 80 minutes or more per week. The available evidence, once again, did not support this hypothesis [t-statistic 0.4954, $p = 0.63$].

Hypothesis 6

Hypothesis six stated that postmenopausal women who exercised regularly (45 minutes or more per week) would have **similar** levels of stored iron as measured by serum ferritin levels compared to premenopausal women who did not exercise regularly (less than 45 minutes per week). This hypothesis was not supported with the available evidence [t-statistic 2.7593, $p = 0.01$]. A second t-test was also performed with regular exercise defined as 80 minutes or more per week. Once again, the hypothesis was not supported [t-statistic 2.9443, $p = 0.009$].

Hypothesis 7

Hypothesis seven stated that men who exercise regularly (45 minutes or more per week) would have **lower** levels of stored iron as measured by serum ferritin compared to men who did not exercise regularly (less than 45 minutes per week). The available evidence supports this hypothesis [t-statistic 3.0351, $p = 0.004$]. This hypothesis was also supported when regular exercise was defined as 80 or more minutes per week [t-statistic 2.8925, $p = 0.005$]. Table 31 provides a summary of the results obtained for the aforementioned hypotheses (with regular exercise defined as 45 minutes or more).

Table 34:
Summary of the results obtained for the hypotheses

	Condition	t-statistic	p value	Decision
Hypothesis 1	Pre vs. Mp	3.11	0.004	ES
Hypothesis 2	Pre vs. Men	8.8	0.0001	ES
Hypothesis 3	Mp vs. Men	5.7	0.0001	ENS
Hypothesis 4	PreE vs. MpN	0.3	0.8	ENS
Hypothesis 5	MpE vs. MpN	0.54	0.6	ENS
Hypothesis 6	MpE vs. PreN	2.76	0.01	ENS
Hypothesis 7	MenE vs. MenN	3.04	0.004	ES

****Note: Significance level at 0.05. ES= evidence supports hypothesis; ENS = evidence does not support hypothesis; Pre = premenopausal; Mp = menopausal; E = regularly exercise, and N = do not regularly exercise.**

5.10 Summary

Fifty-five males and 55 females (33 premenopausal & 22 postmenopausal) aged 21 to 60 years participated in the study. Mean serum ferritin levels obtained were 187.93 ug/L, 47.84 ug/L, 33.06 ug/L and 71.14 ug/L for males, females, premenopausal and postmenopausal women respectively. Statistically significant differences were noted for serum ferritin levels between males and all females; males and premenopausal women; males and postmenopausal women, and between premenopausal and postmenopausal women ($p < 0.05$).

Males who exercised regularly (45 minutes or more per week) were found to have significantly lower levels of serum ferritin compared to sedentary counterparts. Exercise was inversely related to serum ferritin in males ($r = -0.4$, $p < 0.05$). Hemoglobin ($r = 0.36$, $p < 0.05$), hematocrit ($r = 0.35$, $p < 0.05$) and the consumption of alcohol ($r = 0.26$, $p < 0.05$) were found to be positively related to serum ferritin in males.

Premenopausal women who exercised regularly were not found to have significantly lower levels of serum ferritin compared to their sedentary counterparts. Hemoglobin ($r = 0.45$, $p < 0.05$), hematocrit ($r = 0.42$, $p < 0.05$) and the dietary intake of iron per day for both the four day food record ($r = 0.46$, $p < 0.05$) and the lifestyles questionnaire ($r = 0.48$, $p < 0.05$) were found to be positively correlated to serum ferritin in premenopausal females. History of anemia was inversely related to serum ferritin in premenopausal women, but was not significant ($r = -0.56$, $p > 0.05$).

Postmenopausal women who exercised regularly were not found to have significantly lower levels of serum ferritin compared to their sedentary counterparts; however, exercise time was found to be negatively correlated with serum ferritin ($r = -0.23$, $p > 0.05$). History of anemia was found to be negatively correlated with serum ferritin in postmenopausal women, but was not significant ($r = -0.4$, $p > 0.05$). Although dietary intake of iron per day (four day food record) was positively correlated with serum ferritin in postmenopausal females, it was not significant ($r = 0.4$, $p > 0.05$).

CHAPTER 6: DISCUSSION

6.1 Statement of conclusions in relation to hypotheses

Hypothesis 1

The findings of the present study support the hypothesis that premenopausal women have lower levels of stored iron as measured by serum ferritin compared to postmenopausal women. The pattern of an increased level of serum ferritin following menopause is consistent with the patterns reported in the literature for females (Cook et al., 1976; Finch et al., 1977; Milman, Anderson & Strandberg-Pedersen, 1986; Vincente, Porto & deSousa, 1990). The cessation of regular menstrual blood loss, as proposed by Sullivan (1989, 1981) and others (Cook et al., 1976; Finch et al., 1977; Vincente, Porto & deSousa, 1990) results in elevated serum ferritin levels following menopause. The findings from this study suggest a decreasing level of health equity (increased serum ferritin) with the cessation of regular menses.

Hypothesis 2

The hypothesis that premenopausal women will have lower levels of serum ferritin compared to men, is supported by the findings of the present study. The pattern of increased levels of serum ferritin in males as compared to premenopausal females is consistent with those reported in the literature (Cook et al., 1976; Vincente, Porto & deSousa, 1990). Results suggest that loss of iron through regular menses appears to positively affect health equity levels (decreased serum ferritin); whereas, male gender appears to negatively affect health equity (increased serum ferritin).

Hypothesis 3

The results of the present study did not support the hypothesis that postmenopausal women would have similar levels of serum ferritin as

compared to men. Although this finding was not significant, it was consistent with the serum ferritin values reported in the literature for postmenopausal females and males (Cook et al., 1976; Milman, Anderson & Strandberg-Pedersen, 1986; Vincente, Porto & deSousa, 1990).

Hypothesis 4

The hypothesis that premenopausal women who exercise regularly would have lower levels of serum ferritin compared to sedentary premenopausal women, was not supported by the findings of the present study. This finding is not consistent with those reported in the literature related to exercise and iron stores in premenopausal women as measured by serum ferritin (Blum, Sherman & Boileau, 1986; Diehl et al., 1986; Robert & Smith, 1990; Singh et al., 1990). It appears that blood loss through regular menses may have greater positively affects on health equity levels than exercise in premenopausal women. Since the estimate of the average amount of exercise time engaged in per week was retrospective and subjective in nature (lifestyles questionnaire), there may have been either over or under estimates of actual exercise times. It is possible that a more extensive prospective controlled study, involving larger numbers of premenopausal women, may reveal a significant difference between sedentary and active premenopausal women.

Hypothesis 5

The results of the present study did not support the hypothesis that postmenopausal women who exercised regularly would have lower levels of serum ferritin compared to sedentary postmenopausal women. However, a statistically significant negative correlation for exercise with serum ferritin was observed in postmenopausal women. In view of this finding, increasing attention, in the form of longitudinal controlled research is necessary to

determine the possibility that exercise may positively affect health equity levels in postmenopausal women.

Hypothesis 6

The hypothesis that postmenopausal women who exercised regularly would have similar levels of serum ferritin compared to sedentary premenopausal women was not supported by the findings in this study. However, a significant correlation between exercise time and serum ferritin in postmenopausal women was observed. Findings suggest that exercise as method for positively affecting health equity levels is more critical in postmenopausal women than in premenopausal women who deplete iron stores regularly through menstruation.

Hypothesis 7

The results of the present study supports the hypothesis that men who exercised regularly will have lower levels of serum ferritin compared to sedentary men. Exercise time had the strongest significant inverse relationship with serum ferritin levels in males. This finding suggests that exercise appears to positively affect health equity levels in males.

6.2 Health assets and health liabilities

Consumption of alcohol

Although alcohol was positively correlated with serum ferritin in premenopausal and postmenopausal women, it did not reach a level of significance. In males, however, the consumption of alcohol was found to be significantly positively correlated with serum ferritin. This finding is consistent with the effects of alcohol on the absorption of dietary iron reported in the literature (Editorial, 1980; Gordeuk, 1992; Halliwell & Gutteridge, 1985; Harju, 1989; Kreutler, 1980; Lieber, 1988; Stare & McWilliams, 1984; Williams & Caliendo, 1984; Zilva & Pannall, 1975).

The finding suggests that males may positively affect health equity levels (measured by serum ferritin) by limiting and/or eliminating the consumption of alcohol with meals.

Dietary intake of iron

Ihanainen and colleagues (1989, p. 597) argue that the dietary nutrient intake is one of the most difficult aspects of health behavior to assess for the following reasons: (1) Day to day variation in food consumption; (2) difficulty with the estimation of portion sizes of food items; (3) intra-individual variation in dietary intakes seems to be greater than variation between individuals, and (4) problems with lack of compliance. "Neither the dietary history, the 24-hour recall, the food recording nor the dietary questionnaire is without disadvantage" (Ihanainen et al., 1989, p. 597).

The subjectivity involved in describing usual dietary patterns makes the dietary history vulnerable to problems of recall, and possible tendencies to exaggerate or minimize self-described eating habits (Mahalko, Johnson, Gallagher & Milne, 1985). For example, the accuracy of 24 hour dietary recall records has been questioned because of their inability to detect changes and dietary patterns over time (Editorial, 1976b; Mahalko, Johnson, Gallagher & Milne, 1985). Moreover, "the period required to obtain a record representative of the dietary habits of an individual may be considerably more than seven days but the accuracy of record-keeping may decline even before the end of a week" (Mahalko, Johnson, Gallagher & Milne, 1985, p. 542).

In accordance with previous studies that utilized three or four day dietary records to assess iron status (Blum, Sherman & Boileau, 1986; Ihanainen et al., 1989; Singh, Deuster, Day & Moser-Veillon, 1990),

subjects were asked to keep a four day dietary record. The method utilized to calculate the dietary intake of iron appeared to be an effective and efficient means for determining the effects of diet on health equity levels. Although the mean dietary intakes of iron per day (lifestyles questionnaire & four day food record) were found to negatively affect health equity levels in males, this finding was not significant. A positive correlation with the mean dietary intakes of iron per day (four day food record) with serum ferritin was found in both premenopausal and postmenopausal females. Mean dietary intakes of iron per day based on the lifestyles questionnaire, was also found to negatively affect health equity (increased serum ferritin) in premenopausal women. Hence, limiting the consumption of dietary iron (e.g., meat sources) may be a significant health asset in preventing the development of CVD. Longitudinal controlled studies examining the effects of dietary iron on health equity levels (measured by serum ferritin) needs to be undertaken.

Body mass index

Body mass index (BMI) is a value obtained by squaring the height of the subject (in centimeters), dividing this value by the weight (in kilograms) and multiplying by 100. Slack, Ferguson and Banta (1985) argue that the percentage of body fat should not be considered as a primary factor in assessing physical fitness since certain subjects may be fat and fit, while others may be lean and unfit (Slack, Ferguson & Banta, 1985). As an indirect measure of physical fitness, BMI was found to be positively correlated to serum ferritin in both premenopausal and postmenopausal women, but this finding was not significant. There is evidence in the literature to suggest that obesity may enhance iron absorption in menstruating and menopausal women by some yet unknown mechanism

(Fricker, Le Moel and Apfelbaum, 1990). Controlled longitudinal research to determine the effects of exercise and obesity on health equity levels (measured by serum ferritin) in premenopausal and postmenopausal women is required.

6.3 Implications for nursing research and practice

There has been a growing recognition that effective health services must do more than simply respond to illness (Collardo, 1992; Manitoba Health, 1992). Health care costs continue to escalate because of our current, largely retroactive, form of health care service and delivery (Bartfay, 1993). In Canada, 8.6 percent of the gross national product is spent on health care (Laschinger & McWilliams, 1992). Manitobans alone spend in excess of 1.5 billion dollars annually on health care (Manitoba Health, 1989), and CVD accounts for a significant portion of this budget. As noted previously (p. 1), the costs associated with CVD are enormous, whether they are measured in terms of morbidity, mortality, hospitalization, decreased quality of life, human suffering or economic losses incurred.

If we support the conjecture of Sullivan (1992; 1989; 1981) and others (McCord, 1991; Salonen et al., 1992), that accumulated stored iron is a possible risk factor for CVD, then effective nursing interventions to lower iron stores needs to be proposed and empirically evaluated in order to determine their affects on health equity.

> "The trend in nursing research has been toward increased clinical, patient-centered investigations, and this trend is likely to continue in years to come. One result of this trend is an expanded use of measures to assess the physiologic

> status of subjects" (Polit & Hungler, 1991, p. 343).

From the results obtained in this study, the following potential health resources have been identified to positively influence health equity levels as measured by serum ferritin: (a) Regular exercise for men and postmenopausal women; (b) being premenopausal; (c) limited consumption of dietary iron (especially heme iron sources), and (d) limited consumption of alcohol for men. Conversely, the following potential health liabilities were identified: (a) Lack of exercise for men and postmenopausal women; (b) being male or postmenopausal; (c) copious consumptions of dietary iron, and (d) copious consumptions of alcohol.

There is an old adage that an ounce of prevention is worth a pound of cure. Primary prevention and health promotion have become salient topics in Canadian society and nursing during the past two decades. National and provincial emphasis is slowly being redirected from the treatment of disease to primary prevention and health promotion in an attempt to influence the health status of all Canadians (Cheatley et al., 1991; Epp, 1986; Lalonde, 1974; Manitoba Health, 1989; Manitoba Health, 1992, Stone, 1985). The Canadian government has identified prevention of chronic disease as one of three health challenges for Canadians and has advocated the development of provincial programs to address the problem of CVD (Gelsky, Madonna & Young, 1991).

Nurses form the backbone of the Canadian health care system. Nurses are in an ideal position to respond to societal trends in order to meet the perceived health needs of the culture in which they exist (Bartfay, 1993). Although nurses provide health promotion services in the community, these services represent only 1.6 % of the health care dollar (Laschinger &

McWilliams, 1992). Commitment of resources and health care professionals to community-based-heart-health-services must be a fundamental component of recently proposed health care reforms (Manitoba Health, 1992). Prevention efforts are cost effective (Lavin, Sharpiro & Weill, 1992; Levine, 1992); the social, economic, and health care costs of inaction are too high.

Since several of the proposed health assets (e.g., regular exercise) and health liabilities (e.g., sedentary lifestyle, high consumption of dietary iron) reflect specific lifestyles behaviors or habits, they may be potentially altered or changed to positive affect health equity. Lifestyle risk factors associated with the development of CVD are often the result of habits developed early in life (Kolbe, 1992; McGinnis, 1992; Turner, Shelley & Smith, 1961). For example, a national study found that two-thirds of Canadian children surveyed consumed diets high in fat, and only one-third of the 15 year olds participated in daily physical education classes (King, Robertson & Warren, 1984-1985).

As a socializing agent second only to the family, schools exert a profound influence on the conditioning of lifestyle habits that can directly affect health (Susser, Watson & Hopper, 1985; Weitzman, 1989; Whaley & Wong, 1991). Large scale cost-effective macro interventions could easily be carried-out by nurses within these settings. For example, total enrollment in all elementary-secondary schools in Canada in 1989-90 was 5, 084,000 (Minister of Industry, Science and Technology, 1992). With more than 13, 610 public schools in Canada (Mutter, Ashworth & Cameron (1990), large scale developmentally specific heart health interventions could be carried-out and empirically evaluated by nurses within their respected communities.

This study has extended the existing areas of research related to stored iron by examining the relationships between serum ferritin, gender, and exercise in Canadians of Icelandic descent. Longitudinal controlled studies to examine the effects of exercise, BMI, and diet on health equity levels in premenopausal and postmenopausal females are required. Finally, the effectiveness of various nursing interventions to positively affect health equity as measured by serum ferritin, needs to be developed and empirically evaluated. Since this study may not be generalizable to more heterogeneous populations, additional study involving non-Icelanders is planned.

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Appendix A:
Lifestyles questionnaire

Subject No. ____

Age: ____ Sex: Male Female (Please circle)

Personal medical history

(1) Has a physician ever diagnosed you as having a liver disorder or problem (i.e. cirrhosis or hepatitis)?

Yes = 1
No = 2
Don't know = 3

_____

(2) Are you presently under the care of a physician for any blood related disorders?

Yes = 1
No = 2
Don't know = 3

_____

(3) Did you have a cold or infection (i.e. ear) during the past week?

Yes = 1
No = 2
Don't know = 3

_____

Medications & Supplements

(1) Are you currently taking antacids regularly (i.e. Rolaids, Maalox)?

Yes = 1
No = 2
Don't know = 3

_____

(2) Are you currently taking any medications containing iron (i.e ferrous sulfate)?

Yes =1
No= 2
Don't know = 3

_____

(3) Are you currently taking any hormonal replacements (i.e. estrogen)?

Yes = 1
No =2
Don't know = 3

_____

(4) Are you currently taking any mineral supplements containing iron?

Yes = 1
No = 2
Don't know = 3

_____

(5) Do you routinely take vitamin supplements containing vitamin C?

Yes = 1
No =2
Don't know = 3

_____

(6) How long have you been taking birth control pills (in years)?

Never = 1
One to five = 2
Six to ten = 3
Eleven to fifteen = 4
Sixteen to twenty =5
Twenty-one or more = 6

_____

(7) Are you currently taking any antibiotics (i.e. penicillin)?

Yes = 1
No = 2
Don't know = 3

_____

(8) Are you currently taking any medications to thin your blood (i.e. Warfarin {Coumadin}, or heparin)?

Yes = 1
No = 2
Don't know = 3

_____

(9) Do you routinely take aspirin (A.S.A.) (i.e. daily, every other day) ?

Yes = 1
No = 2
Don't know = 3

_____

(10) On average, how many bottles of beer would you say you drink per week?

None =1
One = 2
Two = 3
Three =4
Four = 5
Five = 6
Six = 7
Seven =8
Eight or more = 9

_____

(11) On average, how many glasses of wine do you have per week?

None =1
One = 2
Two = 3
Three =4
Four = 5
Five = 6
Six = 7
Seven =8
Eight or more = 9

_____

(12) On average, how many glasses of spirits (i.e. rum, whiskey, vodka) do you have per week?

None =1
One = 2
Two = 3
Three =4
Four = 5
Five = 6
Six = 7
Seven =8
Eight or more = 9

_____

(13) On average, how many cigarettes do you smoke per day?

None = 1
One to five =2
Six to ten = 3
Eleven to fifteen =4
Sixteen to twenty = 5
Twenty-one or more = 6

_____

(14) On average, how many pipe fulls of tobacco to you smoke per day?

None = 1
One to five =2
Six to ten = 3
Eleven to fifteen =4
Sixteen to twenty = 5
Twenty-one or more = 6

_____

(15) How many years have you smoked total?

None = 1
One = 2
Two = 3
Three to five = 4
Six to ten = 5
Eleven to fifteen = 6
Sixteen to twenty = 7
Twenty one or more =8

_____

Iron status

(1) Has a physician or nurse ever told you that you are anemic (low iron)?

Yes = 1
No = 2

_____

(2) Have you ever been told by a physician or nurse to increase your iron content in your diet?

Yes =1
No = 2

_____

(3) Do you routinely feel tired?

Yes = 1
No = 2

_____

(4) Do you routinely feel weak?

Yes = 1
No = 2

_____

(5) Do you routinely feel faint?

Yes = 1
No = 2

_____

Diet and food preparation

(1) How often do you eat fish or seafood per week on average?

Never = 1
Once = 2
Twice = 3
Three times = 4
Four or more = 5

_____

(2) How often do you eat organ meats (i.e. liver or kidney) per week on average?

Never = 1
Once = 2
Twice = 3
Three times = 4
Four or more = 5

_____

(3) How often do you eat red meats (i.e. steak, roast beef, chicken) per week on average?

Never = 1
Once = 2
Twice = 3
Three times = 4
Four or more = 5

_____

(4) How often do you have eggs per week on average?

Never = 1
Once = 2
Twice = 3
Three times = 4
Four or more = 5

_____

(5) Do you eat vegetables daily (i.e. carrots, lettuce) ?

Yes = 1
No = 2

_____

(6) Do you eat fruit daily (i.e. apples, oranges) ?

Yes = 1
No = 2

_____

(7) Do you have dairy products daily (i.e. cheese, milk) ?

Yes = 1
No =2

_____

(8) On average, how often do you use cast iron frying pans, skillets, or pots to cook you meals with per week?

Never = 1
Once = 2
Twice = 3
Three times = 4
Four or more = 5

_____

Exercise and physical fitness

(1) On average, how often do you exercise (areobic) routinely per week outside of work (i.e. walk, jog, swim, cycle, play racket sports) ?

Never = 1
Once = 2
Twice = 3
Three times = 4
Four or more = 5

_____

(2) Do you hold membership in a fitness club or gym?

Yes = 1
No = 2

_____

(3) **On average, what is the amount of time (in minutes) you spend exercising outside of work (i.e. walk, jog, swim, cycle, play racket sports) ?**

≤ 10 minutes = 1
11- 20 minutes = 2
21-30 minutes = 3
31- 40 minutes = 4
41 or more = 5

_____

(4) **What distance (in kilometers) do you think you could run without being short of breath or in physical discomfort?**

≤ 1 kilometer = 1
2 kilometers = 2
3 kilometers = 3
4 kilometers = 4
5 or more kilometers = 5

_____

(5) **How would you rate your overall fitness level?**

Very low = 1
Low = 2
Medium = 3
High = 4
Superior = 5

_____

Blood transfusion/ donation history

(1) **How many blood transfusions have you received to date?**

None = 1
One = 2
Two = 3
Three = 4
Four = 5
Five or more = 6

_____

(2) How many blood donations have you participated in to date?

None = 1
One = 2
Two = 3
Three = 4
Four = 5
Five or more = 6

_____

(3) How many times have you given blood samples for diagnostic purposes or for experimental studies?

None = 1
One = 2
Two = 3
Three = 4
Four = 5
Five or more = 6

_____

<u>Menstrual and birthing history</u>

(1) How many children have you given birth to (vaginally or by cesarean section)?

None = 1
One = 2
Two = 3
Three = 4
Four = 5
Five = 6
Six = 7
Seven or more = 8

_____

(2) How many abortions have you had?

None = 1
One = 2
Two = 3
Three = 4
Four = 5
Five = 6
Six or more = 7

_____

(3) How many miscarriages have you had?

None = 1
One = 2
Two = 3
Three = 4
Four = 5
Five = 6
Six or more = 7

_____

(4) At what age did you begin menstruating?

10 years old = 1
11 years old = 2
12 years old = 3
13 years old = 4
14 years old = 5
15 years old = 6
16 years old = 7
17 years old = 8
18 or older = 9

_____

(5) Are you still menstruating?

Yes = 1
No = 2

_____

(6) When was your last menstrual period?

≤ 1 month ago = 1
2-3 months ago = 2
4-5 months ago =3
6-8 months ago = 4
9-11 months ago =5
12 or more months ago = 6

_____

(7) On average, are (were) your periods regular or irregular?

Regular = 1
Irregular = 2

_____

(8) Are you currently pregnant?

Yes = 1
No = 2
Don't know = 3

_____

(9) Did you have a hysterectomy (uterus removed)?

Yes = 1
No = 1 _____

(10) Did you have your ovaries removed (oophorectomy)?

Yes = 1
No = 2

_____

****If YES go to question 11****

(11) Where both ovaries removed or just one?

Both = 1
Just one = 2
Don't know = 3

_____

Thank-you for your cooperation.

Appendix B
Dietary Record

Subject No. _____
Phone Number(s): Home_____ Work_____
Age:_____
Sex: Male Female (Please circle)
Day: 1 2 3 4 (Please circle)

Directions:
Please keep a record of the food items and beverages that you consume over a period of four consecutive days. In addition, please indicate if any cast-iron skillets or pots were used to prepare the meals. A sample food record has been included in the package that you received. This information will assist the researcher in determining the iron content of the food items and beverages you consume. Thank-you for agreeing to partake in this segment of the study. Should you have any questions, please feel free to contact Wally Bartfay at (Home) or at 477-8059 (University of Manitoba).

Breakfast
Food items

Beverages

Lunch
Food items

Beverages

Supper
Food items

Beverages

Snacks or additional beverages

Appendix C
Dietary Record Sample

Subject No. 1009
Phone Number(s): Home _____ Work 555-4321
Age: 42
Sex: (Male) Female (Please circle)
Day: (1) 2 3 4 (Please circle)
Directions:
Please keep a record of the food items and beverages that you consume over a period of four consecutive days. In addition, please indicate if any cast-iron skillets or pots were used to prepare the meals. A sample food record has been included in the package that you received. This information will assist the researcher in determining the iron content of the food items and beverages you consume. Thank-you for agreeing to partake in this segment of the study. Should you have any questions, please feel free to contact Wally Bartfay at (Home) or at 477-8059 (University of Manitoba).

Breakfast
Food items
-2 eggs scrambled prepared in cast iron frying pan
-2 whole wheat toasts with margarine
-1 slice of bacon
Beverages
-1 cup of coffee with 2% milk
-1 glass of orange juice

Lunch
Food items
-Ham sandwich with 1 slice of processed cheese, lettuce, mustard on whole wheat bread.
-4 soft oatmeal cookies, 1 apple and 1 orange
Beverages
-1 glass of coke

Supper
Food items
-2 chicken drum sticks baked with the skin on
-A toasted salad with lettuce, tomato, cucumber and 1000 island salad dressing
-2 baked potatoes with sour cream
-1 slice of whole wheat bread with margarine
Beverages
-2 glasses of coke

Snacks or additional beverages
-1 cup of coffee with cream and 1 jelly donut in the morning

Appendix D: Consent form

A study to determine the relationships between serum ferritin, gender, and exercise in Canadians of Icelandic decent
(a component of the Icelandic-Canadian Study)

I have been informed about the methods and procedures to be used in the study involving the relationships between serum ferritin, gender, and exercise in Canadians of Icelandic descent to my satisfaction. I understand that this component of the Icelandic-Canadian Study is an add on to Dr. Barbara Naimark's study, and that my name was obtained from her list.

I voluntarily agree to partake in this component of the Icelandic Canadian Study and I do so on the understanding that should I change my mind, I am free to discontinue my participation at any time without prejudice. I also understand that I will be asked to:

(1) answer questions related to my health and lifestyle on a questionnaire;
(2) keep a four day record of my diet, and
(3) have 10cc (ml) of blood drawn.

I understand that I may choose not to answer all the questions on the questionnaire if I so desire. I also understand that should I decide not to partake in this component of the study, I am free to continue and partake in Dr. Barbara Naimark's study.

I also understand that neither the researchers nor the institutions they represent are able to offer compensation for any discomfort, inconvenience or physical injury that I may incur.

Although the element of risk is minimal, I understand that mild discomfort or bruising may occur at the venipuncture sight used to obtain the blood samples.

If this study should lead to the identification of information which could influence my health or well being, I request that this information be sent to me at the address given below:

Signature: _____ **Date:**_____

Name: (Please print) _____ **Witness:** _____

Address: _____
_____
_____
_____

Wally J. Bartfay
(Home)
477-8059 (University of Manitoba)

Appendix E: Invitation to participate letter

The relationships between serum ferritin, gender and exercise in Canadians of Icelandic decent

You are invited to participate in a study designed to examine the relationships between serum ferritin (measures stored iron in the body), gender (male or female) and exercise (physical fitness level). While there are no immediate benefits to participation in this study, the information obtained will provide a better understanding of how these factors (serum ferritin, gender and exercise) effect each other, and possible their relationship to heart disease.

If you agree to participate in this study, you will be asked questions related to your health and lifestyle on a questionnaire, keep a four day record of your diet, and have 10 cc (ml) of blood drawn. You may experience mild discomfort or bruising at the sight (arm) where the blood will be taken from. However, only a single venipuncture (needle poke) will be required to obtain this sample.

You may decide not to participate and if you decide not to, it is perfectly acceptable for you to refuse. You may withdraw from the study at any time without influencing in any way the care that you may receive at St. Boniface General Hospital, or at the University of Manitoba. The questionnaires and values obtained (e.g. serum ferritin) will be kept in a locked cabinet accessible only to the researcher, the members of his research committee, and members of the Icelandic-Canadian research team.

The results will be published as a masters thesis and may be published in the form of a journal article. Your name will not appear on any published documents. A summary of the study results will be provided to those requesting it. If you have any questions or concerns that you would liked addressed, please feel free to contact Wally J. Bartfay at (Home) or at 474-8059 (University of Manitoba).

Thank-you for your cooperation.

Sincerely yours,

Wally J. Bartfay