Cholelithiasis: A clinical and dietary survey

MARY WHEELER, LOIS LOFTUS HILLS, AND BETTY LABY

From the Department of Surgery and the Department of Statistics, University of Melbourne

SUMMARY Cholelithiasis among male and female patients at the Royal Melbourne Hospital was studied, and the incidence of the disease in relation to various clinical and dietary factors is discussed. The patients are distinguished by sex and country of origin, a distinction being made between patients born in Australia and those born in southern Europe and now living in Australia. Appropriate control groups were also studied.

It was shown that the incidence of cholelithiasis is higher in women than in men (3.0% as opposed to 0.7% in the Melbourne Hospital group), and higher among patients born in southern Europe than in Australia. A correlation was also established between marriage and the disease, and, in women, between having had children and the disease.

The dietary investigations showed that in Australia those patients with cholelithiasis were fatter than the control patients. Equally well there seemed to be a strong family tendency to develop gallstones. No association was found between cholelithiasis and blood grouping.

In the comparison of the southern European group and the Australian-born group it was shown that the former group had a higher incidence of the disease (9.3% as opposed to 2.3%), and that the overall incidence of cholelithiasis increased with age in men and was constant in women. However, when taken separately, the incidence in Australian female patients did increase with age, the higher proportion of women from southern Europe with the disease where the incidence was, in fact, evenly distributed in all age groups, accounting for this apparent constancy. It was also shown that a woman born in southern Europe increased the risk to herself of developing gallstones within two to five years of moving to Australia, and the contributory factors are discussed.

Clinical Investigations

In the clinical survey all patients in the public wards of the Royal Melbourne Hospital with proven gallstones were interviewed between 1 March 1964 and 31 December 1965 (excluding December 1964 and January 1965). Only patients with symptoms attributable to the disease were chosen for the survey, though it is possible that some patients with 'silent' gallstones were included in the control group.

The patients forming the control group were interviewed during the same period, the group

being designed to have the same ratio, male: female, as the patients with gallstones. Using random numbers one male and four females were chosen from the names of each 100 male and female patients on the daily admission lists. Any patient whose gall bladder had been removed previously was automatically excluded from the control group.

During the 20 months of the survey, 396 patients with cholelithiasis were interviewed, 79 men and 317 women. The control group consisted of 397 patients, including 70 men and 327 women.

Country of Birth	Males ¹			Females ²		
	Cholelithiasis Patients	Control Patients	Total	Cholelithiasis Patients	Control Patients	Total
Australia	56	57	113	201	258	459
British Isles	6	7	13	29	34	63
Southern Europe	8	3	11	57	20	77
Other places	9	3	12	30	15	45
Total	79	70	149	317	327	644

Table I Country of birth

¹ $\chi^2 = 4.82$, 2 df not significant.
² $\chi^2 = 30.1$, 3 df significant at 1% level.

COUNTRY OF BIRTH

Approximately 27% of all patients admitted to the Royal Melbourne Hospital were not born in Australia. In Table I patients are grouped according to their country of birth, either Australia, or the British Isles including England, Scotland, Wales, Northern Ireland, and Eire, or southern Europe including Italy, Greece, Malta, and Cyprus. The remaining patients are entered as coming from other places. Almost half of the patients born in the British Isles had lived in Australia for more than 30 years and the majority for more than 10 years. On the other hand, most of the patients from southern Europe had been in Australia for less than 10 years.

When separated into the four geographical regions there was a difference in the proportion of females among the group of cholelithiasis patients and the control group. The high percentage of southern European women with gallstones contributed largely to this result (Table I).

SEX AND AGE DISTRIBUTION

The mean age of the men was 56 years (standard deviation 15) and of the women 51 years (SD 18).

The figure shows the age distribution of patients with cholelithiasis, the control group, the hospital patients, and of the population of Victoria (Commonwealth Census, 1966). The patients with cholelithiasis formed 0.7% and 3.0% of the total male and female hospital population respectively. The greatest proportion relative to the total hospital population of women treated for cholelithiasis was in the third and fourth decades, but relative to the population of Victoria, it was in the fifth and sixth decades.

There was a difference in the distribution of the disease among men and women between the ages of 17 and 90 years. Two thirds of the men were over the age of 50 years, while the women were fairly evenly distributed. This more even distribution of the women was largely due to the inclusion in the group of the southern Europeans who, with a mean age of 14 years lower than that of the Australian women, were in sufficient numbers to affect the incidence of

Fig. The age distribution of cholelithiasis in control and hospital patients, and the population of Victoria.

the disease in relation to age among all the women. For all cholelithiasis patients the overall male to female ratio was 1:4, but under 50 years it was 1:6, and over 50 years, 1:3.

MARITAL STATUS

On dividing the patients, at the time of the diagnosis of cholelithiasis into groups according to marital status—married, widowed, divorced, or single—there was a significant difference, for both men and women, between cholelithiasis patients and controls, gallstones being associated with a change in marital status (Table II).

Marital Status	Males ¹			Females ²		
	Cholelithiasis Patients	Control Patients	Total	Cholelithiasis Patients	Control Patients	Total
Married						
Observed value	61	45	106	220	200	420
Expected value	56.2	49.8		206.7	213.3	
Widowed						
Observed value	12	7	19	76	52	128
Expected value				63.0	65.0	
Separated, divorced						
Observed value				11	26	37
Expected value	10.1	8.9		18.2	18.8	
Single						
Observed value	6	18	24	10	49	59
Expected value	12.7	11.3		29.0	30.0	
Total	79	70	149	317	327	644

Table II Marital status at time of confirmation of gallstones

¹ $\chi^2 = 9.2$, 2 df significant at 1% level.² $\chi^2 = 37.2$, 3 df significant at 1% level.

Number of Children	Australians						Southern Europeans ²		
	All Women ¹			Married Women ³			Cholelithiasis Patients	Control Patients	Total
	Cholelithiasis Patients	Control Patients	Total	Cholelithiasis Patients	Control Patients	Total			
0	15	77	92	8	39	47	1/2	7	9
≥1	185	181	366	184	180	364	55	14	69
Total	200	258	458	192	219	411	56/57	21	78

Table III Number of children of cholelithiasis and control patients

¹ $\chi^2 = 33.7$, 1 df significant at 1% level.² $\chi^2 = 17.5$, 1 df significant at 1% level.³Exact probability $P \sim 0.0011$, approximation not applicable.

ASSOCIATION WITH PREGNANCY

An association between cholelithiasis and pregnancy was demonstrated (Table III). In fact, a woman with children was found to have five times greater a chance of developing symptoms of cholelithiasis than if she had remained childless. On further analysis of the effect of the number of children per patient, allowance was made for the difference in age and for different samplings in each age group. This test was limited to the Australian women because of the difference in age distribution and incidence of gallstones of the migrant women. No significant difference regarding the number of children per patient was found between this group of patients with the disease and their controls. The association found here with pregnancy which was not affected by the number of pregnancies has also been reported by van der Linden (1961).

Fifty-one per cent of the parous women under 31 years of age, and 15% of all parous women reported the onset of the first symptoms of cholelithiasis during pregnancy or within three

weeks of parturition. About half of these women stated that the association was with the first pregnancy.

In order to determine whether pregnancy precipitates the development of symptoms in a patient who already has 'silent' stones or whether it is a cause of their development, cholecystograms and detailed clinical histories would be needed of a large number of women before and after pregnancy.

BODY BUILD

The patients were measured without shoes, and they were weighed wearing light hospital clothing. Skinfold measurements, made with Harpendon calipers (Edwards, Hammond, Healy, Tanner, and Whitehouse, 1955), were taken at the biceps, triceps, subscapular, and suprailiac regions on both sides of the body, and the sums of the readings from the left and right sides were used in the analyses.

Due to the differences in age, and the likely differences in height and weight between Austral-

	Males		Females	
	Cholelithiasis Patients	Control Patients	Cholelithiasis Patients	Control Patients
Age (years)				
n	56	57	201	258
Mean	57.8	53.7	53.9	49.7
Standard deviation	14.8	16.6	18.2	16.9
Height (cm)				
n	55	56	198	248
Mean	171.8	172.2	159.2	160.0
Standard deviation	7.65	7.88	6.43	6.60
Weight (kg)				
n	52	57	199	251
Mean	69.2	67.7	63.6	58.6
Standard deviation	12.3	10.2	11.9	13.1
Biceps (mm)				
n	39	47	159	206
Mean	4.28	3.79	8.75	7.15
Standard deviation	1.48	1.25	3.92	3.44
Triceps (mm)				
n	39	47	159	206
Mean	7.56	6.17	17.41	14.08
Standard deviation	3.08	2.31	6.56	6.03
Subscapular (mm)				
n	39	47	159	206
Mean	10.98	8.74	16.47	12.52
Standard deviation	4.09	3.34	7.28	6.18
Suprailiac (mm)				
n	39	47	159	206
Mean	10.96	7.66	16.55	12.92
Standard deviation	5.02	3.81	7.48	6.84

Table IV *Body build measurements of the Australian patients and controls*

Number of Sisters of Propositus with Gallstones	Family Size ¹ in Cholelithiasis Patients (317)					Family Size ¹ in Control Patients (327)				
	1	2	3	4	5	1	2	3	4	5
None	74	44	23	36	13	76	74	48	20	15
One	6	8	8	4	4	1	2	2	3	0
Two and three	0	0	0	0	3	0	0	1	0	1
Total	80	52	31	40	20	77	76	51	23	16

Table V *Family histories of gallstones*

¹Excluding propositus.

ian and migrant patients, the patients, both male and female, were grouped regionally for multivariate analyses of age, height, weight, and the skinfold measurements.

Because of the small numbers involved, no attempt was made to draw any conclusions regarding the migrant groups, but, with all variables included, a significant difference for both men and women appeared between the Australian patients with cholelithiasis and their controls (Table IV). Although the Australian women with the disease were older, shorter, and heavier than their controls, age, height, and weight did not affect the significance levels. There was, however, a significant difference in the skinfold measurements. In other words, the Australian women with gallstones were fatter than the control patients, as were the Australian men.

FAMILIAL INCIDENCE

Patients were asked if any members of the family (parents, siblings, or offspring) were known to have gallstones. A significantly higher proportion of cholelithiasis patients (64%) had a parent, usually the mother, with a history of the disease than did the controls (49%). Also, the women with gallstones had significantly more sisters who were known to have gallstones than had their corresponding controls. Family size was taken into account when comparing the siblings, and because of the unequal distribution of cholelithiasis between the sexes, brothers and sisters were separated, but the number of brothers was too small for statistical analysis (Table V).

Of the 397 cholelithiasis patients, 12 had 15 offspring between them with the disease; of the 396 controls four had four offspring between them with gallstones. There was only one son in each of these two groups of offspring.

These results confirm a familial tendency for the disease, but no conclusion can be drawn as to whether this is due to environmental or hereditary factors. Van der Linden and Lindelöf (1965) have suggested that there is a genetic factor in the development of cholelithiasis since they found that the disease occurred more often among the brothers and sisters than among the husbands and wives of patients with gallstones.

ABO BLOOD GROUPING

The ABO blood grouping of 384 cholelithiasis patients was compared with that of 4,423 hospital patients who in 1961 had been typed

Blood Group	Cholelithiasis Patients	Royal Melbourne Hospital Population (1961)
	Number	Number
O	171 (44.5%)	2,091 (47.3%)
A	147 (38.3%)	1,732 (39.2%)
B	49 (12.8%)	450 (10.1%)
AB	17 (4.4%)	150 (3.4%)
Total	384	4,423

Table VI *ABO blood grouping*

¹ $\chi^2 = 4.00$, 3 df not significant.

before possible blood transfusion. No significant difference was found between the blood grouping of the men and women, either for the patients with gallstones or for the hospital patients in 1961, and so the men and women were combined for this test. There was no association between cholelithiasis and blood grouping (Table VI).

Because of the relatively high proportion of

southern European patients with cholelithiasis, and the possibility of a different distribution of blood groups, the effect on this distribution was tested but found not to be significant.

An association between cholelithiasis and blood group A has been reported in Europe by Kjølbye and Neilson (1959), and by Czaplicki, Stanowski, and Szepletowski (1964). In the USA Mayo and Fergeson (1953) found no such relationship, while Hauch and Moore (1963) recorded a significant association with group AB.

Dietary Investigations

Investigations into the influence of diet on the development of symptoms of gallstone disease were carried out separately and in two parts.

Initially all patients in the public wards of the Royal Melbourne Hospital with proven gallstones were interviewed from March 1964 to March 1965. Over the following 12 months information from a control group was gathered. To fit the time available to the observer, every 106th patient admitted to the hospital was interviewed. With the male to female ratio set at 2:5, the sex of the patient to be seen next was chosen from a randomized list.

Of the diet histories taken from patients with cholelithiasis, 18% were unsatisfactory and were rejected. Almost 60% of patients considered for the control group were unsuitable as either an interview was not possible, the patient had a history of cholecystitis, diabetes, or endocrine disorders, or insufficient data on diet were obtained. The diet histories obtained from the cholelithiasis patients were for an 'average' week before symptoms of gallstone disease appeared (pain, and/or jaundice), and from control patients an 'average' week at the time of interview. An 'average' week was a composite of summer and winter intake.

A computer was used to calculate the average daily intake in grams of protein, fat, carbohydrate, and alcohol from the assessment of the quantities of food eaten in a week. The

Country of Birth	Cholelithiasis Patients		Control Patients	
	Males	Females	Males	Females
Australia	17	36	15	44
British Isles	0	3	1	1
Southern Europe	1	9	3	4
Other places	1	4	3	1
Total	19	52	22	50

Table VII Country of birth and sex of patients

calorie contribution of this diet to the total, expressed as the percentage of total calories was also included (Loftus-Hills, 1965).

Any change in physical activity during the period of the diet history, together with the date and place of birth of each patient were also recorded.

Satisfactory histories were obtained from 71 cholelithiasis and 72 control patients; they are grouped according to country of origin and sex in Table VII. The high proportion of southern European women with gallstones is similar to that reported in the clinical survey

NUTRIENT INTAKE

There was a significantly greater proportion of control patients, both male and female, who took alcohol. Within the subgroups formed to investigate various aspects of food intake the number of patients and the amount of alcohol they consumed varied greatly, which led to all tests on nutrient intake being repeated after alcohol had been excluded.

The only instance in which the quantity of alcohol taken made a significant difference to the total intake for any of the groups was for the Australian male and female controls. With all nutrients included (protein, fat, carbohydrate, and alcohol, expressed as percentage of total calories) and with the intake in the men greater than in the women, there was a significant difference in their total intake, a difference not present when alcohol was omitted from the test.

	Cholelithiasis Patients				Control Patients			
	Protein	Fat	Carbohydrate	Alcohol	Protein	Fat	Carbohydrate	Alcohol
Males								
n	17	17	17	17	15	15	15	15
Mean	12.4	37.6	46.5	3.52	12.9	37.4	45.1	4.57
Standard deviation	1.93	7.48	7.15	7.28	1.57	4.97	4.48	6.26
Females								
n	36	36	36	36	44	44	44	44
Mean	12.9	37.3	49.5	0.30	12.9	39.9	44.7	1.55
Standard deviation	1.58	5.15	5.65	1.50	1.86	4.75	5.80	2.78

Table VIII Nutrients as a percentage of calorie intake in Australians

With nutrients expressed as a percentage of total calories there was a significant difference between Australian women with cholelithiasis and the control patients in the intake of all nutrients. A smaller intake of fat by the cholelithiasis patients was the biggest contributory factor to the difference. (Later in the survey it was seen that the nutrient intake in the country of their birth of the southern European women with cholelithiasis and their controls showed this same difference when alcohol was excluded.) It may be noted that when nutrients were expressed in actual amounts, no significant differences were obtained.

It is well known that people with gallstones experience difficulty in digesting fat. The significantly lower intake of fat by cholelithiasis patients could be an early reaction to the presence of gallstones which had not, as yet, caused severe symptoms of the disease.

The means and standard deviations for the Australians of the intake of nutrients expressed as percentage of total calories are shown in Table VIII.

CALORIE INTAKE AND ACTIVITY

The mean daily calorie intake of both male and female cholelithiasis patients was not significantly different from that of the controls. Neither was there a significant change in the physical activity

of the patients during the time covered by the diet histories. Table IX shows the means and standard deviations of calorie intake.

The clinical investigations showed that the Australian cholelithiasis patients were fatter than the controls. The dietary investigations showed that there was also no significant difference in calorie intake or change in activity between patients with cholelithiasis and the controls. These findings could be due to the difficulty in recording levels of activity from interview and the small differences in calorie intake which are known to lead over a period to substantial changes in weight.

The second part of the dietary investigations dealt with the food intake of the southern Europeans both in their country of origin and in Australia.

During April and May 1966, and from September to December 1966, all southern European patients with cholelithiasis were interviewed. Every twelfth southern European patient admitted joined the control group, the sex being determined by the randomized list previously used. There were four men and 23 women with cholelithiasis and nine men and 21 women in the control group. Twenty-nine patients supplied a history of their diet in their country of origin and in Australia.

IMMIGRATION AND DIET

Most of the people from southern Europe were found to have suddenly changed their food habits on coming to Australia. The commonest and most obvious change was an increase in the consumption of meat, previously eaten once or twice a week, now once or twice a day. Other major changes were a decrease in the amount of bread, vegetables, and pasta taken and the consumption of manufactured goods, especially soft drinks and biscuits, which previously they had not been able to buy. Traditional ways of preparing and cooking food were retained, even after many years.

Comparing the original diet of the women from southern Europe with their Australian diet

Table IX Calorie intake

	Males		Females	
	Cholelithiasis Patients	Control Patients	Cholelithiasis Patients	Control Patients
All nutrients				
n	19	22	52	50
Mean	2670	2840	2140	2160
Standard deviation	563	582	533	349
Without alcohol				
n	19	22	52	50
Mean	2560	2700	2120	2130
Standard deviation	541	551	532	347

	Cholelithiasis Patients				Control Patients			
	Protein	Fat	Carbohydrate	Alcohol	Protein	Fat	Carbohydrate	Alcohol
In Southern Europe								
n	26	26	26	26	14	14	14	14
Mean	11.6	27.9	58.7	1.79	12.1	34.3	51.2	2.39
Standard deviation	1.28	8.78	9.20	2.78	2.32	8.37	7.63	4.39
In Australia								
n	19	19	19	19	20	20	20	20
Mean	11.9	38.6	47.1	2.38	12.5	41.7	44.4	1.40
Standard deviation	1.58	4.40	5.52	3.67	1.90	6.41	6.86	1.78
t	0.67	4.90	-4.89	0.61	0.47	2.94	-2.71	-0.91
df	43	43	43	43	32	32	32	32

Table X Nutrients as a percentage of calorie intake in Southern European women

it was shown that on coming to Australia they consumed significantly more fat and less carbohydrate. Data for the group of southern European males are not significant because of the small number of histories obtained (Table X).

The increased intake of fat of the females derived primarily from the increased consumption of meat. The protein intake was not significantly changed in quantity; its quality, however, was greatly enhanced, again because of the increased meat intake. The carbohydrate intake was significantly reduced by their eating less bread and pasta.

Confirmation of the dietary pattern obtained for patients in rural Italy is obtained from Fidanza, Fidanza-Alberti, Ferro-Luzzi, and Proja (1964).

With nutrients, including alcohol, expressed as a percentage of total calories for the male cholelithiasis and control patients from southern Europe there was no significant difference in the nutrient intake in Australia. There were too few histories obtained from these groups of their local diet to allow valid testing.

The southern European women with cholelithiasis and their respective controls showed no significant difference in nutrient intake in Australia or in southern Europe. It was also shown that there was no significant difference between the nutrient intake of the southern Europeans in Australia and that of the local Australians.

IMMIGRATION AND CHOLELITHIASIS

Change in incidence

Over a five and a half month period (26 November 1965 to 12 May 1966) the incidence of gallstones among southern European women was 9.3% compared with 2.5% in the Australian women. This difference was significant at the 1% level. There was no significant difference in the incidence in the men.

Figures were obtained from the Istituto Centrale de Statistica, Rome, for patients, male

and female combined, who were discharged from Italian hospitals in 1958. The patients diagnosed as having cholecystitis, but with no mention of stones, were listed separately from those given diagnoses of cholelithiasis. The sum of the numbers in these two categories, to ensure inclusion of all cases of cholelithiasis, might well be an inflated figure. Even so, for Italy as a whole, the incidence was 1.5%, similar to the 1.7% for Australians admitted to the Royal Melbourne Hospital over a six-month period (10 November 1965 to 12 May 1966), and very much less than the 4.8% for the southern Europeans admitted to the hospital over the same period (Table XI).

Incidence in the regions of Italy varied. It was 1.6% in the north, 1.3% in the south, 1.7% in central regions, and 1.1% in the island regions. Of the Italians interviewed in the course of the dietary survey, 80% came from the southern and island regions, and people from these areas therefore appear to have four times a greater risk of developing gallstone disease on coming to Australia.

The ratio of men to women

For southern Europeans with gallstones the ratio male:female was 1:6 compared with 1:4 for Australians, even though, in the five and a half month period in which records were kept, the male:female ratio for southern Europeans admitted to the hospital was 10:7 compared with the Australian ratio of approximately 1:1.

The ratio for southern European to Australian women

The incidence of cholelithiasis decreased with age in the southern Europeans and increased with age in the Australians. It was found that 26 out of the 69 southern European women had symptoms of the disease from two to five years after coming to Australia.

To test if the big increase in incidence of cholelithiasis experienced by these women on coming to Australia was an effect of pregnancy, the proportion of women from southern Europe with cholelithiasis and with children was compared with the proportion of Australian women with cholelithiasis. No significant difference was demonstrated (Table III). The sudden change in nutrient intake is therefore put forward as being the main reason for this greatly increased incidence of cholelithiasis in southern European women coming to Australia.

Conclusions

The findings of the study have been greatly influenced by the substantial proportion of migrant people in the hospital population. Of these the southern Europeans formed a sufficiently

	Cholelithiasis	Cholecystitis (no mention of stones)	Total	In Hospital	Percentage
Patients in Italy, 1958	31,236	20,037	51,273	3,423,580	1.5
Patients at RMH					
From Australia	74			4,442	1.7
From British Isles	8			655	1.2
From southern Europe	22			463	4.8
From rest of Europe	14			388	3.6
From other places	3			152	2.0

Table XI Gall bladder disease in Italy and at the Royal Melbourne Hospital

large and distinct group to allow separate measurement of some of their characteristics.

For the total hospital population the occurrence of cholelithiasis was shown to be associated with age, sex of the patient, change of marital status, pregnancy, and any family history of the disease; for the Australians, the degree of body fat determined by skinfold measurements, and for the southern European females, change in nutrient intake appeared to be linked with increase in incidence of the disease.

The familial effect on the incidence of cholelithiasis could be made up of both hereditary and environmental factors, and could also be reflected in the finding of greater skinfold measurements in Australians with the disease than in controls.

Marriage was shown to be associated with an increased incidence of gallstone disease, and could also bring about changes in subcutaneous fat.

The association of cholelithiasis and pregnancy must be a major factor contributing to the greater incidence of the disease in women than in men. Although no enquiry was made about change of diet with the onset of pregnancy, this could also be a factor.

The marked change in nutrient intake of southern European women on coming to Australia, not experienced by Australian women, is probably the reason for the increased incidence of the disease in the former group of patients, for the effects of pregnancy would not explain this greatly increased incidence. Because of their small numbers it was not possible to demonstrate the influence of nutrient change in the southern European males.

In statistical analyses each variable increases the sample number required. In this study many more patients would be needed to establish fully the effects of age, marriage, pregnancy, ethnic origins, diet, and subcutaneous fat which are all related to each other.

From the separate analyses we have done it would seem that pregnancy and a sudden change in diet, both factors leading to a marked change in the metabolic conditions of individuals, are associated with an increased incidence of cholelithiasis.

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