Long term metabolic effects of two dietary methods of treating hyperlipidaemia

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Abstract

Objectives—To compare the long term metabolic effects of two diets for treating hyperlipidaemia.

Design—Randomised controlled study: after three weeks of normal (control) diet, subjects were randomly allocated to one of two test diets and followed up for six months.

Setting—Lipid clinic of tertiary referral centre in Naples.

Subjects—63 subjects with primary type IIa and IIb hyperlipoproteinaemia entered the study, and 44 completed it. Exclusion criteria were taking drugs known to influence lipid metabolism, evidence of cardiovascular disease, homozygous familial hypercholesterolaemia, and body mass index over 30.

Interventions—Two test diets with reduced saturated fat (8%) and cholesterol (~200 mg/day): one was also low in total fat and rich in carbohydrate and fibre, and the other was low in carbohydrate and fibre and rich in polyunsaturated and monounsaturated fats.

Main outcome measures—Fasting plasma lipid and lipoprotein concentrations; blood glucose, insulin, and triglyceride concentrations before and after a test meal.

Results—In comparison with the control diet, both test diets induced significant and similar decreases in low density lipoprotein cholesterol concentrations (by a mean of 0.72 (SE 0.15) mmol/l, $P < 0.001$, for low total fat diet; by 0.49 (0.18) mmol/l, $P < 0.05$, for high unsaturated fat diet) and plasma triglyceride concentrations (by 0.21 (0.09) mmol/l, $P < 0.05$, for low total fat diet; by 0.39 (0.15) mmol/l, $P < 0.05$, for high unsaturated fat diet), while high density lipoprotein cholesterol concentrations after fasting and plasma glucose and insulin concentrations during test meals were not modified by either diet.

Conclusions—Both test diets are suitable (alone or in combination) for treatment of hypercholesterolaemia.

Introduction

It is generally accepted that dietary saturated fat must be reduced in order to decrease plasma cholesterol concentrations.¹⁻³ However, the best choice of substitutes for dietary saturated fat is less clear, especially with regard to the possible effects that these can have on lipoproteins other than low density lipoprotein, in particular very low density lipoprotein and high density lipoprotein.^{4,5} Theoretically, there are two possible dietary approaches: a reduction in saturated and total fat compensated by an increase in carbohydrate and fibre or a reduction in saturated fat compensated by an increase in unsaturated fat. Both approaches have been evaluated experimentally,⁶⁻⁹ but

many points still need to be clarified. Most important is the lack of any reported long term trials comparing the two diets. Other points are the amount of fibre in a low total fat diet that can have metabolic effects and, in a high unsaturated fat diet, whether polyunsaturated or monounsaturated fat should be preferentially used.

The trials performed so far have been criticised for the large amounts of dietary fibre used.^{10,11} Dietary guidelines for the prevention of cardiovascular diseases recommend a moderate amount of fibre (about 35-40 g/day for an isoenergetic diet),¹ but whether this amount has any metabolic effect is unknown. When dietary saturated fat has been replaced with unsaturated fats, diets extremely high in polyunsaturated fat have generally been used,^{12,13} but these are no longer recommended because of the possible negative effects on health.¹³⁻¹⁵ Recently more attention has been given to monounsaturated fats, which are considered to have a neutral action on lipoprotein metabolism.¹⁶⁻¹⁸

Diets for the prevention of cardiovascular diseases have been evaluated only for their effects on fasting lipid concentrations. Less attention has been given to their influence on other cardiovascular risk factors such as postprandial triglyceride concentrations, blood glucose concentrations, and especially plasma insulin concentrations. Plasma insulin concentrations (or rather the insulin resistance of which they are markers) are considered by many to be a pathogenetic link among the main cardiovascular risk factors (lipid abnormalities, obesity, glucose intolerance, and hypertension),¹⁹ and so the effect of dietary treatment on insulinaemia should be more carefully examined.

In order to answer some of the above points we studied the long term (six months) metabolic effects of two diets (one low in fat and high in carbohydrate and fibre, the other low in saturated fat and high in monounsaturated fat) on people with hyperlipidaemia.

Subjects and methods

SUBJECTS

In order to detect a change in plasma cholesterol concentration of 0.65 mmol/l with an α risk of 0.05 and a power of 0.90 and allowing for a 30% withdrawal, we recruited 63 subjects with primary hyperlipoproteinaemia (type IIa and IIb according to Friedrickson's classification) during six months from all the patients referred to our lipid clinic who met the entry criteria. These were a plasma cholesterol concentration of 5.7-7.8 mmol/l and a plasma triglyceride concentration under 3.9 mmol/l after at least three weeks without any hypolipidaemic drug. Exclusion criteria were secondary hyperlipidaemia, any drugs known to influence lipid metabolism, clinical and electrocardiographic evidence of cardiovascular disease, and a body mass index over 30. Participation in the study was voluntary, and all the subjects gave their informed

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consent to the protocol, which was approved by the ethics committee of the Medical School of Federico II University of Naples.

STUDY PROTOCOL

The subjects were asked to maintain their usual pattern of activities and not to modify their smoking habits, but no alcohol was allowed. For three weeks they followed a control diet similar to that of the general population in Italy²⁰ and relatively rich in saturated fat (14% of total energy intake) and cholesterol (400 mg/day). If compliance with the diet, evaluated by a seven day food record, was not satisfactory subjects were asked to continue the diet for another three weeks. The subjects were then stratified according to sex and plasma triglyceride concentration ($< \text{or} \geq 2 \text{ mmol/l}$) and assigned to one of the two test diets by stratified block randomisation with tables of random numbers.²¹ The subjects followed their diet for six months and were seen each month by a dietitian and a doctor. On each occasion the subjects were weighed in light underwear, and a blood sample was taken after a 12-14 hour fast to measure plasma concentrations of total cholesterol, triglyceride, and high density lipoprotein cholesterol. At the end of both the control diet and the test diet a fasting blood sample was taken to measure lipoprotein concentrations. At the same time a test meal was administered, and blood samples were taken before the meal and at one, two, and four hours after to assess triglyceride, glucose, and insulin concentrations.

DIETS

Before starting the study, the subjects recorded their habitual food intake with a seven day food record to allow us to estimate their usual energy need and to calculate an isoenergetic diet for each subject. Table I shows the composition of the diets: the control diet was the same for all subjects. Both test diets were similarly reduced in saturated fat (8% energy) and cholesterol ($< 300 \text{ mg/day}$). In the high unsaturated fat diet total fat was not decreased, and the reduction in saturated fat was compensated by an increased intake of polyunsaturated (10% energy) and especially monounsaturated fat (20% energy) derived from corn oil and olive oil respectively. In the low total fat diet the amount of total fat was reduced (25% energy) and replaced with carbohydrate (58% energy) and fibre (40 g/day). Care was taken to ensure increased consumption of soluble fibre (unavailable carbohydrate other than cellulose) to 29 g/day compared with 15 g/day in the other test diet and the control diet.

At the start of the control and test diets an experienced dietitian gave the subjects oral and written instructions about the diet. Compliance with the recommended diet was checked each month with a seven day food record, and the dietitian used the results to reinforce the subjects' motivation and to improve adherence to the diet by focusing on any errors made by the subjects.

TABLE I—Recommended composition of diets and composition achieved by hyperlipidaemic subjects. Values are percentages of total energy intake unless stated otherwise

	Control diet	Low total fat diet		High unsaturated fat diet	
		Recommended	Achieved*	Recommended	Achieved*
Total protein	16	17	18	15	16
Total fat:	37	25	27	38	36
Saturated	14	8	6	8	7
Monounsaturated	19	15	17	20	19
Polyunsaturated	4	2	4	10	10
Cholesterol (mg/day)	400	< 300	192	< 300	205
Total carbohydrate:	47	58	55	47	48
Complex	37	42	41	36	38
Simple	10	16	14	11	10
Fibre (g/day)†	18	41	30	19	17

*Measured by seven day food record in two separate weeks during last two months of diet.

†Unavailable carbohydrate.

The composition of the test meal performed at the end of the control and test diets resembled that of the diet followed by the subjects (table II). Amounts of calories, nutrients, and dietary fibre were calculated from tables of food composition in which dietary fibre (unavailable carbohydrate) was measured by the Southgate method.²²

TABLE II—Composition of test meals administered (4598 kJ). Values are percentages of total energy intake unless stated otherwise

	Control	Low total fat	High unsaturated fat
Total protein	14	16	15
Total fat:	39	25	40
Saturated	17	8	6
Monounsaturated	21	14	25
Polyunsaturated	2	3	9
Cholesterol (mg/day)	300	47	78
Total carbohydrate:	47	59	45
Complex	41	46	34
Simple	6	13	11
Fibre (g/day)	8	27	8

BIOCHEMICAL ANALYSES

Serum for lipid analysis was obtained by low speed centrifugation within one hour of venepuncture. One aliquot was stored at 4°C for no more than seven days with merthiolate 0.01% EDTA disodium salt, and sodium azide 0.005% before very low density lipoprotein was separated as described by Carlson.²³ For technical reasons this was not done for four patients on the low total fat diet and three patients on the high unsaturated fat diet. Another aliquot was stored without additives and used to measure total serum and high density lipoprotein cholesterol concentrations and serum triglyceride concentrations. High density lipoprotein was separated by precipitation with dextran sulphate and magnesium chloride,²⁴ and low density lipoprotein cholesterol concentration was calculated as the difference between total cholesterol concentration and the concentration of very low density lipoprotein cholesterol and high density lipoprotein cholesterol.

Concentrations of total and lipoprotein cholesterol and triglycerides were assayed by enzymatic colorimetric methods with commercial kits (Boehringer-Biochemia Robin, Mannheim, Germany). Interassay coefficients of variation in our laboratory were 1% for total cholesterol, 1.2% for triglyceride, and 2.5% for high density lipoprotein cholesterol. Quality control of lipid analysis in our laboratory is regularly checked by the Prague Reference Centre of the World Health Organisation.²⁵ Blood glucose concentration was assayed by the glucose oxidase method with a commercial kit, and plasma insulin concentration by radioimmunoassay.²⁶ Coefficients of variation for insulin in our laboratory were 3% (intra-assay) and 5.8% (interassay). The technicians performing the chemical analyses were unaware of the diets of the subjects.

STATISTICAL ANALYSIS

To evaluate the effects over time of the two test diets on plasma cholesterol, high density lipoprotein cholesterol, and plasma triglyceride concentrations we performed analysis of variance for repeated measurements with SPSS. Differences between parameters at the end of the control diet and the end of each test diet were analysed by paired *t* tests. Before we compared the effects of the two test diets we adjusted the final values for any differences between the groups at the end of the control diet by covariance analysis to compensate for any possible imbalance between the two groups.²¹

The plasma glucose, insulin, and triglyceride concentrations measured after test meals were analysed as means of the concentrations measured at one, two, and

four hours after the meal. Plasma triglyceride and insulin concentrations were log transformed to reduce skewness of the data. The level of significance was set at $P < 0.05$ for a two tailed distribution.

Results

During the study there were six drop outs from the group allocated to the low total fat diet and 13 from the group allocated to the high unsaturated fat diet so that 27 subjects in the first group and 17 in the second group completed the study. Reasons for dropping out (investigated by telephone interview) were based on unwillingness to continue to comply with the diet or the study protocol, or both. The general characteristics of the subjects who finished the study were not significantly different in the two study groups (table III) and were similar to those of the drop outs.

The subjects generally complied well with their recommended diet except for intake of fibre (table I). Few subjects allocated to the low total fat diet increased their fibre intake to the recommended 40 g/day, and the mean consumption of fibre was only about 30 g/day.

The figure shows total plasma cholesterol, total plasma triglyceride, and high density lipoprotein cholesterol concentrations during the control diet and the two test diets. During the control diet plasma cholesterol concentrations increased significantly ($P < 0.05$), triglyceride concentrations remained constant, and high density lipoprotein cholesterol concentrations tended to decrease. Both test diets induced a rapid and significant decrease in total plasma cholesterol concentration by the end of the first month, and this reduced concentration was maintained for the rest of the six months (analysis of variance: $F = 10.23$, $P < 0.001$ for low total fat diet; $F = 6.97$, $P < 0.001$ for high unsaturated fat diet). A similar pattern was seen with plasma triglyceride ($F = 4.09$, $P < 0.001$ for low

Mean plasma lipid concentrations in hyperlipidaemic subjects during control diet and two test diets. Bars are standard errors

total fat diet; $F = 4.23$, $P < 0.001$ for high unsaturated fat diet). There was no significant change in high density lipoprotein cholesterol concentration throughout the study for both test diets ($F = 1.80$, $P > 0.1$ for the low total fat diet; $F = 1.44$, $P < 0.1$ for the high unsaturated fat diet).

Table IV shows the plasma lipoprotein concentrations at the start and end of the two test diets. Both diets resulted in significant decreases in total plasma cholesterol concentration (by 9% for the low total fat diet and 8% for the high unsaturated fat diet), low density lipoprotein cholesterol concentration (by 13% and 9%), and total plasma triglyceride concentration (by 12% and 20%). Very low density lipoprotein triglyceride also decreased with both diets, significantly with the high unsaturated fat diet (by 17%). Neither high density lipoprotein cholesterol or very low density lipoprotein cholesterol concentrations changed significantly.

Neither test diet significantly affected the average plasma glucose concentration or plasma insulin concentration measured after test meals. Mean (SE) postprandial glucose concentrations for control diet and low total fat diet were 4.6 (0.2) mmol/l and 4.7 (1.1) mmol/l; for control diet and high unsaturated fat diet they were 5.0 (1.7) mmol/l and 4.8 (1.2) mmol/l. Insulin concentrations for control and low fat diets were 7.7 (0.7) pmol/l and 6.5 (0.7) pmol/l; for control and high unsaturated fat diets, 7.3 (0.7) pmol/l and 6.6 (0.7) pmol/l. Similarly, no changes were observed for fasting plasma glucose and plasma insulin concentrations after either test diet compared with the control diet. In contrast, the average plasma triglyceride concentration after the test meal decreased after both test diets compared with the control diet (control diet *v* low total fat diet, 2.46 (0.19) mmol/l *v* 2.16 (0.17) mmol/l, $P < 0.1$; control diet *v* high unsaturated fat diet, 3.02 (0.36) mmol/l *v* 2.45 (0.25) mmol/l, $P < 0.02$).

TABLE III—Baseline characteristics of 44 hyperlipidaemic subjects who completed study. Values are means (standard deviations) unless stated otherwise

	Low total fat diet (n=27)	High unsaturated fat diet (n=17)
Sex (M:F)	17:10	14:3
Age (years)	48.6 (8.1)	47.4 (10.3)
Body mass index (kg/m ²)	24.4 (2.9)	25.2 (2.7)
Plasma cholesterol (mmol/l)	7.0 (0.9)	6.7 (0.4)
Plasma triglycerides (mmol/l)	1.6 (0.8)	2.0 (1.1)

TABLE IV—Mean (SE) plasma concentrations of lipoproteins (mmol/l) in 44 hyperlipidaemic subjects at start and end of six month test diets

	Low total fat diet		High unsaturated fat diet	
	Start	End	Start	End
Total lipoprotein cholesterol:	7.44 (0.18)	6.78 (0.15)***	7.23 (0.16)	6.63 (0.14)***
Very low density lipoprotein	0.63 (0.08)	0.76 (0.09)	0.80 (0.15)	0.65 (0.05)
Low density lipoprotein	5.54 (0.20)	4.82 (0.18)***	5.34 (0.25)	4.85 (0.21)*
High density lipoprotein	1.16 (0.06)	1.22 (0.06)	1.07 (0.06)	1.12 (0.04)
Total lipoprotein triglyceride:	1.71 (0.14)	1.50 (0.13)*	1.96 (0.26)	1.57 (0.17)**
Very low density lipoprotein	1.07 (0.13)	1.01 (0.12)	1.29 (0.21)	1.07 (0.17)*

Significance of difference from starting value: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

TABLE V—Plasma concentrations* of metabolic parameters in hyperlipidaemic subjects at end of six month test diets and differences between the two diets. Values are means (standard errors) unless stated otherwise

	Low total fat diet	High unsaturated fat diet	Difference (95% confidence interval)
Fasting cholesterol (mmol/l)	6.62 (0.15)	6.58 (0.14)	0.04 (-0.39 to 0.47)
Fasting triglyceride (mmol/l)	1.55 (0.13)	1.48 (0.17)	0.07 (-0.35 to 0.49)
Fasting high density lipoprotein cholesterol (mmol/l)	1.20 (0.06)	1.11 (0.04)	0.09 (-0.07 to 0.25)
Postprandial glucose (mmol/l)	4.77 (0.22)	4.69 (0.30)	-0.08 (-0.65 to 0.81)
Postprandial insulin (pmol/l)	6.41 (0.69)	6.71 (0.65)	-0.30 (-2.32 to 1.72)
Postprandial triglyceride (mmol/l)	2.29 (0.17)	2.24 (0.24)	0.05 (-0.51 to 0.61)

*Adjusted by covariance analysis for any difference between groups at start of diet.

Table V shows that there was no significant difference between the two test diets with regard to the values of the most relevant metabolic parameters at the end of the two diets (after adjustment by covariance analysis for any difference between the groups at the end of the control diet). Both diets resulted in similar slight but significant decreases in body weight (1.8 kg for the low total fat diet and 1.6 kg for the high unsaturated fat diet).

Discussion

BENEFICIAL EFFECTS

The results of this study show that both test diets induced a significant decrease in total and low density lipoprotein cholesterol concentrations and a decrease in total and very low density lipoprotein triglyceride concentrations without undesirable effects on other lipoproteins. The reduction in total and low density lipoprotein cholesterol is clinically important because it was a stable, long term effect achieved by subjects who otherwise maintained their normal everyday activities.

From the results of clinical and pharmacological trials the reduction in plasma cholesterol concentration achieved in this study should result in about a twofold decrease in cardiovascular mortality.^{27,28} Our results are in agreement with those of other studies, especially those in which a particularly low intake of saturated fat (as in our case) was achieved.⁵ Our results are reasonably close to the values predicted with the Keys formula²⁹: with the low total fat diet, the predicted reduction in total plasma cholesterol concentration would be 0.57 mmol/l whereas the actual decrease was 0.66 mmol/l; with the high unsaturated fat diet, the predicted reduction would be 0.78 mmol while the actual value was 0.60 mmol/l.

The two test diets reduced both fasting and postprandial concentrations of triglyceride. This was not expected with the low total fat diet because such high carbohydrate diets generally have a hypertriglyceridaemic effect.^{5,6,9,30} Our low total fat diet, however, was also rich in fibre, especially of the soluble type. Soluble fibre has been shown to reduce triglyceride concentrations in diabetic patients,^{31,32} and in our study it seems to have counteracted the hypertriglyceridaemic effect of the carbohydrates.

LACK OF DETRIMENTAL EFFECTS

Neither of our test diets affected high density lipoprotein cholesterol concentrations whereas other studies have shown that high carbohydrate diets and diets very rich in polyunsaturated fats (> 10% of total energy intake) reduce high density lipoprotein concentrations.^{5,6,9} Our results may be explained by peculiarities of our diets: the low total fat (high carbohydrate) diet was rich in soluble fibre, which may have counteracted the effect of carbohydrate; the high unsaturated fat diet was especially rich in monounsaturated fatty acids, which have no negative effect on high density lipoprotein.

Neither test diet significantly affected fasting and postprandial concentrations of plasma glucose and insulin, in contrast to the results of previous studies of diabetic and non-diabetic subjects that showed an increase in these parameters with low fat and high carbohydrate diets.^{32,33} Most of these were short term studies, however, and our high carbohydrate diet was also rich in fibre, which has beneficial effects on carbohydrate metabolism.³²

In this study the untoward effects of a high carbohydrate diet on glucose and triglyceride metabolism were apparently prevented by an intake of dietary fibre of about 30 g/day. The metabolic effects of dietary fibre have so far been demonstrated only with diets in which

Clinical implications

- The optimal diet for treating hyperlipidaemia is still not known, largely because of the lack of long term studies
- We studied the long term (six month) clinical effects of two diets on subjects with type IIa and IIb primary hyperlipoproteinaemia
- In one diet reduced saturated and total fat was compensated by increased carbohydrate and fibre (especially soluble fibre), while in the other reduced saturated fat was compensated by increased unsaturated fat (especially monounsaturated)
- Both diets significantly reduced plasma concentrations of low density lipoprotein cholesterol and triglycerides without any reduction in high density lipoprotein cholesterol concentrations or impairment of blood glucose metabolism
- Both diets are suitable for treatment of hyperlipidaemia, but a combination of the two might be more palatable.

fibre consumption was substantially higher.^{10,11} Our results suggest that dietary fibre is also metabolically active in moderate amounts provided that it is largely of the soluble type present mainly in legumes, vegetables, and fruits.

ACCEPTABILITY OF DIETS

Although patients were not able to increase consumption of dietary fibre to the levels recommended, the low total fat diet was the more acceptable of the two test diets. Only six subjects refused to follow this diet while 13 subjects refused to continue with the high unsaturated fat diet, mainly because of its monotony. A high unsaturated fat diet is often not satisfying because of the limited range of foods. It is also rich in vegetable oils, which are difficult to consume in large amounts (about 50 ml/day in the high unsaturated fat diet), even in Mediterranean countries such as Italy where habitual consumption of oil is high.²⁰

CONCLUSIONS

The two test diets were equally effective. The 95% confidence limits of the differences between the effects of the two test diets (table V) indicate that the statistical power of this trial was sufficient to detect any difference that would be meaningful from a clinical standpoint. The only exception might be for plasma triglyceride since any difference less than 0.50 mmol/l would not be detected. In view of the current evidence, however, it is debatable whether such a difference in plasma triglyceride concentration would have any significant impact on cardiovascular risk.³⁴

The results of this study indicate that both of the dietary approaches evaluated here may be suitable for hyperlipidaemic patients. However, a combination of the two approaches to give a diet moderately high in carbohydrate and fibre, and not too restricted in fats (provided that they are unsaturated, especially monounsaturated) might maximise effectiveness and acceptability. Such a diet (in which olive oil, legumes, vegetables, and fruit are present in generous amounts) closely resembles the typical Mediterranean diet consumed, in this area of Italy, at least until a few years ago, where mortality for cardiovascular disease has always been low.³⁵

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Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes

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Abstract

Objective—To compare the cumulative 21 year incidence of admission to hospital for osteoarthritis of the hip, knee, and ankle in former elite athletes and control subjects.

Design—National population based study.

Setting—Finland.

Subjects—2049 male athletes who had represented Finland in international events during 1920–65 and 1403 controls who had been classified healthy at the age of 20.

Main outcome measures—Hospital admissions for osteoarthritis of the hip, knee, and ankle joints identified from the national hospital discharge registry between 1970 and 1990.

Results—Athletes doing endurance sports, mixed sports, and power sports all had higher incidences of admission to hospital for osteoarthritis than controls. Age adjusted odds ratios compared with controls were 1.73 (95% confidence interval 0.99 to 3.01, $P=0.063$) in endurance, 1.90 (1.24 to 2.92, $P=0.003$) in mixed sports athletes, and 2.17 (1.41 to 3.32, $P=0.0003$) in power sports athletes. The mean age at first admission to hospital was higher in endurance athletes (70.6) than in other groups (58.2 in mixed sports, 61.9 in power sports, and 61.2 in controls). Among the 2046 respondents to a questionnaire in 1985, the odds ratios for admission to hospital were similar in all three groups after adjusting for age,

occupation, and body mass index at 20 (2.37, 2.42, 2.68).

Conclusions—Athletes from all types of competitive sports are at slightly increased risk of requiring hospital care because of osteoarthritis of the hip, knee, or ankle. Mixed sports and power sports lead to increased admissions for premature osteoarthritis, but in endurance athletes the admissions are at an older age.

Introduction

Because osteoarthritis is a common and often debilitating joint disorder knowledge about predisposing factors is important. An association between obesity and osteoarthritis of the knee has been shown,^{1,2} but data on the association with osteoarthritis of the hip are inconclusive.³ Strenuous occupational physical loading is associated with osteoarthritis of the hip,⁴ and participation in sports may also influence the risks of developing osteoarthritis. Klünder *et al* and Lindberg *et al* found that osteoarthritis of the hips was more common in former soccer players than in controls.^{5,6} Vingård *et al* found that men who did lots of sport of any kind had an increased risk of developing osteoarthritis of the hip.⁷ There is no general agreement on whether running can predispose to primary osteoarthritis of the hip.⁸⁻¹²

We conducted a national population based study to

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