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β-casein A^1, ischaemic heart disease mortality, and other illnesses

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Summary The risk factors identified with cardiovascular disease studied in the WHO MONICA project have been shown to have a limited relationship with the coronary heart disease mortality rates between centres, and in mirroring the historical rise and decline in deaths from the disease. Here we show that correlation of the calculated consumption of the milk protein, β-casein A^1 (excluding milk protein in cheese) against ischaemic heart disease (IHD) mortality has a $r^2 = 0.86$. In the states of the former West Germany, where the breed composition of regional cattle herds has remained virtually constant since the 1950s, IHD mortality by state correlates with the estimated consumption of β-casein A^1. Information on other recognized dietary risk factors does not indicate any significant regional difference. Similarly, the populations of Toulouse in France and Belfast in Northern Ireland have almost identical collective 'traditional' risk factors for heart disease, yet the respective mortality rates vary more than threefold. People from Northern Ireland are estimated to consume 3.23 times more β-casein A^1, excluding cheese, than the French. The remarkable agreement between mortality and the consumption of this allele suggests that this factor is worthy of serious consideration as a potential source of cardiovascular disease when taken in conjunction with regional variations in the traditional risk factors. β-casein A^1 consumption also correlates strongly with type 1 diabetes incidence in 0–14-year-olds, suggesting that IHD and diabetes may share at least one causative risk factor. © 2001 Harcourt Publishers Ltd

INTRODUCTION

The results of the World Health Organization (WHO) MONitoring in Cardiovascular Diseases Survey of the classically accepted risk factors identified with cardiovascular disease, and their changes with time, have recently been reported (1). In males, the changes in the combined risk factors were found to account for about 40% of event rates while in females they accounted for only 15%. These changes did not reflect the historical rise and fall of disease mortality in any community studied.

The consumption of milk proteins has not been considered as a risk factor in the MONICA or other major studies. However, some researchers have proposed that milk is a potential contributor to coronary heart disease (CHD). These proposals are based on the apparent relationship between milk consumption and CHD mortality across countries (2), from comparisons of the levels of antibodies to milk protein in cases of CHD and non-affected controls (3), and by direct comparison of milk consumption within communities (4,5). In the 1950s and 1960s, milk was used as a major dietary component in both experimental and standard medical treatments for stomach ulcers. These experiments and the treatment regimens were discontinued when pathologists observed that there was a significant increase in cardiovascular mortality amongst participants (6). However, there are communities for whom bovine milk (Masai (7), Samburu (8) and rural Gambians (9)) or goat and yak milk (Tibetan highlanders (10,11)) is an important dietary component and amongst whom there is little or no CHD.

Such comparative data have stimulated an investigation of the possible relationship between the intake of specific

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milk components and the incidence of CHD. Preliminary analyses lead to a focus on the consumption of the β-caseins as a risk factor in CHD. This paper summarizes an extensive series of analyses and then develops the hypothesis that the consumption of a particular variant of β-casein, namely β-casein A^1, is a specific risk factor for CHD.

BACKGROUND

Bovine milk proteins

There are six major proteins (12) in bovine milk, four caseins and two whey proteins. Approximately 80% of bovine milk protein consists of caseins, whereas the two major whey proteins constitute about 14% (13,14). The milk proteins are characterized by considerable genetic (allelic) variation (Table 1) (15–17).

In most cows, the β–casein alleles present are either A^1, A^2, or B, with the other alleles being relatively rare (one allele being contributed by each parent). β-casein A^1 differs from the progenitor A^2 allele in that in position *67* of the A^2 molecule a proline has been replaced by a histidine (due to an adenosine–cytosine change in the codon specifying position *67*). β-casein B differs from A^2 in having a proline in position *67* and an arginine in place of a serine at position 122. β-casein A^1 allele frequencies in various milking breeds vary from ~0–0.09 to 0.6–0.7.

The New Zealand Dairy Research Institute and the NZ Child Health Foundation have filed a patent claiming that consumption of β–casein A^1 and other alleles with a histidine substitution of proline in position *67* will cause diabetes in susceptible children (18). Elliott and others have also published an inter-country correlation of β-casein A^1 and β-casein (A^1 + B) consumption (19).

The analyses reported in this paper required estimates of milk product intake for the populations of particular countries or regions and of the composition of the milk products consumed by such populations. Therefore the methods used to derive these data are of critical importance and are outlined below.

In this study, a standard model of national dairy herds has been constructed and consumption of the major milk proteins has been calculated based on published breed milk phenotype data and published milk protein consumption data.

Table 1 Allelic variation in milk proteins

α_{s1}-casein	A, B, C, D, F
α_{s2}-casein	A, D
β-casein	A^1, A^2, A^3, B, C, E
κ-casein	A, B, C, E
α-lactoglobulin	A, B
β-lactoglobulin	A, B, C, D, H, W, X

Milk protein phenotype data

Data measured in each country for its particular breeds of dairy cows have been used. Where more than one set of data existed, the average value was determined. In some instances, such as the UK, the data for UK Friesians was determined from measurements on limited numbers of animals. In the case of NZ, no genetic polymorphism data was available in 1980, therefore Australian measurements were used. There was considerable interchange of genetic material between NZ and Australia up until the 1970s, with very limited introduction of new material, except from the UK. Calculations for Ireland were based on the Aschaffenburg UK measurements. In the case of Israel, US phenotype data were used.

The values used for the composition of milk were: lactoglobulins 3.7%, α-caseins 30.6%, β-caseins 30.9% and κ–caseins 10.1% of the total milk proteins (12-13).

Dairy protein consumption

Dairy protein consumption data was taken from the Food and Agricultural Organization (FAO) Food Balance Sheets, for 1979–81. Comparison of the 1984 publication, the 1991 revision, and the current on-line FAO database (all reporting on the 1979–81 period) revealed some major discrepancies. For the analysis, the mean figure from the two most recent data sets was taken. The FAO mean figure was then compared with data published by the International Dairy Federation (IDF) for the same period. Where a significant discrepancy existed between the two sets of data, the appropriate national department (i.e. Health, Nutrition or Statistics) for that country was consulted. The data used are set out in Table 4.

Coronary heart disease data

This analysis makes use of the IHD (410–412) mortality data reported by Uemura and Pisa (20), which have been age-standardized to a central European population for 1985 for 30–69-year-old males, and the 1990 IHD, ICD 9 (410–414), data from a WHO 1995 report on cardiovascular disease in the elderly (21). The UK IHD data is a population weighed average of the reported values for England and Wales, Scotland and Northern Ireland.

The analyses also require an estimate of the lag phase between the timing of an event such as IHD and the exposure to the risk factor in question. Therefore the time interval of 5 years was chosen after examination of the Norwegian World War II responses to changes in food consumption and IHD patterns (22). A response time of 5 years has been taken in other studies (23,24), as has 10 years (25). Thus the analysis covers both a 5-year interval in the case of the 1985 IHD data and a 10-year interval with respect to the 1990 data.

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Diabetes mellitus data

The data chosen were taken from estimates of the incidence rate in 1980 (26) and two more recent international surveys (27,28). These are set out below. In the case of New Zealand, white incidence data have been chosen. The USA data used likewise include whites only. Canadian data were also not included because of the wide divergence in the two reported incidence measurements, Montreal and St Johns, Halifax. The reasons for this difference in the two communities have not been established (29). Data for Switzerland were included in its place. No weighting was made for years of consumption of milk as was carried out by Elliott et al. No compelling data have been published to prove that there is any relationship between length of exposure to a dietary antigen, or milk in particular, and the subsequent development of IDDM.

Data interpretation

The relationship between the mortality rate from IHD for males aged 30–*69* years and the consumption of milk protein and milk protein components was calculated. In Figure 1, estimated daily consumption of milk protein is plotted against IHD death rates for 30–*69* year males. There is a weak correlation:

$$\text{IHD rate} = 7.24x + 75 \qquad (r^2 = 0.26); \qquad (1)$$

where x is the consumption of total milk protein in g/d.

In Figure 2, daily consumption of β-casein A^1, in grams, is shown as a function of IHD death rates for the same countries. There is a strong correlation:

$$\text{IHD rate} = 78.8b + 6.6 \qquad (r^2 = 0.71); \qquad (2)$$

where b = casein A^1 in g/d.

In Figure 3, β-casein A^1 (excluding cheese) is plotted against IHD. The following correlation was obtained:

$$\text{IHD rate} = 98.4b + 22.6 \qquad (r^2 = 0.86) \qquad (3)$$

The rationale behind the exclusion of cheese is discussed later. Thus excluding the β–casein A^1 intake from cheese resulted in a significantly better `fit' (increase in the r^2 value). The pattern of cheese consumption varies between countries such that cheese is a major contributor to milk protein intake in France and Switzerland (58–40%) but a smaller contributor in the UK or the USA (~25%).

A plot of IHD death rates for males aged 30–*69* versus β-casein (A^1 + B), excluding cheese gave the following correlation:

$$\text{IHD rate} = 101.2b - 8.87 \qquad (r^2 = 0.84) \qquad (4)$$

In Figures 4 and 5, WHO 1990 IHD death rate data for over *65* year males and females are presented, against A^1 consumption (excluding cheese). The respective results were:

$$\text{IHD death rate(males)} = 598\beta + 371 \qquad (r2 = 0.84)$$
$$\text{females} = 305\beta + 272 \qquad (r2 = 0.73)$$

Correlation of the lactoglobulins and other caseins with IHD mortality gave r^2 values varying from 0.44 to 0.0. Consumption of β-casein A^1 was also correlated against common risk factors in food using data from the FAO 1979–81 Food Balance Sheets. The following values of r^2 were obtained: animal fats 0.26; red meats 0.11. Comparison of the equations are revealing and suggest that the consumption of β-casein A^1 may be a specific risk factor for death from IHD (increase in r^2 from 0.26 to 0.71, $P < 0.01$) (30). In contrast, the commonly cited risk factors (animal fats and red meat) exhibited relatively poor regression relationships.

A multivariate analysis of IHD mortality rates, β-casein A^1 consumption, and traditional MONICA risk factors for 11

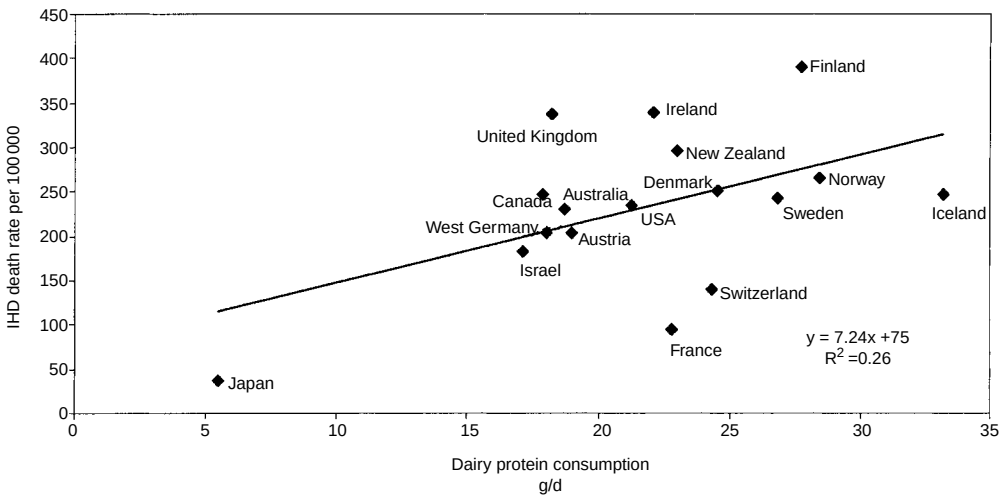

Fig. 1 Dairy protein in consumption and IHD death rate (1985) in males aged 30–69.

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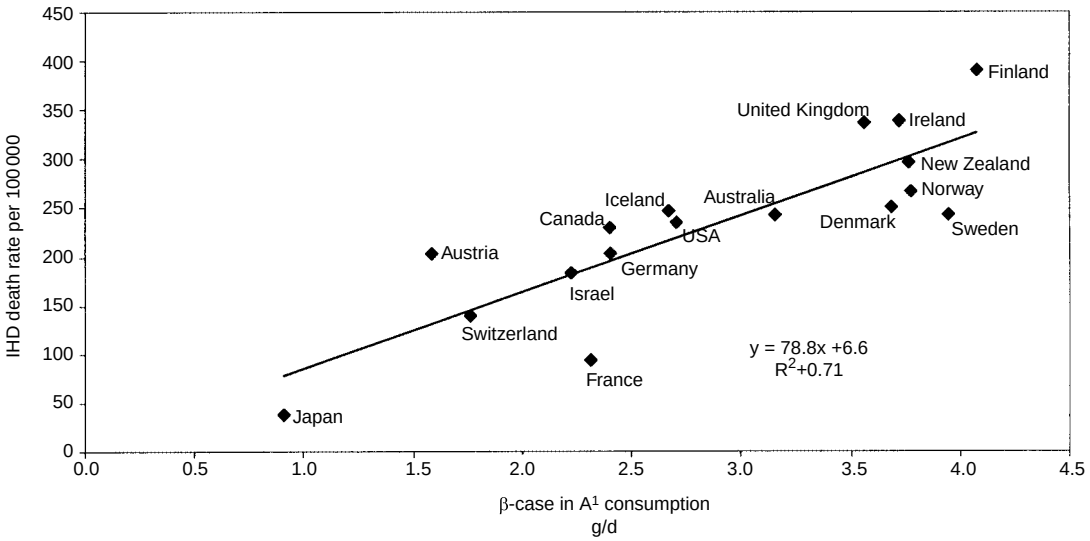

Fig. 2 β-casein A¹ consumption and IHD death rate (1985) in males aged 30–69.

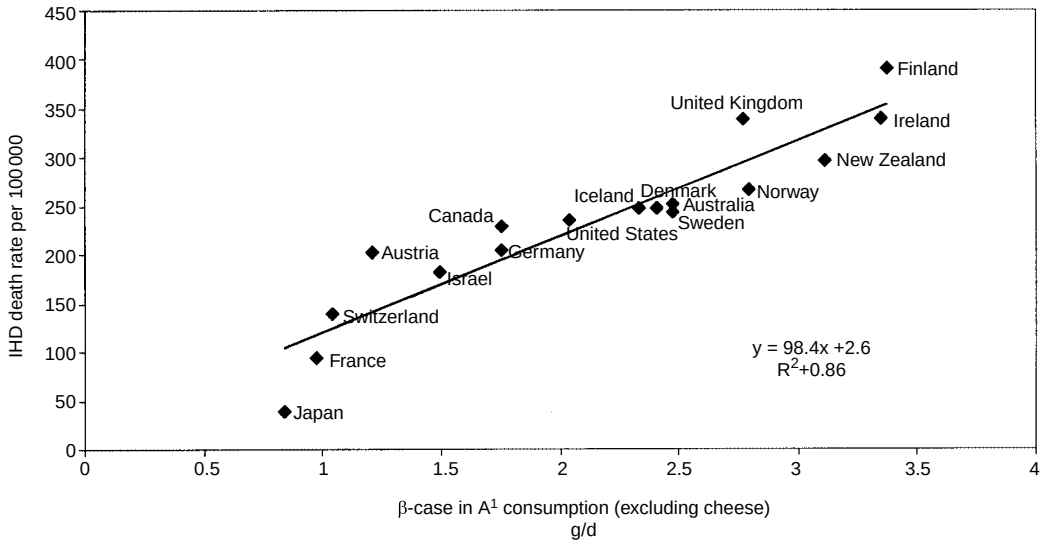

Fig. 3 β-casein A¹ consumption (excluding cheese) and IHD death rate (1985) in males aged 30–69.

countries (Australia, Denmark, England, Finland, France, New Zealand, Northern Ireland, Sweden, Switzerland, West Germany, USA), for 1982–83, was also carried out. The factors included: current smokers; hypertensives (number); body mass index; and serum cholesterol level. The combination of β-casein A¹ consumption and smoking produced the best fit for the data with a R^2 value of 0.78 and a standard error of 53.94. All other combinations with the same correlation coefficient had a greater standard error.

Regional data: West Germany

Regional variations in β-casein A¹ consumption may be estimated in West Germany where cattle breed distribution data by state has been recorded since the 1950s. During the period 1951–1965, dairy cattle breed distribution remained constant (31). During the period 1973–1984, the distribution of the major breeds also remained virtually constant with the German Friesian increasing from 39.9% to 42.0% (32). The daily consumption of the β-casein A¹ allele was calculated using 1965 breed distributions and the FAO consumption data. Herd data were not available for the period 1966–1977. In carrying out the analysis, it has been assumed that the consumption of milk is constant throughout Germany and local production is confined to each state. A dietary survey of 50 000 households was completed in FRG in 1973 as part of a regional cancer survey (33). This found little variation in consumption between states of a wide range of food components.

Greiser et al. have published coronary heart disease distribution data for West Germany as a whole for 1977–79 (34). Comparison of this data with the regional nutritional data shows no relationship between food

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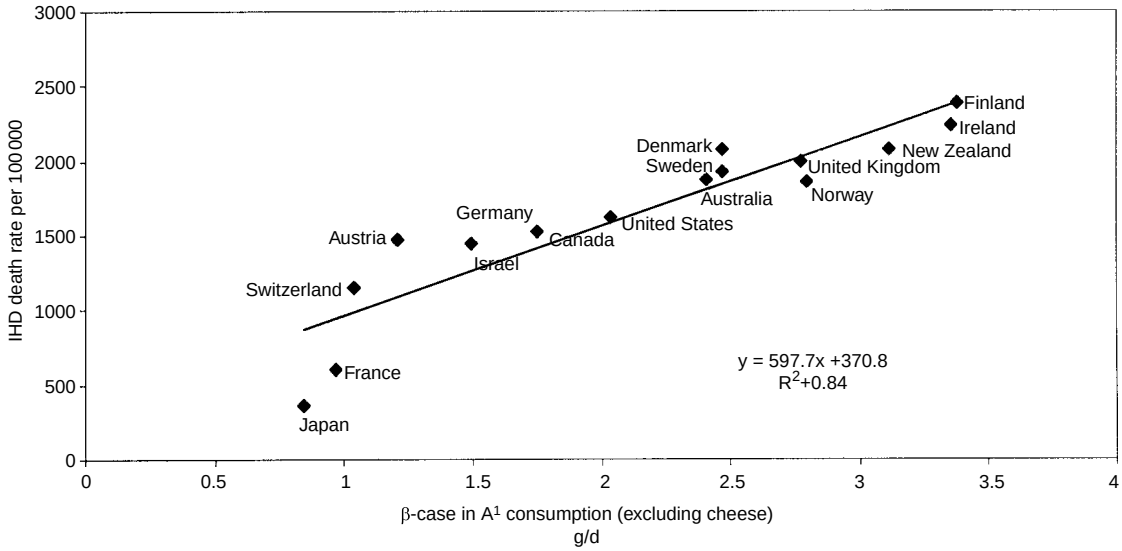

Fig. 4 β-case in A¹ consumption (excluding cheese) and IHD death rate (1990) in males aged 65 and over.

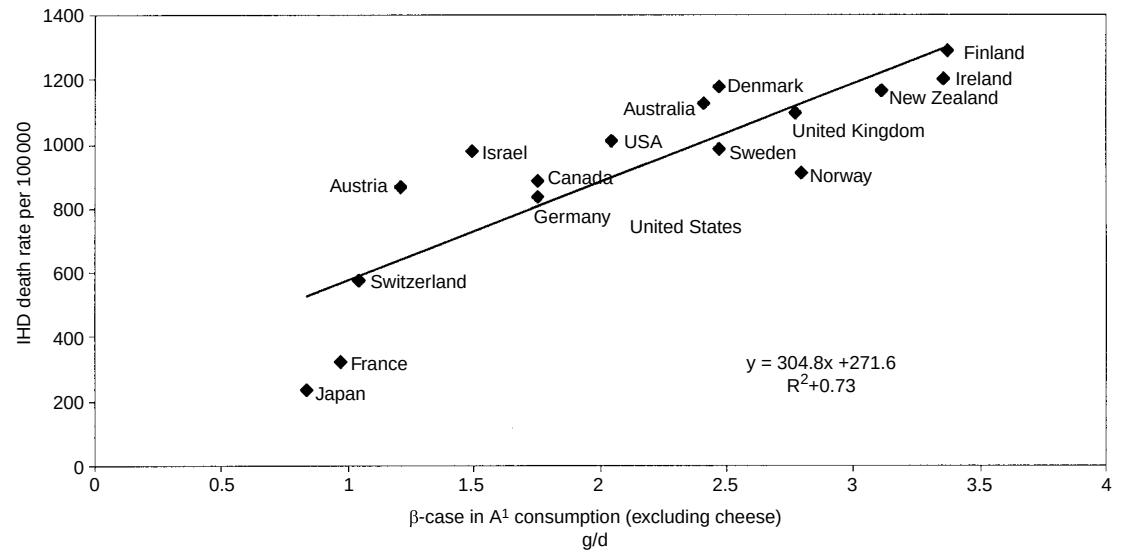

Fig. 5 β-case in A¹ consumption (excluding cheese) and IHD death rate (1990) in females aged 65 and over.

component consumption and the 1.4-fold variation in IHD between states. When smoking was correlated against IHD, Greiser et al. obtained a r^2 value of 0.22 for men and 0.01 for women for the 30 administrative counties of West Germany.

The relative variations in food components that have been associated with IHD together with β-casein A¹ consumption are set out below. The regression relationship between estimated IHD mortality for males all ages and the consumption of β-casein A¹ (1965 consumption data, g/d), (Fig. 6), was:

IHD males, all ages = 70.0β + 176 ($r^2 = 0.66$)

Austria vs West Germany

In Figure 2 Austrian β–casein A¹ data is an outlier. A major reason appears to lie with the definition of IHD used by the Austrians and the changes introduced between International Classification of Diseases, ICD, revisions 7 and 8. Set out below are the relevant ICD 7 and 8 WHO annual statistics for Austria's near neighbours (Table 3).

It appears that Austria and France IHD classifications may not be strictly comparable with Switzerland and Germany. According to the β-casein A¹ estimates, we could have expected Austria to have a CHD rate similar

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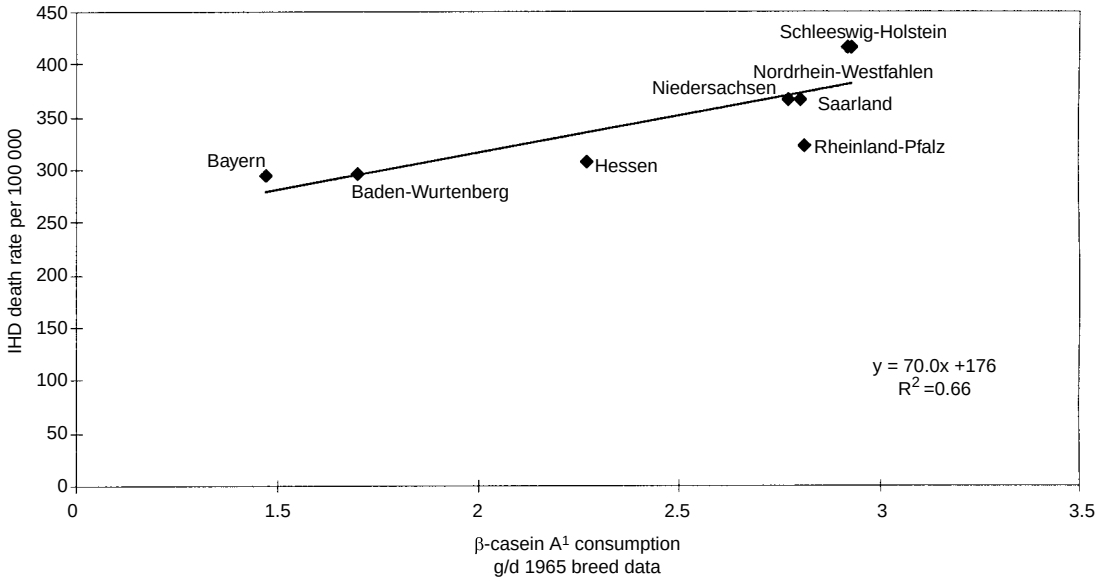

Fig. 6 β-casein A¹ consumption and IHD death rate, West Germany (1977–79) in males of all ages.

Table 2 Food consumption by state, as % of average consumption in the FRG, 1973

	Males					
	Animal Fat %	Cholesterol %	Alcohol %	Protein %	b-A¹est. g/d	IHD est. /100,000
Schleswig Holstein	103	100	96	98	2.92	416
Niedersachsen	100	96	98	96	2.80	367
Nordrhein Westfalen	102	102	95	101	2.93	416
Saarland	97	93	94	96	2.77	367
Hessen	98	96	94	97	2.27	308
Rheinland-Pfalz	98	99	96	98	2.81	322
Baden Wurttenburg	96	102	98	101	1.70	297
Bayern	99	99	117	102	1.47	295

Table 3 ICD (7–8) heart disease classification changes, 1967, 1969

Males all ages CHD/IHD deaths per 100 000					
Code	Year	Austria	Germany	Switzerland	France
A81	1966	259.3	258.1	230.8	93.2
A81	1967	276.3	262.3	234.5	94.6
A83	1969	242.0	201.5	135.5	95.1
A83	1971	254.4	224.9	140.6	99.8
%diff.	67/69	−12.0	−23.0	−42.0	+0.53

to Bayern and Switzerland. Based on the intake of β–casein A¹, excluding cheese, the predicted IHD mortality rate in West Germany should be ~1.38–1.45 times that of Austria, according to Equation 3, or the direct ratio of β-casein A¹ consumption. A direct comparison of IHD values may be obscured by the apparently different A83/A81 standards in use in the two countries. The actual ratios of the standardized data (35) for diseases of the circulatory system (B24–B28 and A80, A81, A83, and A84) for males aged 35–64 for the two countries in the periods 1955–1959, 1960–64, 1965–69, 1970–73 were 1.27, 1.43, 1.60 and 1.47, with an average value of 1.44.

France vs Northern Ireland

The Northern Ireland and the French MONICA centres have collaborated in dietary studies to investigate the relationship of classical risk factors to IHD incidence and mortality rates under a research programme entitled PRIME. These studies confirm that the disease mortality in middle-aged men is between three and four times as common in Belfast as Toulouse (36). Based on the MONICA event registration, cardiovascular event rates are 2.3–2.5 times more frequent in Belfast than in Lille or Strasbourg and 3.3 times more frequent in Belfast compared to Toulouse (37). The corresponding multivariate risk factor analysis, however, found the overall conventional risk factors for both centres were virtually identical. A weighed dietary survey revealed no important differences in macronutrient intake between Belfast and Toulouse. Saturated fat intake was significantly higher in

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Belfast and dietary cholesterol was significantly higher in Toulouse.

The corresponding β-casein A^1 consumption ratio, excluding cheese, is set out below together with the heart disease mortality data for 1985–1987 for Belfast and Toulouse.

Northern Ireland/France β-casein A^1 consumption ratio	3.23: 1
Cardiovascular–stroke mortality ratio males 45–54 years	3.44: 1
Cardiovascular–stroke mortality ratio males 55–64 years	3.33: 1

The data compared were (ICD 410–414 + 390–459), excluding stroke (ICD 430–438). The corresponding ratio for diseases of the circulatory system, including stroke, are 2.93 and 3.11 respectively. Based on equation 3 the IHD ratio between the two communities should be 2.81. If one uses equation 4, including both β-casein A^1 and β-casein B, the following ratio is obtained:

Northern Ireland/France β-casein (A^1 + B) consumption ratio 2.49: 1

Unfortunately, there is insufficient variation in the small amount of β-casein B in milk for its contribution to be confirmed or rejected. IHD data was not directly compared because of similar ICD (7–8) IHD definition concerns raised with Austria.

Prediction of the Icelandic allele frequency

The amount of β-casein A^1 in the Icelandic milk was calculated based on their IHD mortality rate and the inter-country correlation, prior to the measurement of Iceland phenotype data. Based on the cheese-free data the corresponding allele frequency was 0.25. β-casein A^1 allele frequencies were found to be 0.28 in the south, and 0.24 in the west of Iceland (38).

Netherlands

β-casein A^1 for the Netherlands have not been included in the analysis. Using the polymorphism data of Bovenhuis (39) (Dutch Friesian, β-casein A^1 allele frequency 0.77), the quantity of β-casein A^1 consumed by the Dutch is 6.39 g/d. This is significantly more than any other country. All the black and white cattle surrounding the Netherlands have much lower β-casein A^1 allele frequency, German 0.54, Danish 0.55. It is understood that the analytical technique used in the Netherlands measurements has difficulty in distinguishing between β-casein A^1 and β-casein A^2. This may have given rise to the higher than expected values for the Dutch milk. The Netherlands also imports significant quantities of milk and milk proteins.

Diabetes data

The best correlation was obtained using β-casein A^1 data associated with total milk protein consumption, r^2 = 0.73 (Fig. 7). When cheese consumption was excluded, r^2 = 0.72. Most dietary studies indicate that children consume less cheese than adults. Inclusion of the B allele together with A^1 provided a poorer fit in both cases, contrary to the findings of Elliot et al. Total milk protein correlated against IDDM incidence gave a value of $r^2 = 0.23$.

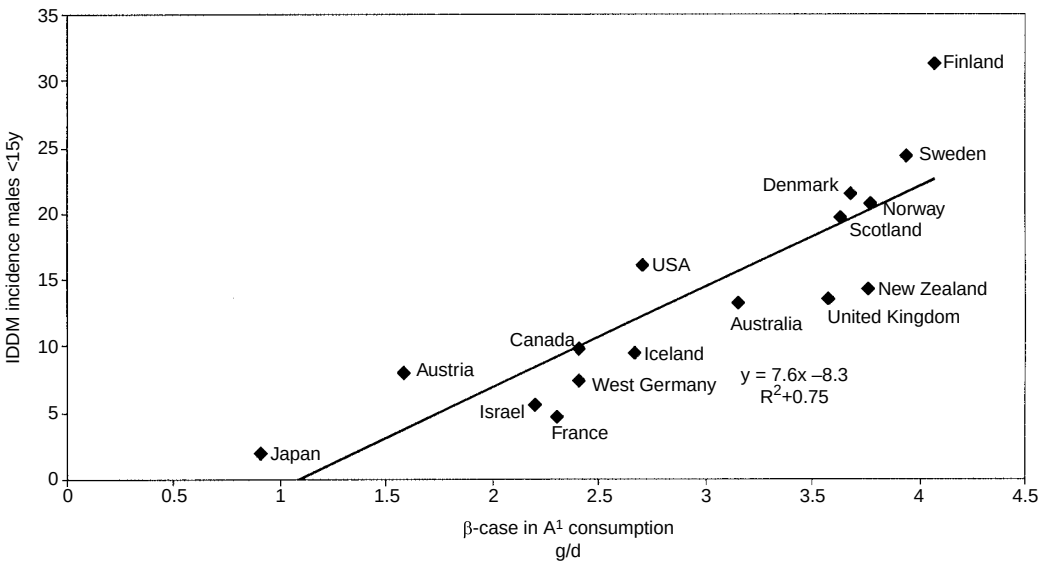

Fig. 7 β-case in A^1 consumption and IDDM incidence data <15y males

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Is β-casein A¹ consumption related to coronary mortality and other illnesses?

There are well-recorded inherent problems present in between-country and regional surveys of disease incidence, or mortality and the identification of causality factors. However, the regression relationships (correlation data) presented here are sufficiently strong that one may postulate that β-casein A¹, or possibly a fragment of the allele, may be a significant contributor to the aetiology of cardiovascular disease. Experimental evidence provides support for the relationship. Casein consumption has been found to cause hypercholesterolaemia, or atherosclerosis, in numerous animal studies including rabbits, pigs, monkeys and rodents (see reviews 40,41,42). Apolipoprotein E-deficient mice are currently regarded as one of the most appropriate models of human atherosclerosis because they develop severe hypercholesterolaemia and atherosclerotic lesions that are similar in distribution and appearance to those observed in humans (43,44). Apolipoprotein E-deficient mice were found to develop significantly more atherosclerotic lesions when fed casein rather than soy protein isolate, with or without the presence of added cholesterol in the diet (45). There was no difference in total serum cholesterol concentration, or homocysteine, between the groups.

In humans, low density lipoprotein (LDL) oxidation is considered to be a primary step in the evolution of arteriosclerotic damage (46). Analysis of protein oxidation products isolated from atherosclerotic lesions implicates the tyrosyl radical, reactive nitrogen species, and hypochlorus acid in LDL oxidation (47). Torreilles and Guerin (48) found that peptides from bovine casein hydrolysates could promote peroxidase-dependent oxidation of human LDLs. The reaction was independent of the free metal ions but required casein-derived peptides with tyrosyl-end residues, implying that the tyrosyl ending peptide is a diffusible catalyst that conveys oxidizing potential from the active site of the haem enzyme to LDL lipids. Casomorphin-7 is a potential source of a tyrosyl-radical. It is produced from β-casein A¹ and β-casein B but not β-casein A² (49). Casein peptides have also been implicated in alterations in platelet functioning, some inhibiting both aggregation of ADP-treated platelets and binding of fibrinogen to ADP-treated platelets (50,51,52). Casein peptides have been found in the aorta plaque of rats fed skim milk (53).

The rationale behind the exclusion of cheese is that the renneting process and the subsequent enzymatic action that takes place as cheese ages causes alterations in the casein structure. This occurs by cross-linking and other modifications so that individual casein molecules are no longer in equilibrium with the micelle. Transport through the gut of intact molecules may therefore be prevented, or hindered. This is supported in observations on cheese structural changes with respect to casein and the absence of casomorphin-7 in a variety of cheeses (54,55). Alternatively, the data may be correlated making use of the traditional risk factors and β-casein A¹ consumption based on total milk protein consumption.

β-casein peptides have been identified as possessing strong opioid properties (56). It is possible that depression, which has been found to be an independent risk factor for increased mortality from heart disease in men (57), may be related to the biological activity of the ingested caseins.

Those communities recorded as being essentially free of CHD but who drink milk, the Masai and Samburu, obtained their milk from Zebu cattle, which do not contain the β-casein A¹ allele. Tibetan highlanders source of milk, the Yak (58), also does not have the β-casein A¹ allele. Surveys of Eskimos in the 1960s showed them not to be susceptible to CHD in Greenland. However, they developed high rates when exposed to European diets. The `protective nature' of their traditional diet has often been ascribed to their eating large quantities of unsaturated fatty acids in their native environment. Lack of β-casein A¹ has not been considered. In the Pacific neither the Solomon Islanders (59,60) nor the people of Kitava (61) suffer from IHD or cerebrovascular disease; neither community has traditionally had access to dairy products.

Annand (62) has pointed out that the introduction of pasteurization in the UK around the early 1920s coincided with a near doubling of heart disease mortality. The pasteurization technique required the holding of milk at 63˚C for 30 minutes. Holder pasteurization, which caused milk to develop a slightly cooked flavour, was generally replaced by the slightly less efficient high temperature short time, pasteurization process, HTST, in the late 1940s to mid 1960s, depending on the country. HTST pasteurization was almost universally adopted by 1980 (63). The USA was the first country to introduce pasteurization of milk, around 1900. Ostler in 1910, reported an increased heart disease prevalence that had been observed in the USA (64). No such increase had been observed in England at the time of his lecture and pasteurization was first introduced in London around 1911. Whether the heat treatment of milk prior to consumption affects the transmission of β-casein through the gut wall or whether it contributes to greater production of specific casein fragments remains to be established. However the two factors, changes in pasteurization and differing β-casein allele frequencies between areas, in conjunction with changes in traditional risk factors, may provide an explanation for the historical changes in CHD and regional variations in the disease.

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Table 4 National consumption statistics and β-casein A^1 estimates

	FAOSTAT 1980 FAO 1999	FAO 79–81 mean FBS 84 & 91	IDF Est. 79/80	Used this work g/d	A^1 g/d	A^1-cheese g/d	IDDM<15y
Australia	19.3	17.9	19.5	17.9	3.15	2.41	13.2
Austria	20.6	19	17.4	19	1.58	1.21	7.7
Canada	16.3	18.7	22	18.7	2.4	1.75	nc
Denmark	17.3	24.5	22.5	24.5	3.68	2.47	14.5
Finland	27.6	27.8	34.1	27.8	4.07	3.37	29.5
France	24.5	22.8	20	22.8	2.3	0.97	4.4
Germany(83)	17.1	18	19.2	18	2.4	1.75	11.6
Iceland	34.1	33.2	32.3	33.2	2.67	2.33	9.4
Ireland	31.1	22.1	20.5	22.1	3.72	3.35	nc
Israel	16.4	17.1	15.6	17.1	2.22	1.49	4.2
Japan	5.5	5.5	5.5	5.5	0.91	0.84	1.7
Netherlands	28.8	27.6	25.9	nc	nc	nc	nc
New Zealand	19.2	28.3	21.4	23†	3.76	2.78	14.3
Norway	29.6	28.4	28	28.4	3.77	2.79	19.7
Sweden	29.9	26.8	31.8	26.8	3.94	2.47	22.4
Switzerland (84)	24.9	24.3	25.2	24.3	1.76	1.04	7.2
UK	18	18.2	17.3	18.2	3.57	2.77	nc
USA	20.9	21.3	19.8	21.3	2.7	2.04	16.7
Engl & Wales				18.2‡	3.53	2.71	16.4
Scotland				18.2‡	3.63	2.79	19.7
N. Ireland				20.1‡	4.08	3.14	16.6

† NZ Public Health Commission; ‡ English Milk Marketing Board

Finally, it appears that atherosclerosis and diabetes mellitus may both have a common step involving β-casein A^1, or the group of β-casein alleles that have had a proline replaced by a histidine at position 67 of the β-casein molecule.

ADDENDUM

Benditt and Benditt (65), in their monoclonal theory of atherosclerosis, proposed a mechanism whose basis was that the initiation of atherogenesis and tumorigenesis were similar. A search was then made for cancers whose incidence might have some relationship with the processing and consumption of milk.

Since the classic epidemiological studies linking lung cancer with the smoking of tobacco, many studies have sought to identify the primary carcinogen(s) in tobacco. If one examines the historical rise in lung cancer in Great Britain and Wales, one is struck by the rapid increase that took place in the early 1920s, apparently unrelated to earlier rates of change of consumption. It is worth pointing out that this apparent increase took place at the same time as holder pasteurization of milk was introduced (66,67). Furthermore, the distribution of lung cancer cases in Great Britain was greatest in the large cities, moderate in the medium towns, and least in villages and rural communities (68). This also fits the distribution of the introduction of pasteurization. Reviews of the data from this time period have suggested that the rural/urban difference may reflect differing levels of air pollution in these communities. However, this difference was also present in other countries, including New Zealand, which had no air pollution. Lung cancer's rapid increase in Copenhagen (69), compared with the rest of Denmark also appears to match the introduction of pasteurization with a time lag associated with the change in rates between Copenhagen, provincial towns and rural areas.

Lung cancer in smokers has been found to have an association with the consumption of dairy products in a number of studies (70–73). In non-smokers, it has also been found to have a direct association with the consumption of dairy products in some reports (74–76) but not in others (77).

If one is looking at allied atherogenesis and tumorigenesis processes in action, one would expect that following the decline in heart disease that occurred in many countries in the early 1970s to 1980s, lung cancer should also have peaked and be in decline. This apparently is the case (78–81). This decline has been attributed to a decrease in the tar content of cigarettes and overall drops in smoking rates. However, the sharp decline in IHD and lung cancer mortality in Poland, which has taken place since 1990, occurred despite no apparent change in cigarette consumption (82). Milk consumption, on the other hand, declined 30% in this period. It appears there may be an intimate relationship between smoking, the consumption of β-casein A^1 and deaths from IHD and lung cancer.

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