Association of High w-6/w-3 Fatty Acid Ratio Diet with Causes of Death Due to Noncommunicable Diseases Among Urban Decedents in north India

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Abstract: Introduction: There is evidence that the Western type of diet has adverse effects, and prudent dietary patterns may have beneficial effects against deaths from cardiovascular and other chronic diseases. In the present study, we examine the association of dietary patterns with causes of deaths among urban decedents in north India.

Methods: Randomly selected records of death of 2222 (1385 men and 837 women) decedents, aged 25-64 years, were examined. Clinical data and causes of death were assessed by a questionnaire based on available hospital records and a modified WHO verbal autopsy questionnaire. Dietary intakes of the dead individuals were estimated by finding out the food intake of the spouse from 3-day dietary diaries and by asking probing questions about differences in food intake by the decedents.

Results: The score for intake of prudent foods was significantly greater and the ratio of w-6/w-3 fatty acids of the diet significantly lower for deaths due to ‘injury’ and accidental causes compared to deaths due to non-communicable diseases (NCD). Multivariate logistic regression analysis revealed that after adjustment for age, total prudent foods (OR, CI: 1.11; 1.06 - 1.18 men; 1.09; 1.04 - 1.16 women) as well as fruits, vegetables, legumes and nuts (1.07; 1.02 - 1.12 men; 1.05; 1.01 - 1.11 women) were independently, inversely associated whereas Western type foods (1.02; 0.95 - 1.09 men; 1.00; 0.94 - 1.06 women); meat and eggs (1.00 - 0.94 - 1.06 men; 0.98; 0.93 - 1.04 women) and refined carbohydrates (0.98; 0.91 - 1.05 men, 0.95; 0.89 - 1.02 women) and high w-6/w-3 ratio of fatty acids were positively associated with deaths due to NCDs.

Conclusions: Increased intake of high w-6/w-3 ratio Western type foods and decline in prudent foods intake may be a risk factor for deaths due to NCDs.

Keywords: Mortality, nutrition, disease, sudden death, stroke, infections, cancer.

INTRODUCTION

The United Nations, High-Level Meeting (UN HLM) was held on Non-communicable Diseases (NCDs) in September, 2011, in recognition of the global threat of these problems [1], mainly heart disease and stroke, cancer, diabetes, and chronic respiratory diseases. The meeting was attended by the world’s Heads of States and governments, creating a unique opportunity to advance globally the prevention and treatment of NCDs. Increased intake of energy characterized with dietary fatty acids; trans fat, w-6 fat, saturated fat and refined carbohydrates, in conjunction with physical inactivity and family history are important risk factors of obesity [1-6]. Western diet and lifestyle are known
to enhance the risk of NCDs; coronary artery disease (CAD), sudden cardiac death (SCD), hypertension, diabetes, insulin resistance, stroke and cancer [3-9]. The risk of death from cardiovascular diseases (CVD), diabetes and cancer increases when people become rich and obese which in part may be due to dietary alterations [2-9]. The present Western diet appears to be deficient in omega-3 fatty acids and a ratio of omega-6 to omega-3 of 15–50/1 has been observed among various populations, instead of 1/1 as is the case with wild animals and presumably human beings (Table 4) [8-13]. Omega-3 fatty acids may be alpha linolenic acid (ALA) which is rich in plant foods as well as eicosapentaenoic acid(EPA) and docosahexaenoic acid(DHA) found in fish and marine foods. Most children were given cod-liver oil before 1940s, as a source of vitamin A and vitamin D, which is rich in w-3 fatty acids. The consumption of cod-liver oil was drastically decreased, when these vitamins were available from synthetic source, contributing further to the decrease of EPA and DHA intake by the modern communities. Thus an absolute and relative increase of omega-6/omega-3 fatty acid ratio in the food supply of Western societies has occurred after 1910 with industrialization and urbanization. It is known that during evolution, omega-3 fatty acids were found in all foods consumed; meat, wild plants, eggs, fish, nuts and berries [8-10]. Experimental studies on wild animals confirm the original observations of previous researchers; Crawford et al., about the validity of high w-3 fatty acids in the evolutionary foods [11-13]. However, rapid dietary changes over short periods of time as have occurred over the past 100 years, is a totally new phenomenon in human evolution resulting in marked increase in the consumption of modern foods deficient in antioxidant nutrients, w-3 fatty acids and essential and non-essential amino acids [2-16] (Table 5).

Recently, dietary patterns have been proposed to be important in the pathogenesis of chronic diseases and all-cause mortality which appears to be due to proinflammatory effects of Western diet [8-17]. According to prospective cohort studies [18-24], dietary patterns consisting of high intakes of vegetables, fruits, legumes, fish, poultry, and whole grains, can be protective against mortality from cardiovascular and malignant diseases [11]. These findings are in parallel with the outcomes of several epidemiological studies, reporting inverse relationships between consumption of fruits and vegetables and the incidence of coronary artery disease (CAD) [17-24]. However, in these studies, the role of w-6/w-3 fatty acids has not been highlighted. The UN HLM concluded that NCDs are a global challenge which occur due to poverty as well as they also cause and entrench poverty, and are a threat to human, social, and economic development [1]. However, their approach to NCDs appears to be restrictive because only salt, tobacco, alcoholism, sedentary behavior and poverty are considered major risk factors, without any consideration of w-6/w-3 ratio of the fatty acids of diets and poor health promotion policies [1]. The burden of death and disability attributable to NCDs is rising in all lower and upper middle- and high-income countries, because of the rapid changes in the diet and lifestyle patterns [7, 15-24]. Millions of deaths occur every year due to poverty as suggested in UN HLM, which appear to be due to lack of health education and poor health policies adopted in these countries. The 36.1 million deaths per year as a result of NCDs represent almost two of three deaths per year worldwide [7]. Of these deaths, 22.4 million arise in the poorest countries, and 13.7 million in high-income and upper-middle-income countries. CVD are number one causes of death globally and are projected to remain the leading cause of death [7]. In the present study, we examined the association of high w-6/w-3 ratio of food consumption patterns with causes of death among urban decedents in north India.

**MATERIAL AND METHODS**

The population of the Moradabad city which is situated in north India, is 0.641 million residing in 306 streets or 60 wards based on the 2001 census. All the deaths that occurred in the city of Moradabad may be verified in the birth and death record section of municipal board office [25-27]. Religious considerations do not allow us to conduct autopsy to find out the exact causes of death. Therefore, records available at the Municipal Board might not be correct. These records are based on certificates issued by the doctors based on clinical diagnosis and laboratory examinations.

We studied the records of randomly selected, 2842 adult victims, aged 25-64 years, of which 2222 victim’s relatives, could respond for this study, during the last two years, July 1999 to July 2001 [25-27]. Of 2222 victims, 1385 were males and 837 were females. All the families of these 2222 victims were contacted individually to find out the causes of deaths by verbal autopsy questionnaire [25-27]. In developing countries due to religious considerations, autopsies are difficult and the causes of death are obtained by detailed questionnaires administered to spouse and the doctors involved. The head of every family was personally called after communication with the help of the local accessible doctor in the street. At least three calls, via letter/telephone and personal contact via lane doctor were made before any subject or family was declared a non-contact or non-responder; one in the morning, one in the evening, around 17.00 hrs. and the last one at the weekend.

The survey team included, a scientist, a health worker and a doctor, who were trained and briefed regarding the details of the questionnaire before starting the survey. The case record form was pre-tested by the concerned committee in roughly 30 to 60 families. It was found that 10% of the families who came within reach of survey were declared non-contact or non-responder as observed in another survey. Detailed interviews were possible among 90% of the families approached. Clinical data on age, sex, height, weight, marital status, occupation, education, past and family history, history of hypertension, diabetes, stroke, heart attack, kidney disease, liver disease, alcohol intake, drug intake, tobacco intake, lung tuberculosis, bronchitis, asthma, cancer, mental diseases, diabetes and syphilis, and brain, CVD, infectious diseases, malaria, dengue and accidents, etc, were recorded based on medical record of the victim, death certificate issued by the doctor, interview of the doctor and the family doctor, interview of the spouse and other family members, with the help of a pretested questionnaire, to know the cause of death. Family doctor or spouses of the victim were asked to suggest a person with identical age, sex, height and weight as that of the victim. In those medical records, in
which data on height and weight were not available, we collected these data from these matching subjects. Subjects were classified according to BMI into underweight (BMI <18.5), normal weight (18.5-22.9kg/m²), overweight (23-24.9 kg/m²), and obese (25-29.9kg/m²) and obesity (>30kg/m²) [26]. The socio-economic status (SES) of the family was classified based on attributes of housing condition, education, occupation, per capita income and ownership of consumer durables like car, television, automobiles, etc. in the household [27]. Per capita income was calculated by dividing the total income of the family, by the number of family members. The diagnosis of risk factors was based on available records, inquiry from the spouse and doctors involved.

Dietary Autopsy

Dietary intakes of the victim were obtained by trained interviewers by finding out the food intake of the spouse by using 3-day dietary diaries and filling of questionnaires, by asking probing questions about differences in food intake by the decedents. Food models, food measures and food portions were used by the dietitian to find out the exact food intakes of the victims. Nutrient intakes were calculated with the help of Indian food composition tables and other sources [28].

Dietary intakes were also assessed with the use of a validated food frequency questionnaire that includes approximately 62 foods and beverages commonly consumed in India [25-28]. Standard portion sizes were used for the estimation of consumed quantities, and nutrient were calculated by using a food composition database modified to accommodate the particularities of the Indian diet. For each participant, grams per day of intake of various food groups and nutrients, as well as total energy intake, were calculated.

For this analysis, we focused on nine nutritional variables: fruits, vegetables, legumes, and nuts, milk and curd, cereals, meat and eggs. Salt intakes were assessed by finding out the amount of salt mixed in the food divided by the number of family members and then adding salt consumed by each member during eating.

Indo-Mediterranean Diet Score

The traditional Indian diet is rich in legumes, seasonal vegetables, wheat and rice and it is enriched with seasonal vegetables, fruits and nuts, it may be called Indo-Mediterranean diet. The conformity of the traditional Indian diet was studied with a 10-unit scale. The scale relies on 8 dietary components that capture the essence of the traditional Indian diet. Fruits, vegetables, legumes and nuts, cereals, tubers, milk and curd and mustard oil that are presumed to be beneficial for health, whereas Western type foods, such as bread, meat and eggs and butter, clarified butter, w-6 rich oils, sugar and salt are presumed not to be beneficial. We assigned values of 0 or 1 to each of the above indicated components, using the sex-specific medians in the studied population as cut-offs. We assigned a value of 0 to people whose consumption was below the median values of components without a beneficial effect and a value of 0 to those whose consumption of these components was above the corresponding median. Thus, the total diet score can take values from 0 (minimal conformity to the Indo-Mediterranean diet) to 9 (maximal conformity to the Indo-Mediterranean diet).

STATISTICAL ANALYSIS

We used the chi-square test for the comparison of frequencies in the two groups. Only P values <0.05 and the two tailed t-test were considered significant to ascertain level of significance. A relation was determined between two measured quantities of food intakes and causes of deaths and the significance of any trend was calculated using Kendall’s τ rank correlation coefficient. It is used to test the strength of a relationship between the two measured quantities such as measured quantities of two different type of food intakes and causes of deaths. Simply it is a non-parametric hypothesis test that measures rank correlation that is similarly to the ordering of data when ranked by each of the quantities.

RESULTS

The results for sex and associated clinical data, based on the records and by verbal autopsy questionnaire, among 2222 victims (1385 males and 837 females), aged 25-64 years, dying due to various causes, are given in the Table 1. The mean age, (42.12** (13.02) vs. 40.05 (11.60), P<0.01) body mass index (23.18* (2.18) vs. 23.65 (2.46), P<0.05) and body weight (60.12** (6.24) vs. 53.10 (6.95), P<0.05) were significantly higher among men compared to women victims.

There was a high prevalence of sedentary behavior, alcohol and tobacco intake and obesity, among men compared to women (Table 1). Social classes 3-5 were comparable in the two sexes. The prevalence of underweight victims was 14.2% (n=315), overweight 29.4% (n=654) and obese 20.8% (n=461) as reported earlier [26].

Table 1. Prevalence of Risk Factors Among Patients Dying Due to Various Causes

<table>
<thead>
<tr>
<th>Risk Factors, n(%)</th>
<th>Male (n=1385)</th>
<th>Female (n=837)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (BMI&gt;25kg/m2)</td>
<td>277(20.0)</td>
<td>184(22.0)</td>
</tr>
<tr>
<td>Overweight (23-24.9kg/m2)</td>
<td>470(33.9)*</td>
<td>184(22.0)</td>
</tr>
<tr>
<td>Hypertension (&gt;140/90mmHg)</td>
<td>457(33.0)</td>
<td>251(30.0)</td>
</tr>
<tr>
<td>Diabetes mellitus (known)</td>
<td>110(8.0)</td>
<td>58(7.0)</td>
</tr>
<tr>
<td>Social class 3-5</td>
<td>774(55.9)</td>
<td>453(54.1)</td>
</tr>
<tr>
<td>Sedentary behavior</td>
<td>747(53.9)*</td>
<td>368(44.0)</td>
</tr>
<tr>
<td>Tobacco intake</td>
<td>623(45.0)**</td>
<td>125(15.0)</td>
</tr>
<tr>
<td>Salt intake (&gt;10g/day)</td>
<td>782(56.4)</td>
<td>491(58.6)</td>
</tr>
<tr>
<td>Alcoholism (&gt;20 drinks/week)</td>
<td>65(4.7)**</td>
<td>1(0.12)</td>
</tr>
</tbody>
</table>

*P <0.05,**P <0.001, P value were obtained by chi square test by comparison of frequencies in the two groups.
As given in Fig. (1), using the modified verbal autopsy questionnaire allowed us to diagnose 57.0% deaths due to NCDs, 25.5% due to communicable diseases and 17.6% due to injury and accidents among both sexes. Among NCDs, 21.2% (n=471) deaths occurred due to CVDs (CAD, sudden cardiac deaths, heart failure), 7.9% (n=175) due to stroke and 2.2% (n=49) due to diabetic vascular disease (Fig. 2). Thus majority of the deaths were due to vascular diseases (31.3%, n=695) (Fig. 3). Renal diseases including acute renal failure and chronic renal failure were the cause of death among 11.2%(n=250) of victims, cancers 5.9% (n=131), chronic lung disease 8.6% (n=192) and cirrhosis liver 1.2% (n=27) of the victims (Figs. 2,3). Using the modified questionnaires most of the victims could be classified relatively more accurately, into various causes of death according to body systems (Figs. 1,2 and 3).

Table 2 shows the food intakes in men and women. The consumption of prudent foods; cereals, fruits, vegetables, legumes and nuts as well as milk and curd were moderate in both the groups. Refined Western type foods; sugar, cola drinks, bread, biscuits, chocolates, cakes, refined cereals; corn flakes; clarified butter, butter, trans fat and w-6 rich oils, meat and eggs and salt were also common food items consumed by both sexes. Table 2 also shows the food intakes among victims who died due to various NCDs; malignant, circulatory, chronic lung diseases, renal diseases and diabetes and communicable diseases, compared to those who died due to injury and accidents. We found an overall decrease in the consumption of prudent foods and an increase in the Western type foods with high w-6/w-3 ratio of fatty acids, among victims who died due to circulatory, malignant, chronic lung diseases, renal diseases and diabetes and infective causes of death compared to injury and accidents among both men and women. The diet score also showed a significant decreasing trend in both sexes as shown in Table 2. The trend for food intakes and dietary score were significant as revealed by the Kendall’s τ (tau) test. Multivariate logistic regression analysis revealed that after adjustment for age, and body mass index, prudent foods and fruit, vegetable, legume and nuts intake were significantly inversely associated with deaths due to various diseases whereas Western type foods, meat and eggs and refined foods intake as well as high w-6/w-3 ratio of fatty acids were positively associated with causes of deaths due to non-communicable diseases (Table 3).

![Fig. (1). Prevalence of broad causes of deaths in north India.](image1)

![Fig. (2). Prevalence of causes of deaths in age 25-64 years, due to non-communicable diseases in north India.](image2)
This study shows that NCDs such as malignant, circulatory, chronic lung disease, renal disease and diabetes mellitus were common causes (57.0%) of death among both sexes (Figs. 1-3; Table 2). Infectious or communicable diseases were also the major causes of death among

**DISCUSSION**

**Table 2. Food Intakes and w-6/w-3 Fatty Acid Ratio of Diet in Relation to Causes of Death Based on Assessment by Dietary Diaries of the Spouse and Questionnaires Filled by the Nutritionist**

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>Prudent Diet</th>
<th>Western Type Diet</th>
<th>Total Foods</th>
<th>Score</th>
<th>w-6/w-3 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1385</td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury-accidents (n=215)</td>
<td>892±252</td>
<td>822±234</td>
<td>1094±302</td>
<td>7.93±2.8</td>
<td>31.3± 5.3</td>
</tr>
<tr>
<td>Communicable Diseases.(n=372)</td>
<td>806±237</td>
<td>736±237</td>
<td>1062±198</td>
<td>7.26±2.7</td>
<td>38.2± 6.6</td>
</tr>
<tr>
<td>NCDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant (n=77)</td>
<td>715±241</td>
<td>657±197</td>
<td>1127±311</td>
<td>6.44±2.5</td>
<td>42.2± 6.8</td>
</tr>
<tr>
<td>Circulatory (n= 406)</td>
<td>757±245</td>
<td>655±205</td>
<td>1194±318</td>
<td>6.81±2.6</td>
<td>45.3±8.3</td>
</tr>
<tr>
<td>Chronic lung diseases(97)</td>
<td>705±202</td>
<td>660±180</td>
<td>1110±302</td>
<td>6.25±2.2</td>
<td>42.0± 7.4</td>
</tr>
<tr>
<td>Kidney diseases (n=163)</td>
<td>617±188</td>
<td>565±155</td>
<td>1122±325</td>
<td>5.72±1.8</td>
<td>41.8±6.1</td>
</tr>
<tr>
<td>Diabetes (n=23)</td>
<td>605±175</td>
<td>553±146</td>
<td>1127±334</td>
<td>5.65±1.7</td>
<td>41.6±5.7</td>
</tr>
<tr>
<td>Kendall’s Γ</td>
<td>0.045*</td>
<td>0.041*</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=837</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury-accidents (n= 139)</td>
<td>822±234</td>
<td>186±23</td>
<td>1008±224</td>
<td>8.40±2.2</td>
<td>25.5± 5.7</td>
</tr>
<tr>
<td>Communicable diseases (n=194)</td>
<td>736±237</td>
<td>218±33</td>
<td>954±201</td>
<td>7.51±1.9</td>
<td>34.5±5.6</td>
</tr>
<tr>
<td>NCDs(n=502)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant (n=54)</td>
<td>657±197</td>
<td>305±35</td>
<td>962±221</td>
<td>6.70±1.8</td>
<td>41.6± 6.8</td>
</tr>
<tr>
<td>Circulatory (n= 240)</td>
<td>655±205</td>
<td>332±41</td>
<td>987±218</td>
<td>6.68±1.7</td>
<td>44.5±7.5</td>
</tr>
<tr>
<td>Chronic lung diseases(95)</td>
<td>660±180</td>
<td>382±48</td>
<td>1029±180</td>
<td>6.12±1.3</td>
<td>40.0±6.5</td>
</tr>
<tr>
<td>Renal diseases. (n=87)</td>
<td>565±155</td>
<td>380±130</td>
<td>995±165</td>
<td>5.57±1.1</td>
<td>39.7±6.8</td>
</tr>
<tr>
<td>Diabetes (n=26)</td>
<td>553±146</td>
<td>387±135</td>
<td>940±153</td>
<td>5.53±1.1</td>
<td>40.0±6.5</td>
</tr>
<tr>
<td>Kendall’s Γ</td>
<td>0.041*</td>
<td>0.067**</td>
<td>0.024</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number mean (Standard deviation), *=P<0.01,**=P<0.001.
intake, indicating inverse association as well as for intake of Western type foods, meat and eggs and refined foods, indicating positive association, were significant (Table 3). We can not compare our results with other studies because such verbal autopsy studies on dietary patterns and risk of death among victims are not available. However, large scales cohort studies such as Nurses’ Health Study [22, 23] based on data collected by questionnaires also confirm our findings about the role of Western diet and prudent diet in the pathogenesis of deaths due to NCDs. There is additional evidence showing ethnic differences in fatty acid concentrations in thrombocyte phospholipids, the ratios of omega-6/omega-3 fatty acids, and percentage of all deaths from cardiovascular disease in Japan and Europe and Greenland Eskimos indicating greater deaths in association with higher w-6/w-3 ratio of fatty acids [6,15].

Randomized, controlled intervention trials also confirm the role of high w-6/w-3 ratio Mediterranean style diet in the pathogenesis of CAD [29-36]. The effect of Paleolithic style diet was examined in patients (n=204 intervention group, n=202 control group) with acute coronary syndromes, which showed significant decline in total cardiac events as well as in total mortality after 6 weeks and the benefit continued after one year [29,30]. Further follow up for 2 years in this study [30] is different from the published work, because its emphasis is on the Paleolithic dietary patterns and ALA content of the diet to be responsible for the significant greater survival in the intervention group compared to control group. Dietary patterns before entry to the study showed higher w-6/w-3 ratio of 32.5 in the diets of both the groups. Intervention group A was advised a Paleolithic style diet with w-6/w-3 fatty acid ratio of 4.3 compared to standard diet group with ratio of 20. After a follow up of 2 years, total mortality was significantly declined in the Paleolithic style diet group compared to control group[30]. The mortality was lowest among subjects with w-6/w-3 ratio of less than 10 which showed graded increase with increase in the fatty acid ratio in both the groups. The Lyon Heart Study was a dietary intervention trial in which a modified diet of Crete (Mediterranean style diet) was compared with the prudent diet [31,32]. The experimental diet provided a w-6 to w-3 ratio of fatty acids of 4/1 in the diet. This ratio was achieved by substituting olive oil and canola (oil) margarine for corn oil. Since olive oil is low in w-6 whereas corn oil is high, 8% and 61% respectively, the w-3 incorporation into cell membranes was increased in the low w-6 diet. In this study, the ratio of 4/1 of w-6/w-3 led to a 70% decrease in total mortality at the end of two years [32]. It is possible that
decedents dying due to various causes. This observation is in agreement of UN HLM as well as WHO and World Bank [1,7]. These victims were consuming a diet characterized with high w-6/w-3 ratio of fatty acids (>40:1) with lower amount of prudent foods and greater amount of proatherogenic western type foods compared to food intakes among victims dying due to injury and accidents (Table 2). The odds ratios for consumption of high w-6/w-3 ratio of fatty acids rich prudent foods, fruit, vegetable, legume and nuts

Table 3. Multivariate Logistic Regression Analysis for Association of Food and Nutrient Intakes with Risk of Death from Non-communicable Diseases, after Adjustment of Age and Body Mass Index Among Men and Women

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prudent foods</td>
<td>1.11 (1.06-1.18)**</td>
<td>1.09 (1.04-1.16)**</td>
</tr>
<tr>
<td>FVL and nuts</td>
<td>1.07 (1.02-1.12)**</td>
<td>1.05 (0.99-1.11)**</td>
</tr>
<tr>
<td>Western type foods</td>
<td>1.02 (0.95-1.09)*</td>
<td>1.00 (0.94-1.06)*</td>
</tr>
<tr>
<td>Meat and eggs</td>
<td>1.00 (0.94-1.06)*</td>
<td>0.98 (0.93-1.04)*</td>
</tr>
<tr>
<td>Refined foods</td>
<td>0.98 (0.91-1.05)*</td>
<td>0.95 (0.89-1.02)*</td>
</tr>
<tr>
<td>w-6/w-3 fat ratio</td>
<td>1.12 (1.01-1.19)**</td>
<td>1.11 (1.00-1.18)**</td>
</tr>
</tbody>
</table>

*P value <0.01, ** <0.001. OR= Odds ratio. FVL= fruit, vegetable, legume.

Table 4. Omega-6: Omega-3 Ratios of Dietary Fatty Acids in Various Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>α6/α3</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleolithic</td>
<td>0.79</td>
<td>[2]</td>
</tr>
<tr>
<td>Greece prior to 1960</td>
<td>1.00-2.00</td>
<td>[16]</td>
</tr>
<tr>
<td>Current Japan</td>
<td>4.00</td>
<td>[16]</td>
</tr>
<tr>
<td>Current India, rural</td>
<td>5.61</td>
<td>[6]</td>
</tr>
<tr>
<td>Current United Kingdom and northern Europe</td>
<td>15.00</td>
<td>[16]</td>
</tr>
<tr>
<td>Current United States</td>
<td>16.74</td>
<td>[15]</td>
</tr>
<tr>
<td>Current India, Urban</td>
<td>38-50</td>
<td>[15]</td>
</tr>
</tbody>
</table>

Table 5. Ethnic Differences in Fatty Acid Levels in Thrombocytes Phospholipids and Percentage of All Deaths from Cardiovascular Disease

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Europe &amp; USA %</th>
<th>Japan%</th>
<th>Greenland Eskimos%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachidonic acid(20:4ω6)</td>
<td>26</td>
<td>21</td>
<td>8.3</td>
</tr>
<tr>
<td>Eicosapentaenoic acid(20:5ω-3)</td>
<td>0.5</td>
<td>1.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Ratio of ω-6/ω-3</td>
<td>50</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Mortality from cardiovascular disease</td>
<td>45</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Modified from Singh et al. 2011, their references [6,15].
olive oil increases the incorporation of omega-3 fatty acids whereas the w-6 fatty acids from corn oil competes [33]. Similar findings were observed by Singh et al., in the Indian experiments of infarct survival [34,35]. The Diet and Reinfarction Trial (DART) by Burr et al., reported a decrease in sudden death in the group that received fish advice or took fish oil supplements relative to the group that did not [36]. The GISSI Prevenzione Trial participants were on a traditional Italian diet plus 850–882 mg of omega-3 fatty acids at a ratio of 2/1 EPA to DHA [37]. The intervention group had a decrease in sudden cardiac death by 45%. Although there are no dietary data on total intake for omega-6 and omega-3 fatty acids, the difference in sudden death is most likely due to the increase of EPA and DHA and a decrease of arachidonic acid in cell membrane phospholipids. Prostaglandins derived from arachidonic acid are proarrhythmic, whereas the corresponding prostaglandins from EPA may be protective [8].

Singh et al., 2002, tested an ‘Indo-Mediterranean diet’ in 1000 patients in India, with existing coronary disease or at high risk for coronary disease [38]. Half of the patients (n=499 vs. 501) were administered a diet rich in fruits, vegetables, whole grains, nuts, mustard and soy bean oil as a source for w-3 fat and the rest viz. 501 patients were advised to take prudent diet advised by the National Cholesterol Education Program step 1 diet in 1988. At the end of 2 year follow up, the Paleolithic style diet group consumed significantly more fruits, vegetables and legumes than did the control group (537± 127 vs. 231±19 g/day, p<0.001) as well as more mustard and soy bean oil (31±6.5 vs. 15.2±5.5g/day). The mean intake of ALA was over two fold greater in the Paleolithic style diet group compared to control group.(1.8±0.4 vs. 0.8±0.2 g/day, p<0.001). The w-6/w-3 ratio of fatty acids calculated by Pella et al., was slightly higher at baseline in the intervention group than in the control group (39±12 vs. 34±10) yet both these values are extremely high, reflecting a diet with a very high w-6 content yet low w-3 [39]. At the end of two years follow up, this ratio showed a marked decline in the intervention group, which was greater than that observed in the control group consuming control diet (9.1 ± 12 vs. 21±10, p<0.001). The study end points were; significant decline in the total cardiac events, sudden cardiac death and non-fatal infarction in the intervention group compared to the control group. Except for the Lyon Heart Study, most of the cardiovascular disease omega-3 fatty acids supplementation trials did not attempt to modify the consumption of other fat components, and specifically did not seek to reduce the intake of omega-6 fatty acids despite the fact that there is convincing support for such studies. Yokoyama et al., investigated the effects of EPA on major coronary events in hypercholesterolemic patients in a randomized open label, blinded analysis [40]. Patients were randomly assigned to receive either 1800 mg of EPA with statin or statin only in a 5-year follow up. The results showed that EPA is a promising therapy for prevention of major coronary events, and especially nonfatal coronary events, in Japanese hypercholesterolemic patients. This is a very important finding because the Japanese already have a high fish intake. These findings further support the data from the study by Iso et al., that showed, compared with a modest fish intake of once a week or about 20 g/d, a higher intake was associated with substantially reduced risk of coronary heart disease, primarily nonfatal cardiac events, among middle-aged persons [41].

The role of balancing the w-6 to w-3 ratio of fatty acids was shown in a randomized, controlled, 3-diet, 3-period crossover study in which 22 hypercholesterolemic subjects were assigned to 3 experimental diets; a diet high in w-3 diet; (6.5% of energy) a diet high in w-6 (w-6, 12.6% of energy), and an average American diet for 6 weeks [42]. The results showed that on the w-3 diet, IL-6, IL 1β, and TNF-alpha production by peripheral blood mononuclear cells and serum TNF-alpha concentrations were lower (P<0.05 and P<0.08 respectively) than with the w-6 diet or American diet. The production of TNF-alpha by mononuclear cells was inversely correlated with w-3 (P = 0.07) and with eicosapentaenoic acid (P = 0.03) concentrations in mononuclear cells lipids with the w-3 diet. Changes in serum alpha linolenic acid(ALA) were inversely correlated with changes in TNF-alpha produced by mononuclear cells (P<0.05). In this study the increased intake of dietary w-3 elicited anti-inflammatory effects by inhibiting IL-6, IL-1β, and TNF-alpha production in cultured cells. Changes in mononuclear ALA and EPA derived from ALA are associated with beneficial changes in TNF-alpha release. The cardio-protective effects of ALA are mediated in part by a reduction in the production of inflammatory cytokines, IL-6, IL-1β, and TNF-alpha. Since Paschos et al., reported a decline in blood pressures by ALA [43], these results are important because they strongly suggest that the w-3 (ALA) intake at a ratio of 1–2/1which is simple to implement, is beneficial. Further studies in which the ratio of w-6/w-3 was not balanced, failed to decrease C-reactive protein or IL-6, IL-1β, or TNF-alpha leading to wrong conclusions that w-6 is not inflammatory [44]. Raheja et al., reported a higher ratio of w-6/w-3 fatty acid in the diet in India which was associated with type 2 diabetes [45]. In patients with rheumatoid arthritis, decrease in w-6/w-3 ratio was reported to cause beneficial effects [46]. In a further study by James and Cleland, the potential use of omega-3 fatty acids within a dietary framework of an omega-6/omega-3 ratio of 3–4/1 was studied, by supplying 4 g of EPA+DHA and using flaxseed oil rich in ALA [46]. In their studies, the addition of 4 gm EPA and DHA in the diet produced a substantial inhibition of production of IL-1β and TNF-alpha when mononuclear cell levels of EPA were equal or greater than 1.5% of total cell phospholipid fatty acids which correlated with a plasma phospholipid EPA level equal to or greater than 3.2%. The potential for complementarity between drug therapy and dietary choices appears to be clear from this study, that increased intake of omega-3 fatty acids and decreased intake of omega-6 fatty acids may lead to drug-sparing effects. It is possible that fat composition of the background diet, and the issue of concurrent drug use should be evaluated in further studies. A diet rich in omega-3 fatty acids and poor in omega-6 fatty acids provides the appropriate background biochemical environment in which drugs function and show their activity and ability.

Apart from cardiovascular diseases and diabetes mellitus which caused 31.3% (n=695) of deaths in our study, chronic lung disease including asthma were the cause of death among 8.6% (n=192) victims (Figs. 1-3). These victims were
consuming a high w-6/w-3 ratio of 41:1 diet. Asthma is a mediator-driven inflammatory process in the lungs and the leukotrienes and prostaglandins are implicated in the inflammatory cascade that occurs in asthmatic airways [47, 48]. Mast cells, macrophages, eosinophils, and lymphocytes are common cells involved in asthma. The leukotrienes are potent inducers of bronchospasm, airway edema, mucus secretion, and inflammatory cell migration, all of which are important to the asthmatic symptomatology. The inflammatory mediators include cytokines and growth factors (peptide mediators) as well as the eicosanoids, which are the products of arachidonic acid metabolism, which are important mediators in the underlying inflammatory mechanisms of asthma (Fig. 3). Broughton et al., [47] studied the effect of omega-3 fatty acids at a ratio of omega-6/omega-3 of 10/1 to 5/1 in an asthmatic population in ameliorating methacholine-induced respiratory distress. Methacholine-induced respiratory distress increased in presence of low w-3 fatty acids. However, increase in omega-3 fatty acid ingestion, was associated with increase in urinary 5-series leukotriene excretion, predicted treatment efficacy and a dose change in 40% of the test subjects (responders) whereas the non-responders had a further loss in respiratory capacity. A urinary ratio of 4-series to 5-series of <1 induced by omega-3 fatty acid ingestion may predict respiratory benefit. There is evidence of airway inflammation even in newly diagnosed asthma patients within 2–12 months after their first symptoms [48].

Our study shows that 5.9% (n=131) deaths were due to cancers (Figs. 2 & 3) and these victims were consuming high w-6/w-3 ratio of 42:1 diet. In a case-control study by Shannon et al., in China on the relationship between fatty acids and breast cancer, the results supported a positive effect of omega-3 fatty acids on breast cancer risk and provide additional evidence for the importance of evaluating the ratio of fatty acids when evaluating diet and breast cancer risk [18]. Bartram et al., [49] administered fish oil in order to suppress rectal epithelial cell proliferation and prostaglandin E2 (PGE2) biosynthesis. This was achieved when the dietary omega-6/omega-3 ratio was 2.5/1 but not with the same absolute level of fish oil intake and an omega-6/omega-3 ratio of 4/1. Recently, Maillard et al., reported their results on a case control study [50]. They determined omega-3 and omega-6 fatty acids in breast adipose tissue and relative risk of breast cancer. Fatty acid levels in breast adipose tissue reflect dietary intake of fatty acids and suggested a protective effect of omega-3 fatty acids on breast cancer risk and support the hypothesis that the balance between omega-3 and omega-6 fatty acids plays a role in breast cancer.

Osteoporosis represents a major challenge in bone and joint diseases, particularly with increases in the elderly population worldwide. Bone mineral accrual during childhood and adolescence plays a vital role in preventing deaths and disability due to osteoporosis in the later life. The identification of factors influencing peak bone mass are important for the prevention of osteoporosis and related fractures. Genetic factors are responsible for about 70% of the variance in bone mass [51] and the rest viz. 30% may be due to nutrition, physical activity, and body mass index [52]. Experimental studies have shown that dietary intake of long-chain w-3 fatty acids may influence both bone formation and bone resorption and an increase in periosteal bone formation [53]. Karikey et al., observed a higher dietary w-6/w-3 fatty acid ratio of the diet and higher levels of proinflammatory cytokines IL-6 and TNF-alpha with risk of osteoporosis and hip joint fracture [54].

The Rancho Bernardo Study by Weiss et al., [55] was carried out in 1532 community-dwelling men and women aged 45–90 years, between 1988 and 1992 on the association of dietary w-6/w-3 fatty acid ratio and bone mineral density. The average intake of total w-3 fatty acids was 1.3 g/d and the average ratio of total w-6/w-3 fatty acids was 8.4 in men and 7.9 in women. There was a significant inverse association between the ratio of dietary LA (w-6) to ALA (w-3) and bone mineral density (BMD) at the hip in 642 men, 564 women not using hormone therapy, and 326 women using hormone therapy. Age, body mass index, and lifestyle factors and increasing ratio of total dietary w-6/w-3 fatty acids was also significant and independently associated with lower BMD at the hip in all women and at the spine in women not using hormone therapy. It is possible that the relative amounts of dietary omega-6 and omega-3 fatty acids may play a vital role in preserving skeletal integrity of old age. In a cohort study by Hogstrom et al., [56], the aim of the 8-year study was to investigate a possible role of fatty acids in bone accumulation and the attainment of peak bone mass in young post-pubertal males. This study is the first to examine the association between individual PUFAs, BMD, and bone mineral accrual. BMD of the total body measured at 22 years of age showed a significant negative correlation with serum oleic acid and mono-unsaturated fatty acids and a significant positive correlation with DHA and omega-3 fatty acids. BMD of the spine showed a positive association with DHA and omega-3 fatty acids. Changes in BMD of the spine between 16 and 22 years of age showed a positive association with DHA and w-3 fatty acids, and a negative association with the w-6/w-3 ratio [56]. The study adds to the growing body of evidence that omega-3 fatty acids are beneficial to bone health. Animal models have suggested that omega-3 fatty acids may attenuate postmenopausal bone loss.

Inflammation of the lacrimal gland, the meibomian gland, and the ocular surface plays a significant role in dry eye syndrome (DES) [57]. Increased concentrations of inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha have been found in tear film in patients with DES [57]. In the Women’s Health Study [58] by Miljanovic et al., a higher ratio of w-6/w-3 consumption was associated with a significantly increased risk of DES (OR: 2.51; 95% CI: 1.13, 5.58) for 15:1 versus <4:1 (P for trend = 0.01). A higher dietary intake of w-3 fatty acids is associated with a decreased incidence of DES in women and a high w-6/w-3 ratio is associated with a greater risk. After 65 years of age, age-related macular degeneration (AMD) is the leading cause of vision loss. Both AMD and cardiovascular disease share similar modifiable factors [59]. Fish intake has been reported to have protective properties in lowering the risk of AMD, especially when LA intake was low [60]. In a study involving twins, Seddon et al., showed that fish consumption and omega-3 fatty acid intake reduce the risk of AMD whereas cigarette smoking increases the risk for AMD [61].
Psychological stress appears to be associated with an imbalance of w-6 and w-3 PUFA in the peripheral blood causing, an overproduction of proinflammatory cytokines interferon gamma and TNF-alpha, IL-6 and IL-1. There is evidence that changes in fatty acid composition are involved in the pathophysiology of major depression and suicides among patients with depression [62]. Changes in serotonin (5-HT) receptor number and function caused by changes in PUFA provide the theoretical rationale connecting fatty acids with the current receptor and neurotransmitter theories of depression [63-65].

The increased C20:46/C20:53 ratios and the imbalance in the w-6/w-3 PUFA ratio in major depression may be related to the increased production of proinflammatory cytokines and eicosanoids in that illness [64]. There are a number of studies evaluating the therapeutic effect of EPA and DHA in major depression. Kiecolt-Glaser et al., studied depressive symptoms, w-6/w-3 fatty acid ratio and inflammation in older adults [66]. As the dietary ratio of w-6/w-3 increased, the depressive symptoms, TNF-alpha, IL-6, and IL-6 soluble receptor (sIL-6r) increased.

Fig. (4) shows the association of high w-6/w-3 ratio of the diets with various causes of death in our study indicating higher death rates due to NCDs with increase in ratio compared to lowest ratio among decedents dying due to injury and accidents. The causes of deaths due to injury and accidents also included deaths due to suicides and depression and, osteoporotic hip joint fractures which need further analysis to emphasize the role of high w-6/w-3 ratio diet in the pathogenesis of these NCDs.

In brief, it is possible that w-3 fatty acids play an important role in health and disease and favorably affect cardiovascular function, beta cell function, skeletal and neuronal growth. The attainment of peak bone mass in adolescence and the prevention of age-related macular degeneration are potential positive effects of omega-3 fatty acids [67-74]. High w-6/w-3 fatty acid ratio appears to be important in the pathogenesis of other NCDs. The findings in our study indicate that low w-6/w-3 fatty acid ratio, Indo-Mediterranean dietary patterns may be inversely associated and a Western type foods intake, are significant predictors of deaths due to circulatory diseases and other chronic diseases. Larger studies are necessary to confirm our findings.

RESPONSIBILITIES

Study design, questionnaire, writing of manuscript by RBS, collection of data by VS, SKK, RBS. Others experts; VM, DP, SS helped in the analysis of data and other authors in the writing of manuscript, calculations, review of references and editing.

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CONFLICT OF INTEREST

Declared none.

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