

The emergence of cardiovascular disease during urbanisation of Africans

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Abstract

Objective: To review the available data on risk factors for cardiovascular disease (CVD), the influence of urbanisation of Africans on these risk factors, and to examine why stroke emerges as a higher risk than ischaemic heart disease (IHD) in the health transition of black South Africans.

Design: A review of published data on mortality from and risk factors of CVD in South Africans.

Setting: South Africa.

Subjects: South African population groups and communities.

Methods: The available data on the contribution of stroke and IHD to CVD mortality in South Africa are briefly reviewed, followed by a comparison of published data on the prevalence and/or levels of CVD risk factors in the different South African population groups. The impact of urbanisation of black South Africans on these risk factors is assessed by comparing rural and urban Africans who participated in the Transition and Health during Urbanisation of South Africans (THUSA) study.

Results and conclusions: The mortality rates from CVD confirmed that stroke is a major public health problem amongst black South Africans, possibly because of an increase in hypertension, obesity, smoking habit and hyperfibrinogenaemia during various stages of urbanisation. The available data further suggest that black South Africans may be protected against IHD because of favourable serum lipid profiles (low cholesterol and high ratios of high-density lipoprotein cholesterol) and low homocysteine values. However, increases in total fat and animal protein intake of affluent black South Africans, who can afford Western diets, are associated with increases in body mass indices of men and women and in total serum cholesterol. These exposures may increase IHD risk in the future.

Keywords
Urbanisation
Nutrition transition
Black South Africans
Non-communicable disease
Stroke
Ischaemic heart disease
Hypertension
Obesity

South Africa is a land of stark contrasts. It extends from highly industrialised cities, with an urban Western culture, to remote rural areas, where many people still follow traditional African lifestyles. Of the total population – just over 43 million in 2000 – there were 77.6% Africans (black), 2.5% Asians (Indian), 8.7% coloureds (mixed origin) and 10.4% whites (European)¹. The percentage of Africans living in urban areas increased from 35.8% in 1993 to 43.3% in 1996². During the same period, the percentages of coloureds, Indians and whites in urban areas remained within a relatively constant range (coloureds, 83.2–83.4%; Indians, 96.2–97.3%; whites, 91.1–90.6%)². This illustrates that the increase in urbanites from 48.3 to 53.7% over this period² was mainly because of the rapid migration of Africans.

The health status of black South Africans, compared with people in other middle-income countries, is poor³. South Africa is suffering from a triple burden of disease: (1) a combination of poverty-related infectious diseases, including human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), (2)

violence-related injuries, and (3) an increase in lifestyle-related non-communicable diseases (NCDs), probably associated with the demographic transition mentioned above. A comparison of available mortality figures of some NCDs for the different South African population groups from 1984 to 1986⁴ showed that, in urban blacks, stroke had the highest mortality (96.4 per 100 000 population per annum), followed by hypertension, diabetes mellitus (DM) and then ischaemic heart disease (IHD) (13.1 per 100 000 population per annum). IHD had the highest mortality rate in urban whites and Asians (162.7 and 206.9 per 100 000, respectively) followed by stroke, DM and then hypertension. Coloured South Africans have high mortality from stroke and IHD, followed by DM and hypertension⁴. These mortality patterns suggest that, although a number of NCDs contribute to mortality in urban blacks, urbanisation of black South Africans may be characterised by an early emergence of stroke.

The objective of this paper is to review available data on the risk factors for cardiovascular disease and examine why, and how, urbanisation of Africans leads to a higher

prevalence of stroke or cerebrovascular disease than of IHD. In addition to the data on mortality from cardiovascular disease (CVD) in South Africa, the impact of urbanisation on CVD risk factors will be evaluated by comparing these risk factors in rural and urban Africans with other population groups, where data are available.

Mortality from CVD in South Africa

Cerebrovascular disease accounted for 7.35% of the total mortality (199 537 deaths) in 1990³. It was the third highest cause of death³, while IHD, accounting for 4.86%, was the fifth highest cause³. Bradshaw and co-workers⁴ reported that stroke was the fourth highest cause of premature death in men and the second highest in women (6.3% and 10.1%, respectively) in 1995 in the age group 45 to 59 years. The comparative figures for IHD were fifth highest cause in men (5.6%) and seventh in women (3.8%); globally, this order is reversed. Murray and Lopez⁵ reported that, world-wide, IHD was the highest cause of death in 1990 and estimated that it will remain the highest cause to 2020, while cerebrovascular disease was and will be the second highest cause. Although there are insufficient recent data available on the epidemiology of stroke in South Africa, it seems that it is the main contributor to the excessive mortality rate from CVD in black South Africans⁶. A similar situation has been reported for black Americans⁷.

Risk factors for CVD in South Africans

Some of the major risk factors for IHD and stroke are compared for the different South African population groups in Table 1. All groups had relatively high

hypertension prevalences, with black women and white men having the highest. Obesity prevalence in black women was higher than in other groups of women, while white men showed the highest prevalence among male groups. Smoking prevalence seems to be highest in the coloured population^{2,8}. The data indicate that the total smoking prevalence in South Africa is decreasing. Black men and women have low mean serum total cholesterol (TC) levels compared with other South Africans. Seftel *et al.*⁹ mentioned that almost all blacks have high-density lipoprotein cholesterol (HDL-C) levels above 20% of TC, indicative of a protective effect against IHD. From the limited data available^{10,11}, plasma fibrinogen levels seem to be highest in the Indian population and lowest in whites, with blacks having intermediate levels.

Influence of urbanisation on CVD risk factors of black South Africans

The effect of urbanisation on CVD risk factors is evaluated in Table 2 by comparing mean values of these risk factors between rural and urban blacks. The data are from the THUSA study¹². THUSA is an acronym for Transition and Health during Urbanisation of South Africans and means 'help' in the Tswana language. In this baseline, cross-sectional study, there were 1854 'apparently healthy' adult volunteers recruited from 37 randomly selected sites in the North West Province of South Africa from 1996 to 1998. Subjects were stratified according to their level of urbanisation, based on demographic indicators. Stratum 1 consisted of people living in deep rural areas, following traditional lifestyles under the authority of a tribal head. Stratum 2 included dwellers on commercial farms and Stratum 3 included those living in informal housing areas

Table 1 Prevalence and levels of some cardiovascular disease risk factors in South African population groups

South Africa population group	Hypertension ² prevalence (blood pressure \geq 160/95 mmHg or subjects of treatment) (%)	Obesity ² prevalence (BMI > 30 kg m ⁻²) (%)	Smoking prevalence (%)		Dyslipidaemia ⁹ TC, mean (age 45–54 years) (mmol l ⁻¹)	HDL-C/TC > 20% ⁹ prevalence (protective) (%)	Plasma fibrinogen ^{10,11} (age 15–24 years) (g l ⁻¹)	
			1998 ²	1990 ⁸ , 1995 ⁸			Mean	Standard deviation
Black			28.4					
Men	10.3	7.7			4.20	96	2.31	\pm 0.88
Women	13.0	30.5			4.70		2.62	\pm 0.88
Coloured			48.7					
Men	12.4	9.1			6.09	75		
Women	17.1	28.3			6.30			
Indian			27.6					
Men	9.9	8.7			6.28	56	2.45	\pm 0.59
Women	9.3	20.2			5.86		2.75	\pm 0.55
White			33.7					
Men	15.2	19.8			6.39		2.10	\pm 0.42
Women	12.0	24.3			6.62		2.09	\pm 0.55
All								
Men	11.0	9.1	52	42				
Women	13.2	29.4	17	11				

Table 2 Influence of urbanisation on some cardiovascular disease risk factors (mean and 95% confidence interval (CI) or standard deviation (SD)) of black South Africans from the THUSA study^{12–14}

Black South African stratum level	Blood pressure (mmHg)				Body mass index (kg m ⁻²)		Smoking (% of group)	Total serum cholesterol		Plasma fibrinogen (g l ⁻¹)			
	Systolic		Diastolic		Mean	95% CI		Mean	95% CI	15–25 years		45–55 years	
	Mean	95% CI	Mean	95% CI						Mean	SD	Mean	SD
Stratum 1 – deep rural, tribal areas													
Men	125 ^{ab}	123–128	76 ^{ab}	74–77	20.7	20.2–21.3	48.6	3.9 ^a	3.8–4.0	2.56	0.53	3.28	1.16
Women	128 ^{efg}	126–130	78 ^{ghi}	76–79	25.6	24.8–26.3	19.8	4.0 ^e	3.9–4.1	2.91	0.66	3.39	0.91
Stratum 2 – farms													
Men	125 ^c	120–129	76 ^{cd}	73–79	20.6	19.9–21.3	66.5	4.1 ^b	3.8–4.2	3.14	0.69	3.76	0.79
Women	138 ^{eh}	133–143	82 ^{gi}	78–85	26.3	25.2–27.4	27.3	4.1 ^f	4.0–4.3	3.42	0.78	3.79	0.87
Stratum 3 – informal housing areas (squatter camps)													
Men	134 ^{acd}	130–137	81 ^{ace}	78–83	20.3	19.7–20.9	63.2	3.9 ^c	3.7–4.0	3.01	1.19	3.13	1.39
Women	136 ^{fi}	132–140	84 ^{hk}	81–87	26.7	25.7–27.7	20.7	4.1 ^g	4.0–4.3	3.78	1.78	3.87	1.32
Stratum 4 – rural (townships)													
Men	132 ^b	130–135	79 ^{aef}	77–81	21.3	20.8–21.8	60.7	4.0 ^d	3.9–4.1	2.97	1.01	2.95	1.01
Women	135 ^{gi}	133–138	83 ^{il}	82–85	28.0	27.3–28.8	11.5	4.4 ^{efg}	4.3–4.5	3.80	1.55	3.93	1.47
Stratum 5 – urban (professionals)													
Men	125 ^d	120–130	80 ^{bdf}	76–84	23.1	22.2–24.0	42.3	4.7 ^{abcd}	4.5–4.9	3.14	0.80	3.19	0.83
Women	121 ^{hij}	115–127	75 ^{kl}	71–79	28.1	26.7–29.4	1.0	4.8 ^{efg}	4.6–5.0	3.64	0.88	3.57	1.34

Means with the same superscript letter differ significantly ($P \leq 0.05$; general linear model (GLM) multivariate test).

around towns and cities. People in Stratum 4 were living in former black 'townships'. Stratum 5 mainly consisted of professional people living in affluent, Westernised circumstances. Strata 1 and 2 were regarded as rural, 3 as transitional, and 4 and 5 as urban.

Table 2 shows that, except for Stratum 5, the mean blood pressures of subjects living in transitional and urban areas (Strata 3 and 4) were significantly higher than those of subjects in the two rural areas (Strata 1 and 2). Van Rooyen *et al.*¹³ found that more than 20% of the 'apparently healthy' THUSA subjects had systolic pressures above 140 mmHg and diastolic pressures above 90 mmHg. The highest prevalences (32.9% with increased systolic and 25.1% with increased diastolic pressures) were seen in people from informal housing areas, where most newcomers to urban areas live. Because only subjects without known diseases, and not using chronic medication, were included in the study, subjects identified with hypertension were untreated and did not know they suffered from the condition. Therefore, the lower blood pressure levels of subjects in Stratum 5 could mean that fewer professional urban blacks have untreated hypertension because of better access to health services.

All groups of women had mean body mass index (BMI) $>25 \text{ kg m}^{-2}$, and a clear increase with urbanisation was observed. In men, all groups had BMI $<24 \text{ kg m}^{-2}$ and subjects from Stratum 5 had the highest levels.

Smoking prevalence was higher in men than in women, and higher in men than the national prevalence of 42%², except in Stratum 5 where 42.3% of men and only 1.0% of women smoked.

Total serum cholesterol levels of men and women in Stratum 5 (4.7 and 4.8 mmol l⁻¹) were significantly higher than those in other strata, but substantially lower than mean levels of other population groups shown in Table 1.

Table 2 includes mean plasma fibrinogen levels of two age groups in order to compare with the younger subjects shown in Table 1. The values of the women were consistently higher than those of the men, probably related to the higher BMI of women¹⁴. There seems to be an increase in plasma fibrinogen with urbanisation, except for subjects living on farms who had high levels. James *et al.*¹⁴ showed that these high levels in men correlated with low nutritional status. The mean fibrinogen levels of men and women in all five strata, except 15- to 25-year-old men from Stratum 1, were higher than the level of 2.8–3.0 g l⁻¹ thought to be associated with an increased CVD risk¹⁴.

Table 3 shows some selected nutrient intakes of the THUSA subjects, illustrating the increase in total fat and animal protein intake, at the expense of carbohydrates, with urbanisation. The table also indicates that the 'quality' of the diet of Stratum 5 subjects, reflected in their higher fibre, iron and vitamin A intakes, was better than that of subjects in the other strata, probably because of intakes of fruits and vegetables.

Discussion

The available CVD mortality data on different South African population groups suggest that urbanisation of black South Africans is accompanied by an 'earlier' emergence of stroke than of IHD. This may be a unique feature of the South African health transition and the question is whether the emergence of specific CVD risk factors and/or protective mechanisms against IHD may be responsible. The risk factors examined were hypertension, obesity, dyslipidaemia, smoking habit and hyperfibrinogenaemia.

Clearly, hypertension cannot be the only factor for the

Table 3 Selected nutrient intakes of the THUSA subjects^{12–14} (mean \pm standard deviation)

Black South African stratum level	Energy from total fat (%)	Energy from total protein (%)	Animal protein (g)	Energy from total carbohydrates (%)	Dietary fibre (g)	Iron (mg)	Vitamin A (retinol equivalents)	Total energy (MJ)
Stratum 1 – deep rural, tribal areas								
Men	22.9 \pm 6.8	11.6 \pm 2.2	26.0 \pm 15.9	67.4 \pm 9.2	19.2 \pm 10.9	9.4 \pm 4.8	610 \pm 579	9.6 \pm 3.8
Women	3.6 \pm 7.1	11.4 \pm 2.0	22.2 \pm 12.3	67.0 \pm 9.4	15.8 \pm 7.3	8.4 \pm 4.2	569 \pm 572	7.9 \pm 3.1
Stratum 2 – farms								
Men	22.5 \pm 7.4	12.1 \pm 2.1	27.9 \pm 14.1	67.6 \pm 9.5	15.6 \pm 7.5	7.8 \pm 3.9	596 \pm 642	9.0 \pm 3.9
Women	22.5 \pm 6.7	11.3 \pm 2.1	21.9 \pm 12.8	68.4 \pm 9.0	15.4 \pm 6.8	7.4 \pm 3.9	534 \pm 404	8.0 \pm 3.1
Stratum 3 – informal housing areas (squatter camps)								
Men	24.2 \pm 7.8	11.9 \pm 1.9	27.0 \pm 13.4	65.5 \pm 10.1	17.3 \pm 8.1	9.1 \pm 4.7	731 \pm 670	9.3 \pm 4.1
Women	25.7 \pm 7.7	11.8 \pm 2.0	25.7 \pm 16.8	64.0 \pm 9.7	16.1 \pm 7.8	8.2 \pm 4.2	766 \pm 693	7.8 \pm 3.2
Stratum 4 – rural (townships)								
Men	26.0 \pm 7.1	11.8 \pm 2.1	29.2 \pm 15.7	64.0 \pm 9.4	18.8 \pm 9.2	9.1 \pm 3.9	765 \pm 586	9.9 \pm 3.8
Women	27.7 \pm 6.8	12.1 \pm 2.3	29.1 \pm 15.8	61.5 \pm 9.3	17.1 \pm 7.9	8.8 \pm 4.0	892 \pm 731	8.0 \pm 2.9
Stratum 5 – urban (professionals)								
Men	30.6 \pm 6.7	13.2 \pm 1.8	44.1 \pm 19.9	57.3 \pm 8.6	19.7 \pm 9.1	10.8 \pm 4.5	899 \pm 677	9.8 \pm 3.8
Women	31.8 \pm 5.7	13.4 \pm 2.3	42.6 \pm 16.6	55.6 \pm 7.5	17.7 \pm 8.1	10.4 \pm 3.9	1246 \pm 1030	8.5 \pm 3.1

Dietary intakes measured with a validated quantitative food-frequency questionnaire and analysed with a program based on the South African Food Tables.

early emergence of stroke since all population groups showed high prevalences of hypertension. The changes observed in risk factors during urbanisation suggest that a specific combination of factors – for example, hypertension plus obesity and increased fibrinogen in women, and hypertension plus smoking and increased fibrinogen in men – may favour the development of stroke.

The health consequences of obesity in black women were examined in some depth in the THUSA study. Malan¹⁵ compared the metabolic profiles and fibrin network characteristics of selected android (upper-body) and gynoid (lower-body) obese women with those of age-matched normal weight women. The fibrin network characteristics (permeability coefficient, mass length ratio and compaction) reflect the type of fibrin clot formed (porosity, thickness and length of fibres, and their tensile strength) and ease with which clots can be lysed. Her results demonstrated that the plasma from both android and gynoid obese women reflected a prethrombotic state compared with normal weight women. It seems that the biochemical milieu of plasma from the obese women (lower albumin and HDL-C and increased insulin, uric acid and triglycerides) promoted the formation of tighter and more rigid gel structures that are more resistant to thrombolysis. This haemostatic profile may possibly contribute, together with other risk factors, to an increased risk for stroke in women.

The slower emergence of IHD than of stroke in the African population could possibly also be related to their favourable lipid profiles^{9,12}. Although total serum cholesterol increases with urbanisation^{9,12}, HDL-C levels remain high⁹. But, other protective factors may also operate. Loktionov *et al.*¹⁶ found that black South Africans in the THUSA study had a very low frequency of the 677C \rightarrow T mutation of the methylene tetrahydrofolate reductase (MTHFR) gene (20%, compared with 56% in Caucasians).

They could not detect any homozygotes for this mutation in blacks, compared with 12% in their Caucasian sample. The mutation causes thermolability of the MTHFR enzyme, impairing homocysteine remethylation. The result is increased levels of homocysteine, an accepted risk factor for CHD. It seems that black South Africans may be protected against CHD by genetically determined low homocysteine levels¹⁷. However, the THUSA study demonstrated that, although TC levels of urban Africans are lower than reported levels of other population groups, professional urban Africans had significantly higher levels than their rural counterparts. It could be that with more urban Africans exposed to affluence and Western lifestyles over longer periods, dyslipidaemia and obesity may increase to such an extent that the above-mentioned protective mechanisms against IHD are no longer effective.

It is generally accepted that NCDs precipitate in genetically susceptible individuals because of exposure to a combination of environmental factors, including nutrition¹⁸. The dietary changes observed across strata in the THUSA subjects were small, except in the urban professionals. These subjects had the highest levels of education and income¹² and their increased energy and fat intakes are reflected in higher levels of serum TC and BMI. However, these subjects also had higher intakes of several micronutrients (Table 3), lower smoking prevalence and lower mean blood pressures (Table 2). These risk factors (except for serum TC and BMI in men) were higher in Strata 3 and 4, representing subjects either in transition or poor urban areas. These poorer subjects in transition had higher fat and animal protein intakes compared with rural subjects, but lower micronutrient intakes than dietary recommendations¹⁹. It seems, therefore, that the impact of urbanisation on risk factors for CVD may be determined by the type of diet that can be afforded.

Conclusion

Comparison of mortality rates from CVD between South African population groups indicates that stroke, rather than IHD, may be a unique feature of the health transition associated with urbanisation of black South Africans. An analysis of CVD risk factors across population groups, and a comparison of these risk factors between rural and urban black South Africans, suggest that Africans may presently be protected against IHD because of favourable lipid profiles (low serum TC and high ratio of HDL-C) as well as genetically determined low homocysteine levels. Their high rates of stroke may be related to a combination of risk factors: hypertension, obesity and hyperfibrinogenaemia in women, and hypertension, smoking habit and hyperfibrinogenaemia in men. These risk factors can be prevented or treated. However, in a climate where undernutrition and infectious diseases (including HIV/AIDS) are the major public health problems using the largest portion of the health budget, addressing these risk factors in affordable, effective and culturally sensitive programmes remains a major challenge.

References

- 1 Anon. *Statistics South Africa 2000* [Online]. Available at <http://www.statssa.gov.za/RELEASES/DEMOGRAP/2000/po302.htm>. Accessed 10 September 2001.
- 2 Anon. Health and related indicators. In: Ntuli A, Crisp N, Clarke E, Barron P, eds. *2000 South African Health Review*. Durban: Health Systems Trust, 2000; 467–77.
- 3 Bradshaw D, Masiteng K, Nannan N. Health status and determinants. In: Ntuli A, Crisp N, Clarke E, Barron P, eds. *2000 South African Health Review*. Durban: Health Systems Trust, 2000; 89–124.
- 4 Bradshaw D, Bourne D, Schneider M, Sayed R. Mortality patterns of chronic diseases of lifestyle in South Africa. In: Fourie J, Steyn K, eds. *Chronic Diseases of Lifestyle in South Africa*. Medical Research Council (MRC) Technical Report. Tygerberg: MRC, 1995; 5–31.
- 5 Murray CJL, Lopez AD. Alternative visions of the future: projecting mortality and disability, 1990–2020. In: Murray CJL, Lopez AD, eds. *The Global Burden of Disease*. Boston, MA: World Health Organization/World Bank/Harvard University Press, 1996; 325–95.
- 6 Wyndham CH. Mortality from cardiovascular diseases in the various population groups in the Republic of South Africa. *S. Afr. Med. J.* 1979; **56**: 1023–30.
- 7 Broderick JP, Brott T, Tomsick T, Husster G, Miller R. The risk of subarachnoid and intercerebral hemorrhages in blacks as compared to whites. *N. Engl. J. Med.* 1992; **326**: 733–6.
- 8 Yach D. Smoking: review of research and identification of future priorities. In: Fourie J, Steyn K, eds. *Chronic Diseases of Lifestyle in South Africa*. Medical Research Council (MRC) Technical Report. Tygerberg: MRC, 1995; 51–60.
- 9 Seftel HC, Raal FJ, Joffe BI. Dislipidaemia in South Africa. In: Fourie J, Steyn K, eds. *Chronic Diseases of Lifestyle in South Africa*. Medical Research Council (MRC) Technical Report. Tygerberg: MRC, 1995; 61–71.
- 10 Venter CS, Vorster HH, Silvis N, Kruger A, Mia F, Seftel HC. Determinants of plasma fibrinogen in South African communities. In: Ernst E, Koenig W, Lowe GDO, Meade TW, eds. *Fibrinogen: A "New" Cardiovascular Risk Factor*. Vienna: Blackwell-MZV, 1992; 166–71.
- 11 Vorster HH, Jerling JC, Steyn K, Badenhorst CJ, Slazus W, Venter CS, Jooste PL, Bourne LT. Plasma fibrinogen of black South Africans: the BRISK study. *Public Health Nutr.* 1998; **1**(3): 169–76.
- 12 Vorster HH, Wissing MP, Venter CS, Kruger HS, Kruger A, Malan NT, De Ridder JH, Veldman FJ, Steyn HS, Margetts BM, MacIntyre U. The impact of urbanization on physical, physiological and mental health of Africans in the North West Province of South Africa: the THUSA study. *S. Afr. J. Sci.* 2000; **96**: 505–14.
- 13 Van Rooyen JM, Kruger HS, Huisman HW, Wissing MP, Margetts BM, Venter CS, Voerster HH. An epidemiological study of hypertension and its determinants in a population in transition: the THUSA study. *J. Hum. Hyperten.* 2000; **14**: 779–87.
- 14 James S, Vorster HH, Venter CS, Kruger HS, Nell TA, Veldman FJ, Ubbink JB. Nutritional status influences plasma fibrinogen concentration: evidence from the THUSA survey. *Thromb. Res.* 2000; **98**: 383–94.
- 15 Malan MM. *Fibrin network characteristics of obese African women*. PhD thesis, PU vir CHO, Potchefstroom, 1999; 1–233.
- 16 Loktionov A, Vorster H, O'Neill I, Nell T, Bingham SA, Runswick SA, Cummings JH. Apolipoprotein E and methylene tetrahydrofolate reductase genetic polymorphisms in relation to other risk factors for cardiovascular disease in UK Caucasians and black South Africans. *Atherosclerosis* 1999; **145**(1): 125–35.
- 17 Ubbink JB, Vermaak WJH, Delport R, Van der Merwe A, Becker PJ, Potgieter H. Effective homocysteine metabolism may protect South African blacks against coronary heart disease. *Am. J. Clin. Nutr.* 1995; **62**: 802–8.
- 18 Vorster HH, Bourne LT, Venter CS, Oosthuizen W. Contribution of nutrition to the health transition in developing countries: a framework for research and intervention. *Nutr. Rev.* 1999; **57**(11): 341–9.
- 19 Ralph A. Dietary reference values. In: Garrow JS, James WPT, eds. *Human Nutrition and Dietetics*, 9th ed. London: Churchill Livingstone, 1994; 782–96.