OECD Health Working Papers No. 1

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https://dx.doi.org/10.1787/237273475872

OECD

DELSA/ELSA/WD/HEA(2003)1

OECD OCDE

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OECD HEALTH WORKING PAPERS

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

20-Feb-2003

English - Or. English

DIRECTORATE FOR EMPLOYMENT, LABOUR AND SOCIAL AFFAIRS
EMPLOYMENT, LABOUR AND SOCIAL AFFAIRS COMMITTEE

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JEL Classification I11, I18, L65.

JT00139638

DELSA/ELSA/WD/HEA(2003)1 Unclassified

English - Or. English

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ACKNOWLEDGEMENTS

The authors thank Dr. Jill Michels, Assistant Director of the University of South Carolina, College of Pharmacy, Drug and Poison Information Center and her staff for their technical assistance. M. Dickson, currently Professor at the college of Pharmacy, University of South Carolina, was a consultant to the OECD at the time of the study. We thank for useful comments and discussions on an earlier version of the paper the following OECD staff: J. Hurst, P. Scherer and S. Mattke. We thank V. De Fontenay for her wonderful research assistance. The responsibility for remaining errors rest with the authors. The views expressed here do not necessarily represent those of the OECD nor those of its Member countries.

SUMMARY

1. This study presents the results of a joint analysis of patterns of consumption, expenditure, and unit expenditure for a core set of drugs aimed at preventing and treating cardiovascular disease. The current study examines the relationships among three pharmaceutical variables (expenditure, volume of drug use, and unit expenditure) classified according to eight therapeutic categories which are specific for the prevention and treatment of cardiovascular disease and stroke. It covers an 11-year time period, and specifies relevant country-specific structural features in a sample of 12 OECD countries.

2. The data presented in this report show how the three descriptive pharmaceutical variables vary across these countries. The study also contains a preliminary exploration of factors associated with variation in these variables across countries and through time. Findings for each of the eight cardiovascular disease and stroke drug therapeutic categories investigated in this study are discussed in relationship to volume of use, expenditure, and unit expenditure to provide a basis for discussing the value of pharmaceuticals. In addition, findings are presented for subcategories of cardiovascular drugs to better understand how more specific drug classifications affect the results.

3. The main finding is that cross-country variations in the use of less expensive effective drugs such as diuretics and betablockers seem to be related to "needs", as measured by the Ischaemic Heart Disease burden of disease. The pattern for newer, more expensive agents is more difficult to interpret. While expenditure is higher, it is not clear whether this is due to changing patterns of use, a perception of increased need, or a willingness to pay. Much of the increase appears to be in the serum lipid group which has experienced rapid growth in utilisation recently. This may be due, at least in part, to increasing evidence that lowering serum lipid levels has benefits for segments of the population not previously treated.

4. Overall, the results show that use of “newer” pharmaceutical agents (calcium channel blockers, ACE inhibitors, and serum lipid reducers) is higher among those countries that spend a greater percentage of GDP on health. A range of factors could have contributed to these trends, including clinical judgement that the new compounds are more effective and marketing efforts which concentrate more on new in-patent products.

5. Beyond their descriptive value, the results invite a retrospective examination of the effect of different policies on pharmaceutical expenditure. Although policy and expenditure decisions on pharmaceuticals are ultimately qualitative judgements, they can, and should, be informed by better data. In particular, this study contributes to a better understanding of the underlying trends driving the increase in pharmaceutical expenditure.

RESUME

6. Cette étude présente les résultats d'une analyse simultanée des tendances de consommation, de dépenses et de dépenses unitaires d'un ensemble de médicaments clés destinés à la prévention et au traitement de la pathologie cardiovasculaire. Elle examine les relations entre les trois variables pharmaceutiques (dépense, volume de médicaments et dépense unitaire) classées en huit catégories thérapeutiques, qui sont spécifiques à la prévention et au traitement des maladies cardiovasculaires et des attaques cérébrales. Elle couvre une période de onze années et met en lumière un certain nombre de caractéristiques structurelles nationales pertinentes pour un échantillon de douze pays membres de l'OCDE.

7. Les données présentées dans le rapport comparent les variations de ces trois variables à travers les pays. L'étude menée comprend également une recherchce préliminaire sur les facteurs associés à l'évolution de ces variables à travers les pays et au cours du temps. Les résultats pour chacune des huits catégories thérapeutiques abordées dans cette étude et relatives à la pathologie cardiovasculaire et aux accidents cérébraux sont discutés en relation au volume d'utilisation, à la dépense, et à la dépense unitaire pour offrir une base de discussion quant à la valeur des médicaments. De plus, les conclusions sont présentées par sous-catégories de médicaments cardiovasculaires pour mieux saisir comment des classifications plus spécifiques des médicaments affectent les résultats.

8. La conclusion principale est que les variations d'un pays à l'autre dans l'utilisation de médicaments peu chers et efficaces (diurétiques, agents beta-bloquants) semblent être liées aux « besoins » (mesurés par le poids des maladies cardio-ischémiques). Le schéma pour les médicaments plus récents et plus onéreux (tels que les hypolipémiants, et parmi eux les statines) est plus difficile à interpréter. Tandis que leur dépense est supérieure, il n'est pas clair si cela est dû à un changement de leur utilisation, la perception d'un besoin accru ou une propension à payer. La plus grande part d'augmentation est observée dans l'utilisation récente plus marquée des hypolipémiants. Ceci peut être dû, du moins en partie, à l'évidence croissante qu'une réduction des taux de serums lipidiques peut avoir des bénéfices pour des segments de la population qui n'était pas traités auparavant.

9. Dans l'ensemble, les résultats montrent que l'utilisation d'agents pharmaceutiques plus récents (les inhibiteurs calciques, les inhibiteurs de l'enzyme de conversion (IEC), les réducteurs de serums lipidiques) est supérieure dans les pays qui consacrent une plus grande part de leur PIB dans la santé. Un éventail d'autres facteurs peut avoir contribué à ces tendances, notamment les jugements cliniques quant à l'efficacité des nouveaux composants et les efforts marketing qui sont plus concentrés sur les produits innovants.

10. Au-delà de leur valeur descriptive, les résultats invitent à un examen rétrospectif des effets de différentes politiques sur les dépenses pharmaceutiques. Bien que les décisions publiques et de dépenses dans le domaine des produits pharmaceutiques soient finalement qualitatives, elles peuvent et doivent être complétées par des données quantitatives de meilleure qualité. Dans cette perspective, la présente étude contribue à une meilleure compréhension des évolutions sous-jacentes à l'origine de l'augmentation des dépenses pharmaceutiques.

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INTRODUCTION

11. Cardiovascular disease (CVD) and stroke (cerebrovascular disease) are among the top three leading causes of death in OECD countries (OECD 2001). Cardiovascular disease, cancer and stroke rank number one through three respectively. These diseases have significant economic implications from a health policy perspective. The most cost-effective approach in the long run is prevention which will require adjustments in health-related behaviour. In the short run, at least, the health care system will continue to be responsible for management of CVD and stroke through medical interventions. These interventions include surgery, rehabilitation, and pharmacotherapy, of which the latter is the most frequently used. Pharmacotherapy is used to ameliorate a variety of CVD and stroke risk factors, to provide symptomatic relief, to offer maintenance care, and to directly address the causes of disease. For CVD and stroke, drug therapy is the mainstay of maintenance care and a significant component of medical strategies designed to prevent acute events. Once CVD and stroke patients begin drug therapy it continues for the remainder of their lives. Thus, pharmacotherapy has the potential for significant clinical, economic, and humanistic impact which is likely to increase in importance as the population in OECD countries becomes more elderly.

12. Much is known about the benefits and risks of pharmaceuticals in humans at the individual level because clinical trials are required to demonstrate safety and efficacy before a new drug can be used in the general population. In the last 10 years clinical trials have begun to include assessments of the economic and humanistic elements of new drugs. These patient level studies are essential for identifying *ex ante* the potential role of new pharmaceuticals in medical care. However, very few studies have examined the role of pharmaceuticals *ex post* at the population level. Because of the broad scope of pharmaceutical therapy, population level data are only useful if aggregated at an interpretable level, such as for a particular disease or by well defined therapeutic categories. These data provide a national perspective on realised drug use patterns that serve as the starting point for retrospective analyses of costs and drug utilisation. The overall purpose of this study is to fill a gap by providing data on volume of drug use and expenditure for drugs used in the prevention and treatment of CVD and stroke in an international context. The following questions will be addressed:

- What are the patterns of drug use for CVD and stroke in a group of OECD countries over a recent 11-year period?

- How are these patterns of use affected by health policies, economic circumstances, and burden of disease?

13. Ideally, a study such as this would look at whether there was any affect of drug use on outcomes from CVD and stroke, such as rates of one-year survival following heart attack and stroke. However, data of that kind is difficult to obtain across countries and did not become available during the time period of this study. Therefore, descriptive data will be used to address questions regarding differences among countries and across time to provide a broader understanding of pharmaceutical use in CVD and stroke, and to ask questions about the forces that may account for the observed patterns of use. Addressing the first question will involve presenting data on the volume of drugs used, changes in the mix of drug use, and

patterns of expenditure in relation to drug use. Such data was not available in the last OECD pharmaceutical report (Jacobzone, 2000).

14. These questions will be addressed using pharmaceutical utilisation data for eight therapeutic categories from 12 countries. (The countries included in the study are Canada, France, Germany, Italy, Japan, The Netherlands, New Zealand, Spain, Sweden, Switzerland, the UK and the USA). Drug utilisation data are for the years 1989, 1991, 1993, 1995, 1997, and 1999. The therapeutic categories, described in detail later, are oral vitamin K antagonists for the prevention of stroke, antihypertensives of several therapeutic categories, diuretics, vasodilators, and serum lipid reducing agents.

15. The remainder of this paper is organised into four sections. First, some background information on drug utilisation in general and this study in particular is provided. The second section introduces the data and methods and includes a brief description of the therapeutic categories of drugs in the study. Section three presents and discusses results in terms of their economic and health policy implications. The final section offers conclusions and suggestions.

BACKGROUND

Purpose and limitations of drug utilisation studies

16. Pharmaceutical use, drug use, drug utilisation, drug consumption, and similar terms are used interchangeably in this report although the technical literature tends to prefer the term drug utilisation. There is no precise definition for these terms so drug use is defined here as "apparent drug use by a population estimated from secondary data." Utilisation data come from many sources, but in this case they are the result of sales from producers. While these are generally regarded as the most complete data available, it is important to acknowledge some assumptions made in linking secondary data to population consumption.

17. First among these is the difference between units of drug available (purchased) and those consumed. There is a large body of literature to document the difficulty of determining the quantity of prescribed drugs that are consumed by those for whom they were intended. The numbers vary widely, but everyone agrees that actual compliance is less than 100%. This is especially a problem in CVD because many patients are asymptomatic, and therefore do not perceive an immediate need for their medication. Secondly, some of the drugs for treatment of cardiovascular disease have undesirable side effects that may deter patients from complete adherence to the prescribed medication regimen. Hypertension is the classic example since its symptoms are often not evident to the patient.

18. Comparative studies of drug utilisation also make the assumption of biological and metabolic equivalence across populations so that the same dose would suffice for users in all populations. There is now evidence that for some classes of pharmaceutical compounds this may not be entirely correct. A more obvious lack of equivalence is seen in differences in the body mass of among some populations. This becomes important when dosage for a drug depends on body mass (*e.g.*, dosage for agents to prevent stroke is determined in part by body mass). In some cases, we would expect populations with larger average body mass to require more drug to achieve the same effect as populations with relatively smaller average body mass.

19. These two examples serve to illustrate that comparative drug utilisation statistics must be interpreted in the context of the populations being compared. This study does not make adjustments for these or other possible affects on drug utilisation because the necessary coefficients for adjustment are unknown and we expect factors influencing drug use behaviour to be evenly distributed across populations. Specific drug utilisation measurement issues are considered in the next section.

20. This study is based on retrospective data and therefore has the limitations and strengths inherent in non-experimental studies using this approach. The data are a historical record of drugs purchased, which, within the limits described above, will be used as a measure of actual drug use. Retrospective data do not permit controlling for a variety of confounding factors thus limiting our ability to make inferences about associations observed in the results. On balance, the data provide a useful way to examine drug use at the population level and provide the basis for more specific studies.

Research on international comparisons of pharmaceutical consumption and expenditure

21. There have been numerous studies and editorial reports on drug use and drug expenditure, but relatively few international comparisons of pharmaceutical consumption or expenditure. Many of the comparative studies have focused on product price differences rather than on examining differences in consumption and expenditure. A notable exception to this is the 1992 CREDES study of four European countries (Lecomte and Paris, 1994). The authors document large differences in consumption by therapeutic categories as well as differences in expenditure for pharmaceuticals that constitute 38% to 49% of consumption in the four countries studied. They note these differences are due to variation in multiple factors such as expenditure controls, industry promotional practices, type of pharmaceutical industry in a country, and "sociocultural" factors (*Ibid.*, pp.1-2, 75-76). An OECD econometric study of about the same time, supports this view by demonstrating statistically significant relationships between several sociodemographic and institutional variables and expenditure on pharmaceuticals. The study also does not find a significant relationship between population age structure and pharmaceutical expenditure (OECD, 1995).

22. More recently, an OECD study reviewed the "determinants" of pharmaceutical expenditure and the public policies that affect both pharmaceutical consumption and expenditure. In addition to the factors cited above that are associated with demand, the report also notes that R&D activities, patent policies, and marketing strategies have an influence on consumption and expenditure (Jacobzone, 2000). As with the other studies, there is recognition that pharmaceutical use is driven by many factors. Public policies designed to rationalise consumption and control expenditure must be cognisant of these components.

23. The recent work by Danzon has investigated the questions of volume consumed and product mix relative to public policies on pharmaceuticals. Of interest here are the observations on product mix and volumes in national pharmaceutical markets. For example, the US has the largest number of cardiovascular products (710) of the major world markets and also the largest number of products per molecule (average of 6.7), but lower levels of expenditure per capita than some other countries. Products per molecule is a proxy for generic competition (more products per molecule means more competition). France, on the other hand, has an average of 1.8 product per molecule, and much higher per capita expenditure than in the US, due largely to volume and, by inference, less generic competition (Danzon, 1997).

24. A recently completed study of pricing policies in Canada, France, Germany, Japan, Mexico, Russia, and the UK raised additional issues for pricing of pharmaceuticals including, promotional costs, customer mix (*e.g.*, retail, hospital, government, etc.), patent systems, and the product development life cycle (United States International Trade Commission, 2000). This same report explains the difficulties of conducting international price comparison studies and briefly reviews the resources needed to do such work.

25. Often, price comparison studies use a market basket approach in which the prices for a group of drug products available in one country are compared to prices for the "same" products in other countries (See for example Fraser Institute, 2000). These studies almost never achieve the stated objectives because of the lack of comparability of products across countries, the inability to create a common basket of products, the absence of valid pricing data, and a lack of information with which to properly weight differences in consumption across countries (i.e., product mix). Danzon has reviewed international price comparison studies and argued that they: "...often have not clearly articulated their planned objectives, and this has led to a mismatch between methods and policy conclusions" (Danzon, 1996). She offers two other examples where methods have not been adequate to the task of making policy conclusions.[1] A more

[1] General Accounting Office. Prescription Drugs: Companies Typically Charge More in the United States than in Canada. Washington: Government Printing Office, 1992. A second study was conducted by the

therapeutically oriented approach avoids these problems by not focusing on products but on drug therapies for a common condition. This study adopts the therapeutic category approach so that product matching is not required and national differences in therapy are captured rather than differences in the use of drug products.

26. Thus, this study attempts to update earlier work on expenditure and drug consumption rather than examining price differences. It will examine whether the previously reported associations of expenditure and drug use to structural variables continue to hold, and search for new trends in pharmaceutical consumption and expenditure. The work cited above included studies of markets at the macro level and in some cases specific pharmaceutical markets such as cardiovascular drugs. This study will focus only on drugs used for the prevention and maintenance care for cardiovascular disease and stroke. This is a clinically and financially important market segment to study. Combining data obtained in this study with that in *OECD Health Data* reveals that the cardiovascular drugs included here account for about 10% of annual pharmaceutical sales between 1989 and 1997, and that the percentage is slightly increasing (see Table 1) (OECD, 2001). These percentages are only approximate for two reasons. First, the *OECD Health Data* expenditure data (the denominator) includes medical non-durable goods that are not pharmaceuticals. Second, the numerator is in ex-factory sales, while the denominator is expressed in "retail" sales which include taxes and markups that are not included in the numerator. It is difficult to know which way to interpret these two opposing affects, but it seems reasonable that about 10% of pharmaceutical sales (at retail) are accounted for by the products included in this study.

Table 1: Expenditure on cardiovascular drugs as a percent of total annual drug expenditure*

	Years				
	1989	1991	1993	1995	1997
Study drugs as a % of total drug expenditure	9.4	9.8	10.7	10.8	11.0

Note: * numerator is expenditure at the ex-factory level but denominator is at the consumer level.

same agency in 1994: Prescription Drugs: Companies Typically Charge More in the United States than in Great Britain.

DATA AND METHODS

27. Measuring drug utilisation, as will be seen, is more than counting the number of tablets consumed. It entails specifying the pharmaceutical compounds to include in a study, creating therapeutically comparable groups of products, and establishing a standardised unit of measurement. Each of these methodological issues is addressed briefly below and in greater detail in Annex A.

Data

28. The pharmaceuticals included in this study are directly related to the prevention and maintenance care of CVD and stroke patients as defined by the relevant therapeutic categories of the Anatomical Therapeutic Chemical (ATC) system of classifying pharmaceuticals (WHO, 2000*a* and 2000*b*). The ATC categories used in the study are shown in Table 2. Specific inclusion and exclusion criteria are listed in Annex A.

29. The categories in Table 2 cover a wide range of newer and older pharmaceutical interventions that form the core of pharmacotherapy for CVD and stroke. The specific products available within these categories vary across countries, but drugs within a therapeutic group have a common purpose and are therefore comparable at this level of aggregation. The breadth of compounds included reflects a compromise between a narrow range of agents as opposed to a broader list. A narrow range promotes precision (*e.g.*, antihypertensives for hypertension), whereas a broader range decreases the likelihood of omitting important agents (*e.g.*, including additional categories such as serum lipid reducers for reducing the risk of cardiovascular disease associated with elevated cholesterol[2]). Finally, it is important to note that drugs within the selected ATC groups were included whether they were prescription or non-prescription agents (this trait is sometimes referred to as "legal status"). This approach includes a drug with a different legal status across countries and one that changes legal status over time in the same country.

Table 2: ATC therapeutic categories for cardiovascular disease and stroke

ATC code	Category name	Condition
B01AA	Antithrombotic agents (vitamin K antagonists)	Stroke
C02	Antihypertensives	CVD
C03	Diuretics	CVD
C04	Peripheral vasodilators	CVD
C07	Beta blocking agents	CVD
C08	Calcium channel blockers	CVD
C09	ACE inhibitors	CVD
C10	Serum lipid reducing agents	CVD (high cholesterol)

[2] On the link between cardiovascular disease, cholesterol and the use of statins see: Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. The Lancet vol 360 (July 6, 2002), pp. 7-22.

Standardised unit of measurement

Comparisons in this study will be made at two levels:

-- by generic categories

30. Generic comparisons are relatively straightforward since a single compound is involved and one unit of the substance in product A is equivalent to one unit from product B (with the possible exception of differences in dosage form).

-- by therapeutic categories

31. Therapeutic category comparisons are more difficult, because these groupings are composed of different generic substances that have similar therapeutic consequences (which are not necessarily identical). In this case one milligram of generic compound X, may be more potent than one milligram of generic compound Y, even though they are both in the same therapeutic category. Analysis at the therapeutic category level requires a unit of measurement that standardises these differences.

32. The "defined daily dose" (DDD) methodology is used to resolve these measurement issues (WHO, 2000*b*). Equivalence among different compounds in the same therapeutic category is established by specifying a DDD for each compound. The DDD is defined as, "the assumed average maintenance dose per day for a drug used for is main indication in adults". This is not necessarily the average prescribed dose, nor is it necessarily the recommended daily dose. It is a therapeutically reasonable approximation that allows comparison of drug utilisation among population groups for therapeutically similar, but generically different drugs. Drug use measured in DDDs is reported as the rate per 1000 population per day. This gives an approximation of the proportion of a population treated daily with the agent or category measured. For example, a DDD of 10.0 indicates that about 1% of the population is treated daily with a given compound.

Combination products and creating therapeutically comparable groups

33. This study classifies products according to their active ingredients. When a product has only one active ingredient the classification is simple. However, some products are combinations of two or more active ingredients that may be from more than one therapeutic class. Because combinations can be quite different across countries (and at different times in the same country), it is useful to divide them into their unique compounds and classify each into its appropriate ATC group (see Table 2). This method promotes cross-country comparability and is therapeutically appropriate.

34. One implication of this method is that consumption of products is not measured; rather it is the consumption of specific generic substances represented by products. The active ingredient orientated approach is used in this study to enhance comparability at the therapeutic level with the understanding that it is not possible to directly compare product consumption. This approach also avoids the need to create DDDs for every combination product.

Missing information

35. Unfortunately, not all generic compounds have been assigned a DDD by the Collaborating Centre. When a DDD was not available, their guidelines were used to estimate a DDD based on manufacturer data and other readily available credible sources. However, a complete review of the clinical literature was not conducted. Many of these sources are now available on the internet or are referenced by internet drug information services. Technical assistance also was provided by the Associate Director of the USC Drug and Poison Information Center and her staff. The complete list of sources is found in Annex B.[3]

36. Much of the missing data occurred for combination products and is an artefact of the source data reporting system. Because combination products are not evenly distributed across all countries, and because they can represent a significant proportion of therapy, it was desirable to keep these agents in the study database. In some instances it was necessary to estimate strengths of the components in a combination. To eliminate them would have introduced a country and time specific bias. Various sources of information (see Annex B) were used to assign missing strengths to compounds in combination products. Missing information also was a problem for herbal products because many of the ingredients in these substances are not standardised in the manner of traditional pharmaceuticals. Again, various sources of information were used to assign strengths to dosage units (see Annex B).

Data sources and the sample of countries

37. The pharmaceutical utilisation and expenditure data for this study were extracted from a comprehensive IMS[4] database. Data from this source have already been used in the past as the basis for international comparisons (Lecomte and Paris 1994, Danzon and Chao 2000). Products in the database are classified by the ATC system developed and maintained by EphMrA.[5] This system is similar to the WHO classification of the same name, but some linkages were required to use the WHO system (WHO, 2000*a*).

38. Drug use data were obtained for a sample of 12 OECD countries that were selected to give geographic diversity and to include a variety of health system types with the expectation it would enhance the possibility of observing variation in pharmacotherapy and possibly outcomes from care. Countries included in the study and the availability of data are summarised in Table 3. Data for each year include the number of units sold and expenditure by product and ATC category. All data are at the ex-factory level which does not include taxes, markups, and rebates that may occur after leaving the producer. Therefore, these data do not represent the final cost to payers for prescriptions provided to consumers nor do they represent the number of prescriptions dispensed. However, they are thought to be unbiased indicators of utilisation and expenditure across countries, notwithstanding any differences in distribution systems which fall outside the scope of the current study. These data also reflect changes in preferences and needs that occur in each national market.

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3 Dr. Jill Michels, PharmD, Assistant Director, University of South Carolina Drug Information Center and her staff served as a clinical pharmacy consultants to the project.

4 IMS Health, IMS MIDAS (1989-1999).

5 EphMrA (European Pharmaceutical Marketing Association) sponsors and maintains the system. Some information is available at www.EphMrA.org.

Table 3: Data series of pharmaceutical use for CVD and stroke by country		
Country	Years of data by type*	
	Retail	Hospital
Canada	all years	all years
France	all years	1989 to 1991, 1999
Germany	all years	all years
Italy	all years	all years
Japan	all years	all years
The Netherlands	1989 to 1995, 1999	1989 to 1995, 1999
New Zealand	all years	all years
Spain	all years	None
Sweden	all years	None
Switzerland	all years	all years
UK	all years	all years
USA	all years	all years

Note: * A complete set of data includes (1989, 1991, 1993, 1995, 1997, and 1999).

Overview of pharmacotherapy for CVD and stroke

39. Interpretation of the results is facilitated by some appreciation of how the eight therapeutic categories of pharmaceuticals are used in the treatment and prevention of CVD and stroke. The purpose of this brief overview is to show the extent to which agents are and are not substitutable for CVD and stroke therapy.

40. For treatment decisions, CVD and stroke patients are typically differentiated on the basis of the severity of their condition, and the extent of their comorbidities. Comorbidity refers to the other medical conditions of a patient that are likely to have consequences for their CVD therapy. For a population-based study, it is well to keep in mind that treatments represented in the data cover the complete range of disease from those with mild severity and no comorbidities to those at the other extreme. To the extent that countries have different rates of CVD and perhaps different levels of comorbidity and severity, we may expect to see differences in the aggregate use of interventions even if all other factors affecting utilisation are equal.

41. Of all the different conditions given the CVD label, hypertension (high blood pressure) is the most prevalent. It is estimated that approximately 20% of the population in developed countries has abnormally high blood pressure. Depending on the cause of hypertension, its severity, and comorbidities, different pharmaceutical interventions are used. The general classification of pharmaceuticals used to treat CVD and stroke are briefly described below:

42. ***Antihypertensives (ATC = C02):*** agents traditionally labelled antihypertensive reduce blood pressure by relaxing blood vessels or reducing the amount of blood being pumped by the heart. Blood pressure is reduced because blood circulates with less resistance. These agents exert their action centrally (in the brain) and peripherally (on the heart, blood vessels, kidneys, etc.). Most of the compounds in this category have been used for many years. Their use has declined in recent years because of undesirable side effects and the availability of newer compounds with more specific actions, more favourable side effect profiles, and marketing efforts by producers.

43. ***Diuretics (ATC = C03):*** diuretics are used to treat a variety of cardiovascular diseases including hypertension. One effect of diuretics is to reduce blood pressure by reducing excess fluid in the body and

hence pressure on the vascular system. There are many types of diuretics, but all have the same purpose. A diuretic is most useful only when fluid volume is excessive. Generally, diuretics cannot be used to directly replace an antihypertensive such as those in the C02 category, however, in selected conditions (*e.g.*, uncomplicated high blood pressure), diuretics are often the first line of treatment. Diuretics are sometimes found in combination with antihypertensives due to their additive pressure lowering capacity.

44. ***Peripheral vasodilators (ATC = C04):*** like the antihypertensives, peripheral vasodilators have their primary effect by reducing resistance to blood flow in the blood vessels. Most of these agents act directly on the blood vessels (peripherally). The basic purpose is the same as for the antihypertensives, to reduce peripheral resistance. We also should note that this class of drugs is used for non-cardiovascular purposes precisely because they have a peripheral vasodilation effect. They are sometimes used to reduce leg pain caused by inadequate blood flow to muscles, for example, since they improve circulation through vasodilation. This is a good example of how the same drug can be used for multiple purposes.

45. ***Beta adrenergic blocking agents (C07):*** beta blockers are a specific type of antihypertensive that first became available in the late 1960s. They decrease the heart rate and cardiac output which may reduce blood pressure. Their use after a heart attack has been shown to reduce mortality by decreasing the probability of suffering a second heart attack. Within the beta blocker group there are two subcategories based on their selectivity for beta adrenergic receptors (selective and non-selective). While these are somewhat substitutable, in some cases it may be inappropriate, such as substituting a non-selective acting beta blocker for a selectively acting beta blocker.

46. ***Calcium channel blockers (C08):*** this relatively new class of compounds first appeared in the 1980s. They act by blocking the flow of calcium ions into the muscle tissue of the heart and blood vessels which causes them to relax and there is a consequent reduction in blood pressure. Calcium channel blockers (CCBs) also have demonstrated efficacy in the treatment of other CVD problems such as angina and arrhythmias.

47. ***ACE inhibitors (C09):*** agents acting on the renin-angiotensin system are generally referred to as ACE inhibitors. They act by inhibiting angiotensin converting-enzyme thereby reducing resistance in blood vessels. Like CCBs, ACEs are also useful in the treatment of other cardiovascular problems, especially the condition known as congestive heart failure (CHF).

48. ***Serum lipid reducing agents (C10):*** this classification of drugs, also called hypolipidemics, are a diverse group of compounds all with the purpose of reducing the level of cholesterol and triglycerides (fats) in the blood. It is important to control serum lipids because they are a risk factor for CVD and stroke. The newest subcategory within the C10 group is the "statins" which have enjoyed rapid and widespread adoption because they are generally much more effective for lowering blood levels of cholesterol than alternative drug treatments.

49. The foregoing discussion illustrates that substitutability exists across some therapeutic categories, and some are used together to offer a more comprehensive treatment of CVD. It also illustrates areas where substitutability is low or non-existent. Finally, there are subtle differences within some categories of agents used to treat hypertension for different genetic and age groups.

50. ***Vitamin K antagonists (B01AA):*** just as there are differences in CVD therapy, there also are differences in the drug therapy for the prevention of stroke which are, in general, related to the type of stroke for which a patient is at risk. Therapies included in this study are for the prevention of strokes caused by a clot that blocks blood flow to the brain (sometimes called a dry stoke). Vitamin K antagonists do this by reducing the clotting potential of the blood (*e.g.*, "blood thinners"). Because some clotting

potential in the blood is essential, it is critical that blood levels of these agents are maintained in a narrow range.

Hospital drug use

51. Pharmaceuticals are generally available to the consuming public from two sources:

- in the community from retail pharmacies,
- through hospitals to inpatients and from outpatient pharmacies.

52. Distribution from hospitals poses a methodological problem because some hospital use may be more related to acute care than prevention or maintenance care. On the other hand, hospitals in some countries are significant sources of pharmaceuticals for ambulatory consumers. Thus, it was necessary to consider whether to include or exclude hospital-based drug use in the study.

53. The decision was made to include hospital drug use so that the study was as inclusive as possible, and to avoid the loss of data. Therefore, the main presentations of data are based on total drug use and expenditure (hospital and retail). Table 4 shows the extent to which hospital distribution either occurred or was available for each year in each country. Hospital data are missing for all years in Spain and Sweden and also not available for three years (1993, 1995, and 1997) in France. Finally, no data are available for The Netherlands in 1997.

54. A decision on how to resolve this lack of comparability on hospital data was reached after examining the data in Table 4. Discarding all hospital data would have introduced a substantial bias for Japan which has a high percentage of consumption through hospital facilities. Hospital distribution is also relatively high in the UK and the USA, but does not approach the level in Japan. On the other hand, distribution from French hospital outlets (where the data are available) is well below the average for other countries and appears to be trending downward as a percentage of all drug use. To be as inclusive as possible, and to avoid the loss of data, the main presentations of data are based on total drug use and expenditure (hospital and retail). The practical effect of this decision is to under-represent utilisation in Sweden and Spain, and to a small degree for three years in France. This compromise is more transparent and interpretable than the alternatives.

*Table 4: Average percent of drug use from hospital outlets by country for 1989 to 1999**									
	ATC categories***								
Country	B01AA	C02	C03	C04	C07	C08	C09	C10	average**
Canada	5.6	3.3	4.5	5.4	3.4	3.0	2.4	1.2	3.6
France	2.3	1.1	16.0	8.3	0.9	3.0	1.4	0.4	4.2
Germany	4.8	2.8	17.7	4.3	1.4	2.6	2.3	1.4	4.7
Italy	2.9	2.6	18.8	3.8	1.0	2.1	1.3	0.3	4.1
Japan	74.0	28.8	36.7	38.0	38.9	4.05	38.9	35.6	36.9
Netherlands	4.1	4.4	14.8	2.8	1.5	2.7	1.9	0.4	4.1
New Zealand	2.3	1.0	9.5	5.4	0.8	1.0	0.8	29.0	6.2
Spain	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sweden	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Switzerland	5.9	2.8	17.4	5.2	1.2	14.6	2.1	0.8	6.3
UK	17.2	3.1	10.4	6.0	4.8	2.3	2.2	1.9	6.0
USA	12.2	17.5	19.5	11.5	8.9	12.1	10.3	10.9	12.9
average	13.1	6.7	16.5	9.1	6.3	8.4	6.4	8.2	9.3

Notes:

* Average is calculated over all years in the data.

** Percentages were calculated using only the years for which hospital data were available.

*** Please see the previous discussion for definitions of the ATC abbreviations.

RESULTS

55. The discussion of results is presented in two parts:

- A review of drug utilisation and expenditure patterns by drug categories,
- A review of the inter-relationships between those patterns and key demographic, economic, and policy related characteristics.

56. The first sub-section will describe in detail the empirical findings from an analysis of the data described above. The second sub-section will focus on policy implications of the findings by comparisons of results on key variables. Drug use data for the treatment and prevention of CVD are presented first followed by a section on stroke. Indicators used in the analysis are defined in the box that follows.

BOX: Indicators used in the analysis

Three indicators have been created to describe drug use and expenditure:

-- Drug utilisation (volume of use)

Drug use is expressed in DDDs per 1000 population per day (please see earlier definition).

-- Expenditure

Expenditure is measured in US dollars. In all cases, expenditure is converted to US dollars using Purchasing Power Parities (PPP$).[6]

-- Unit expenditure (value as expressed by PPP$/DDD)

Computed by dividing expenditure by drug use or PPP$/DDD. Since volume has been standardised by DDDs, as described earlier, it is possible to compare unit expenditure across generic and therapeutic categories.

These variables are used to present cross-sectional results (six time periods) for generic and therapeutic categories.

[6] There is a small discontinuity between expenditure and utilization due to the way in which pharmaceutical product data are aggregated. As was described earlier, drug use data are accumulated by generic category, whereas expenditure data are organized by ATC category. When the latter includes combination products there may be a lack of comparability between expenditure and drug use. The differences are small because most products are composed of only a single generic entity. Differences in the definitions disappear when data are aggregated at the therapeutic category level because these categories are broad enough to include all generic compounds that would logically be found in a combination product.

Trends in cardiovascular disease drug therapy from 1989 through 1999

57. Included in this discussion of CVD drug therapy are ATC categories for traditional antihypertensives (C02), diuretics (C03), vasodilators (C04), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09), and serum lipid reducers (C10). These drugs are used primarily for the prevention and treatment of CVD. However, we should acknowledge that some drugs have multiple uses so we cannot be certain that all of the use recorded here is for CVD, and it is possible that some use was recorded elsewhere. Finally, not all of these drugs can be directly substituted for each other. However, the ATC classification system is sufficiently robust to manage these problems and the data are thought to be accurate within reasonable limits.

Trends in Expenditure

58. Detailed expenditure data for each ATC category are found in Figures 1 through 7. Figure 8 summarises the expenditure data in Figures 1 through 7 and reveals two main trends for the period 1989 to 1999.

Average expenditure is rising for relatively newer drugs.

59. This includes calcium channel blockers (C08), ACE inhibitors (C09), and serum lipid reducers (C10). The most dramatic trend is for the C10 category which increased at an average annualised growth rate of 22.7%. The growth rates for C08 and C09 were 7.6% and 11.0% respectively.

Average expenditure on relatively older drugs is mostly stable or declining.

60. Beta blockers (C07) had negligible expenditure growth at 1.5%. The other two ATC categories, diuretics and vasodilators (C03 and C04) exhibited negative growth (-0.9% and -4.2% respectively). The exception here is traditional antihypertensives (C02) which registered a moderate 5.5% expenditure growth rate.

Trends in volume of drug use

61. Drug utilisation data reveals there are three different groups (see Figures 9 through 16): firstly, a group of older drug categories for which there was no growth; this group includes the traditional antihypertensives (C02), diuretics (C03), and vasodilators (C04). A second group includes the beta blockers (C07) for which there was modest growth. A third group includes the newer agents including calcium channel blockers (C08), ACE inhibitors (C09), and serum lipid reducers (C10) for which there was substantial growth.

62. It is important to distinguish between levels of use and trends in the data. For example, diuretics (C03) have the highest level of use, but the flattest growth curve (see Figure 16). In addition, shifts in drug treatment occurred between 1989 and 1999. Whereas, ACE inhibitors (C09) represented 9.8% of CVD drug use in 1989 their share had increased to 22.0% in 1999. During this same time period, traditional antihypertensives (C02) experienced a decrease in use from 9.5% of the total to 3.1%. The other major category shift was for serum lipid reducers (C10) which was 6.4% of the total use in 1989 and more than double that in 1999 (14.0%). If attention is focused on just the last two years of data we see a sharp increase in C10 utilisation from the 10.2% share in 1997 (see Figure 16).

Trends in expenditure per unit

63. Trends for this variable are a bit more complex (see Figures 17 through 24).

Unit expenditure was relatively high for newer drugs

64. Unit expenditure was slightly decreasing for calcium channel blockers (C08) and ACE inhibitors (C09), but on the increase for serum lipid reducers (C10). For serum lipid reducers this reflects a substitution effect in which statins, the newer and more expensive agents in the C10 category, have an increasing share of C10 utilisation.

Unit expenditure was relatively low for older drugs

65. Unit expenditure for diuretics (C03) remained flat over time while the trend for traditional antihypertensives (C02) was clearly upward.

66. The findings for traditional antihypertensives (C02) and serum lipid reducers (C10) warrant further attention. A more detailed analysis of these trends is presented later. The trend for traditional antihypertensives (C02) is of interest because expenditure and utilisation trends appear to be moving in opposite directions.

67. The trend for C10 is noteworthy because of its high growth rate.

Overall trends

68. Figure 25 presents a summary of total CVD drug use in three trend lines. Each line is the sum of all units for that measure:

- the top line, average drug use, is the sum of all DDDs for the seven previously described ATC categories.
- the middle line represents average expenditure in PPP$/1000 population/day for the same entities, and
- the bottom line is the ratio of the first two (PPP$/DDD).

69. In general we see that use of cardiovascular drugs is rising, as is total expenditure. However, because utilisation is rising faster than expenditure, the unit expenditure line is rather flat. This may be a bit surprising given the number of new drugs now available for treatment of CVD. The relatively flat trend for unit expenditure poses interesting questions regarding the source of change in total expenditure. The previous figures and discussion have focused on specific components of these lines, but when combined the upward movement in drug use and expenditure is clearly identifiable. An increase in the use of drugs for CVD is not surprising. It reflects the combined effects of ageing, the diffusion of new medical knowledge, and new pharmaceutical technology. There are now more compounds for treatment and prevention of CVD than were previously available.

Country comparisons of drug therapy for cardiovascular disease

70. For these comparisons the average annualised growth rates for 1989 to 1999 are calculated for each of the descriptive variables used above. Growth rates for expenditure, consumption, and unit expenditure are shown by country and ATC category in Figures 26 through 28.

Expenditure

71. Figure 26 illustrates that the highest expenditure growth rate in every country was in the serum lipid reducer category (C10). In Germany the rate was slightly higher for ACE inhibitors (a virtual tie) and in Italy the C10 growth rate was tied with the rate for calcium channel blockers (C08). The average growth rate across all countries for the C10 category was 22.8%, more than twice as high as any other category. At the opposite end of the continuum was the vasodilator category (C04) with the lowest average growth of -4.2%. Again, there were two virtual ties (diuretics (C03) and vasodilators (C04) in Sweden and the USA), but the rates were not quite as similar as for the high growth group. Only New Zealand had a positive growth rate in the C04 category.

72. Absolute measures of expenditure at the country level are found in Figures 1 through 7. Simple visual inspection of these charts confirms that by 1999, expenditure in C10 was, on average, the highest among the seven ATC groups (average of 26.9). Thus, it is not just the rate of change, but the absolute level that focuses attention on the serum lipid reducers. Conversely, the lowest level of expenditure was in the traditional antihypertensive category (C02), although the level increased over the study period from 2.1 in 1989 to 3.8 in 1999. If the USA is not included in the mean calculation (on the basis that it is an outlier), the levels are 1.8 and 3.2 respectively.

Drug use

73. Figure 27 presents a summary of average growth rates for drug use by country and ATC group. Serum lipid reducers had the highest average growth rate across all countries (16.9%) as well as the highest absolute levels by 1999 (average of 32.4). In 1999 the highest levels of use were in France (70.6) and the USA (52.8). The lowest average growth rate for drug use was for the vasodilator (-5.2) and traditional antihypertensive (-4.9) categories. Levels of use fell in both categories during the study, but vasodilators remained about twice as high as traditional antihypertensives in 1999 (13.4 compared to 7.1) and France maintained a substantial lead in use throughout the study period. As with the expenditure side of the equation, utilisation of serum lipid reducers is rising much more rapidly than the offsetting trends for traditional antihypertensives (C02) and vasodilators (C04).

74. Trends in drug use over time can be driven by many different factors, including the introduction of new drugs, but also the expanding indications of existing drugs. Examples include the trend to defining lower threshold blood pressure levels and threshold cholesterol levels as being "hypertension" and "hypercholesterolaemia" respectively[7]. In addition, the utilisation of drugs may extend to new patients, such as the secondary prevention of myocardial infarction using betablockers, low dose aspirin, and the statins, or cardiac failure with the ACE inhibitors.

[7] See for example: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Washington, DC: NIH (NIH publication number 01-3670), May 2001, pp. 2-10.

Unit expenditure

75. Combining data from expenditure and drug use yields the average growth rate data on unit expenditure in Figure 28 (detailed country specific data are in Figures 17 through 23). Not surprisingly (because of the divergence in expenditure and drug use trends), the highest average growth rate is for the traditional antihypertensives (11.3) followed by serum lipid reducers (5.4). As with the variables shown above, serum lipid reducers had the highest average level of use in 1999. The average was 0.56 in 1989 and 0.87 in 1999. Because of the rising expenditure pattern for traditional antihypertensives, that group did not have the lowest absolute level of unit expenditure. The lowest level was for diuretics (C03) at 0.09 in 1989 and 0.08 in 1999.

Summary

76. Figure 29 summarises the three average growth rate statistics by country and across all ATC categories. Views on the results will differ based on perspective of the observer and which indicator is chosen. Expenditure grew at an annualised rate of 6.2% across all countries. Expenditure growth was highest in Spain (10.1%), the UK (8.7%), and Sweden (8.0%) and lowest in France (3.3%), The Netherlands (4.4%), and Switzerland (4.8%).

77. For drug utilisation the highest growth rates for drug use were in The Netherlands, New Zealand, and Spain (7.1%, 7.1%, and 6.9% respectively). Utilisation growth declined slightly in France (-1.1%) and Japan (-0.2%). Whether or not increased drug use in a country is desirable is very situational. If, for example, the prevalence of CVD in a country is increasing and these patients have lower than desirable drug use for the treatment and prevention of CVD, then increased use may be appropriate. Conversely, if drug use is rising above levels that are appropriate for the prevalence rates and patients were not being under-served, then the marginal benefits of drug use will decrease. These data will take on more meaning for individual countries where CVD morbidity and mortality statistics are available.

78. Unit expenditure data is the last dimension that we investigated. Caution should be exercised in interpreting this aggregate, as the lower average unit expenditure can either be the result of lower prices or of a different mix of drugs. In this study of CVD, negative growth in average unit expenditure over the study period were observed for The Netherlands (-2.4%), New Zealand (-1.9%), and Germany (-0.1%). Conversely, the highest rates of growth in the average unit expenditure were found in Japan (7.2%), France (4.7%), and Sweden (4.5%). However, it is well to recall that unit expenditure is a ratio of expenditure to average daily consumption so that changes could be due to more than one source which calls into question the assumption of "all other things being equal." If, for example, there are differences in the quality of pharmacotherapy or if drug use is inappropriate for CVD, then this assessment of value would be uninterpretable.

Special analysis of traditional antihypertensives (C02) and serum lipid reducers (C10)

79. The findings for traditional antihypertensives (C02) are interesting because expenditure is rising while utilisation is decreasing, and because it includes a diverse group of compounds. It is not at all certain that drug use is evenly distributed across the generic compounds in the C02 group. From the previous aggregate analysis of C02 it is not possible to know if there are substitutions occurring across generic compounds within C02 or if the trend is due to a decline in use of a single compound. The serum lipid reducer category invites closer inspection because of the rapid increase in use of this group of agents. A more detailed analysis of this group will reveal where growth is occurring and whether substitutions are taking place across subcategories.

Traditional antihypertensives

80. The C02 group is composed of five subcategories for which drug use data are presented in Figure 30.

- C02-A (centrally acting antiadrenergic agents),
- C02-B (ganglion-blocking adrenergic agents),
- C02-C (peripherally acting antiadrenergic agents),
- C02-D (agents acting on arteriolar smooth muscle), and
- a group of "other" compounds here labelled as C02-X.

81. The use of C02-B and C02-X agents is virtually zero and will not be discussed further. C02-D is of interest because it reflects the general downward trend in use of traditional antihypertensives (a decrease from 32.8 DDDs in 1989 to 3.16 in 1999). A similarly dramatic decrease is shown for C02-A which dropped from 134.7 DDDs in 1989 to 36.9 in 1999. The only upward trend in the use of C02 agents was for C02-C which rose from 17.2 to 40.4 DDDs. We cannot state with certainty why the C02-C group is rising, but it is known that this class of compounds is now being used more often to treat the non-cardiovascular condition of benign prostatic hyperplasia (BPH), which might explain the shift in utilisation. The average annualised growth trend for subcategories of C02 is shown in Figure 31.

Serum lipid reducers

82. The serum lipid reducer category is composed of five subgroups:

- the statins (C10-AA),
- the fibrates (C10-AB),
- the bile acid sequestrants, also called resins, (C10-AC),
- nicotinic acid and its derivatives (C10-AD), and
- a group of "other" diverse compounds (C10-AX).

83. Figure 32 displays the trends in use of these categories (in DDDs/1000 population/day) from 1989 through 1999. The dramatic growth in the use of statins is obvious. Growth in the serum lipid reducer category is primarily due to increased utilisation rather than a shift from other categories to statins. Figure 33 shows the same trend differently by plotting statin use as a percentage of the total serum lipid reducer drug use. There has been a steady shift toward the statins from the other compounds in this class, but the majority of unit expenditure growth is due to increased use of statins rather than a shift in patterns of use in the serum lipid reducer category. Utilisation of the other subcategories is relatively stable with the exception of a small decline in the resin category. The average annual growth rate in use of statins was approximately 40% (see Figure 31) while all others declined from -1.0% to -8.0%.

84. The fibrate subcategory (C10-AB) is slightly different from the other serum lipid reducers because its effect is primarily on triglycerides in the blood. Thus, it is not surprising that its use remained relatively stable because the other subcategories are not exact substitutes for fibrates.

85. Statins are the newest group of compounds in the serum lipid reducer category and have attracted the attention of patients and prescribers for many reasons. It is clear from an inspection of the earlier figures that statins have a higher unit expenditure than any of the other subgroups. The clinical literature suggests that statins are effective agents with an important role to play in reducing CVD risk for those patients at risk[8]. However, some investigators believe that statins have been used for patients not at risk which would have the effect of reducing their cost-effectiveness. The statins also are much easier to use than the resins (C10-AC) because the latter have a disagreeable texture, and generally require mixing a powder with liquid or food before using. Whereas the statins are available as tablets or capsules and have a more flexible dosing schedule. Recent experience with one of the more potent statins has caused some concern, but similar problems have not been reported with other statins (SCRIP 2001).

Exploring factors that influence drug use

86. The trends in drug utilisation discussed above result from the interaction of many factors. Of the many possibilities, we have chosen to examine variables representative of four general areas: age distribution of the population, income per capita, health expenditure, and burden of disease. For this exploratory analysis only univariate relationships are discussed. In each case the data are presented as scatter diagrams with ordinary least squares (OLS) regression lines included to show the general trend in the data. As mentioned earlier, drug use and expenditure are the result of many forces acting together. Therefore, these univariate comparisons show only where it may be productive to pursue further research using more country and disease specific data in multivariate models. Age distribution of a population

87. It is often argued that OECD countries with a higher proportion of aged in the population face higher demands on their health care systems simply because advancing age brings with it an increase in chronic disease. This relationship is investigated by relating drug utilisation patterns to the percentage of population age 65 and over. The choice of a point for dividing the population by age is admittedly arbitrary. With respect to CVD this point will be more appropriate for some populations than others, however, age 65 is a rather traditional dividing line and will serve for the purpose of this analysis as a first proxy for demographic factors.

Income per capita of payers (ability to pay)

88. The cost of pharmacotherapy for chronic diseases can be expensive for individual patients and also at a country level. At an aggregate level, the volume of consumption may be related to the relative income of a country. We will use per capita GDP as a measure of relative national income to examine the association of income to drug use. Furthermore, as drugs in this study differ in their unit expenditure we might expect to see an effect of relative income on volume of use across countries. The relationship of GDP per capita to volume of use is examined for total drug use and three subcategories of drugs.

Levels of health and pharmaceutical expenditure

89. Drug use can be related to the relative propensity to spend on health and on pharmaceuticals. We will explore the relationship of pharmaceutical use to levels of spending in two ways. First, the association of drug use with the percentage of GDP spent on health is examined. Countries with a higher percentage

[8] See: Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. The Lancet vol 360 (July 6, 2002), pp. 7-22.

devoted to health are likely to use more expensive pharmaceutical therapies and to spend more on pharmaceuticals in general.

Disease burden (e.g., prevalence of CVD)

90. The prevalence of a particular disease can be used as an indicator of its burden on a health care system. However, prevalence data for measuring the total burden of CVD was not available across all countries for this study. In addition, more detailed data have shown that prevalence was highly correlated to IHD mortality at an aggregate population level (Moise and Jacobzone 2002). Therefore, ischaemic heart disease (IHD) mortality was used as a proxy measure of CVD disease burden. IHD mortality is not used here as a measure of disease outcome or health system performance since we were not able to control for other factors that influence mortality in this study. However, in this study, it does serve as a reasonable measure of disease burden.

Ageing

91. In general, the conventional view that age would be strongly and positively associated with CVD drug use was not supported. The percentage of the population age 65 and over in 1989 and 1999 has been plotted against total CVD drug use, diuretic use, ACE inhibitor use, and serum lipid reducer use (in DDDs) for the same years in Figures 34 through 37. The age-related pattern for total drug use in 1989 and 1999 are both weak (see Figure 34), but there is an upward shift in the level of total drug use from 1989 to 1999.

92. The plot of data for diuretic (C03) use and percentage of the population age 65 and over reveals little change over time (Figure 35). The weak relationship that exists in 1989 has disappeared by 1999. Figure 36 shows an upward shift in the use of ACE inhibitors from 1989 to 1999, however, this shift does not appear to be age related. Although these two categories are quite different in use and the nature of their technology (ACE inhibitors (C09) are in general a newer technology than diuretics (C03)), they show similar patterns of use relative to the percentage of the population age 65 and over.

93. Data for serum lipid reducer (C10) use, shown in Figure 37, is a bit more interesting. The level of use has increased, as shown previously, however, it appears that use increased more in countries with a lower percentage of population age 65 and over, than in countries with a higher percentage (although the difference is small). However, from these data we cannot determine whether there is over- or under-utilisation by any age group. As noted earlier, levels of drug use are multidimensional so it is not surprising that one particular dimension (age) has only a modest relationship to drug use.

Income per capita

94. Figure 38 shows the trend in drug use expressed as DDDs per 1000 population per capita relative to levels of income as measured by GDP per capita in PPP$. There is a shift in overall drug use from 1989 to 1999, but there does not appear to be a relationship between relative income levels and total CVD drug use. Figures 39 (for diuretics) and 40 (for ACE inhibitors) show different relationships of volume to income levels. There has been a small decline in the level of use of diuretics, relative to income, and an upward shift in use for ACE inhibitors. As with total drug use, there is no apparent relationship to income.

95. Figure 41, for serum lipid reducers (C10) shows both a shift in volume of use and a linear relationship between volume of use and GDP per capita. The previous examination of C10 subcategories (see Figures 32 and 33) shows that increased consumption in the serum lipid reducer group is the result of

a marked rise in the use of the "statins". Because "statins" are relatively new compounds compared to others in the C10 category, there can be some therapeutic competition, but little or no generic competition, which may explain why they are more expensive than other members of the general class (see Figure 24 for a comparison). Thus, Figure 41 shows there is an income effect for serum lipid reducers in which higher utilisation is associated with higher relative income levels.

Levels of health and pharmaceutical expenditure

96. Expenditure on health as a percentage of GDP is an expression of the relative propensity of a country to spend on health care. It is of interest to know whether those countries that spend relatively more on health care also have higher drug utilisation, and whether qualitative differences in drug use are related to health care expenditure as a percentage of GDP. Figure 42 shows the relationship between total CVD drug use and total health expenditure as a percentage of GDP in 1989 and 1997.[9] From 1989 to 1997 there is an across the board rise in the level of consumption relative to total health care expenditure as a percentage of GDP. We also can observe a small upward trend in the data for 1997 but in general the overall relationship is very weak: the aggregate level of use is not sensitive to the share of health expenditure in GDP.

97. It is possible that, the mix of drugs is influenced by the relative propensity to spend on health. To address this question drug use was divided into two groups described as "older" and "newer" therapies. For this analysis, the older therapy group includes traditional antihypertensives (C02), diuretics (C03), and vasodilators (C04). This older group is characterised by a high percentage of generically available products that have been marketed for many years, however, they are quite different therapeutically. The newer group is composed of beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09), and serum lipid reducers (C10), which also are therapeutically different. Compounds in the newer group were generally discovered more recently, and many are available only as single entity products, whereas the older products are more likely to be incorporated into combinations. The most common exception to this is that diuretics (C03) are sometimes found in combination with the newer antihypertensives (C07, C08, and C09).

98. Data for the comparison of the newer and older drug groups for 1989 and 1997 are found in Figures 43 through 44 respectively. An examination of these data shows that the use of newer therapies was related to total health expenditure as a percentage of GDP in 1989, and that the link was even more pronounced in 1997 (compare Figures 43 and 44). Those countries who spent relatively more on health in 1989 used less of the older drugs in 1989. In 1997 there is no relationship between the share of health in GDP and the use of older drugs. The level of use was relatively unchanged in high spending countries. Note, however, that there was a sizeable upward shift in the level of use for newer drugs from 1989 to 1997. In brief, there seems to be a clear indication that for newer compounds the relative propensity to spend on health plays a role in the consumption level of these drugs, whereas, this does not seem to be the case for the older drugs.

Disease burden

99. Ischemic heart disease (IHD) mortality was used as a proxy measure for CVD burden. IHD mortality data were obtained from *OECD Health Data* (OECD, 2001). The most recent "complete" data were for 1997 but this also had missing values for some countries. Where data were missing, some

[9] The latest complete data for total health expenditure as a percentage of GDP is for 1997.

estimates were made by projecting recent trend data. For Sweden and Switzerland 1997 IHD mortality was extrapolated from past changes observed for the 1989 to 1995 period..

100. Figure 45 presents IHD mortality for 1989 through 1997 for the study countries. The rankings have been reported already and there are no deviations from published data in Figure 45 (Moise and Jacobzone 2002). Figure 46 shows virtually no relationship between burden of disease (IHD mortality) and total CVD drug use and very little change from 1989 to 1997. The remaining figures (47 through 53) show the relationship of each ATC category to IHD mortality. For example, Figure 47 (traditional antihypertensives - C02) and Figure 49 (vasodilators - C04) respectively show lower levels of consumption for these agents at higher levels of disease burden and generally show lower levels of drug use in 1997 compared to 1989. The convergence of C02 use at about 10 DDDs for 1989 and 1997 may reflect the previously mentioned trend of using a subset of C02 for the treatment of BPH.

101. For diuretics (category C03 in Figure 48) we observe a strong positive association of drug use and burden of disease in 1989 and an even stronger association in 1997. The trend line in Figure 48 shows that diuretic use in 1997 is beginning to exceed 1989 levels. This is consistent with common wisdom that diuretics are a low cost first-line treatment for hypertension. We see a similar pattern for beta blockers (C07) in Figure 50, but in this case utilisation in 1997 is consistently above that for 1989. It is impossible to determine whether the recent increased use associated with rising burden of disease is due to their lower cost or proven effectiveness, or both. Beta blockers (C07) have been available for at least 25 years and are therefore relatively inexpensive. Furthermore, there have been suggestions that virtually everyone who has experienced a heart attack (MI) should be on a beta blocker to reduce the probability of a second MI.

102. The newer therapies (C08, C09, and C10) are charted in Figures 51 through 53. There seems to be a weak relationship between the consumption of these drugs and disease burden. The lines are shifting up over time without changing the overall pattern. Therefore, it seems that the consumption of drugs is relatively unrelated to the burden of disease, and that countries experiencing faster growth in consumption are not necessarily those with the greatest burden of disease. Based on the results presented earlier in this report, it seems more likely that the upward shift is related to relative income levels.

103. In summary, it appears that use of traditional antihypertensives (C02) and vasodilators (C04) are not related to burden of disease. Diuretic (C03) and beta blocker (C07) use is strongly related to burden of disease and is increasing. For these relatively inexpensive and effective drugs, the burden of disease strongly influences the patterns of use. Use of calcium channel blockers (C08), ACE inhibitors (C09), and serum lipid reducers (C10) has increased between 1989 and 1997, but there does not appear to be a strong association to burden of disease.

Drug treatment for stroke

104. Drugs included in the study for stroke prevention are a much smaller and more homogeneous class of compounds than the group for treatment of CVD. This group is known as vitamin K antagonists (B01AA) because they reduce the risk of blood clots by inhibiting vitamin K, an essential component for blood clotting. Most of these agents have been available for many years. There generally is very little switching among vitamin K inhibiting compounds once a patient has begun therapy. The lack of switching is due to the narrow therapeutic index of these drugs and the need to titrate each patient individually to an endpoint and then maintain that patient within a very narrow range around the endpoint for an extended period of time. Thus, prescribers are reluctant to change drugs for an individual patient, and often choose to use only one drug to treat patients because they have become familiar with it. Evidence from this study supports this view.

Trends in expenditure

105. Figure 54 shows the expenditure patterns for all 12 countries over the 11 years of the study. Total expenditure was very steady from 1989 through 1999 with the exception of the USA and Canada. In the case of the USA, the upward shift was quite dramatic with an average annualised growth rate of 21.3% which was nearly double the 12 country average of 12.1%. Canada and Japan had nearly the same amount of growth with 21.2% and 20.2% respectively. Also note the sharp decrease in expenditure for New Zealand. This is likley the result of changes in reimbursement polices implemented during the latter part of the 1990s. Reasons for the changes in expenditure are more apparent after viewing drug use and unit expenditure data.

Trends in drug use

106. The highest level of use for vitamin K antagonists (B01AA) is in France followed at a distance by other countries (see Figure 55). The spread between France, with the highest utilisation at 15.4 DDDs in 1999, and Japan at 1.0 DDDs is dramatic and demonstrates how cultural and other differences can influence drug utilisation. Growth rates tell quite a different story. The highest growth rates were in Spain (13.6%), Germany (13.2%), and New Zealand (13.0%). It is not possible to ascertain whether these trends result from increased need, better accessibility to the drugs, or other possibilities. Even though there was substantial growth in use for New Zealand the rate of use remains modest compared to most other countries. Growth in use of these drugs in New Zealand is opposite to the reduced level of expenditure. Again, the explanation is likely to be changes in pharmaceutical reimbursement policy.

Trends in unit expenditure

107. Trends in unit expenditure for vitamin K antagonists are shown in Figure 56. Unit expenditure remained below 0.2 for seven of the 12 countries for the entire 11 years. Japan saw modest rise from 0.2 to 0.3 while Canada and the USA had sharper increases to much higher levels in 1999 (0.7 and 1.0 respectively). The trend in Italy was a bit unusual and probably is the result of policy changes. In Italy, unit expenditure was 0.1 in 1989, rose to 1.2 in 1993 and then fell to 0.2 in 1999. The highest growth rate among all countries was in the UK at 21.8%. However, the absolute values were quite small (0.03 in 1989 and 0.23 in 1999).

108. Unit expenditure for Canada and the USA doubled from 1989 to 1997. The reasons for this appear in Figures 54 and 55 in which we see that expenditure increased faster than utilisation, thereby raising average unit expenditure. The largest change was for New Zealand where unit expenditure fell from about 1.6 to just below 0.2; a substantial decrease. The reasons for this appear to be the policy change, referred to above, in which reference prices and other policies were used to constrain drug expenditure.

Exploring factors that influence use of vitamin K antagonists

109. The final three figures (Figures 57 through 59) relate vitamin K antoagonist utilisation to three descriptive variables. Figure 57 shows that, as was the case for CVD, there is no clear relationship of vitamin K antagonist use and percentage of population age 65 and over, although there was a rise in use between 1989 and 1999. Figure 58 again indicates no relationship between GDP per capita and vitamin K antagonist use and an increase in the level of use from 1989 to 1999. This is similar to the less expensive CVD drugs, but in contrast to the newer CVD drugs. Vitamin K antagonists are relatively inexpensive so their similarity to the CVD pattern might be expected. That is, no relationship to income for the utilisation

for lower priced drugs. The final figure for vitamin K antagonists (Figure 59) illustrates a positive association between the use and the propensity to spend on health. This relationship holds in both 1989 and 1999.

POLICY IMPLICATIONS

Antihypertensives

110. The data presented in this study strongly points toward increases in the volume of new drugs for hypertension. It would be important to know whether decisions on which drugs to reimburse or the level of reimbursement is encouraging this trend beyond the point where it is medically appropriate.

111. The findings on the use of traditional antihypertensives are interesting because of the rising level of expenditure, both in absolute terms and as measured by unit expenditure. The apparent rise in the unit expenditure of traditional antihypertensives raises questions. It also demonstrates the difficulty of attributing all antihypertensive drug use to CVD because, as noted in the discussion, some of this use is likely to be for BPH.

112. The trends for diuretics (C03) raise different questions. The level of diuretic utilisation varies from being flat to slightly downward. Since these are very effective and relatively low cost agents the trend may be surprising from a clinical perspective. From an economic perspective, based on the evidence supporting the use of diuretics and their relatively low cost, we might have expected an increase in their use rather than a decrease. This would be what would be expected from a negative demand price elasticity playing a role in balancing supply and demand. However, in the field of pharmaceuticals, clinical and marketing factors can be hypothesised to play a role. Clinical factors point to the higher quality of newer products (*e.g.* improved side effect profile and more targeted therapeutic action) which can justify their use[10]. Also, marketing efforts are concentrated on newer products and demand can be shifted towards newer higher priced products. The results could be explained from a marketing perspective since diuretics are mostly off-patent (with some exceptions for combination products) and therefore not promoted to prescribers. There also is the possibility of problems in the data, because some diuretics are combined with other antihypertensives, but otherwise the suggestion is that there is substitution occurring from diuretics to other compounds which is consistent with the marketing explanation. Some experts believe that diuretics should be first-line therapy for hypertension with use of other compounds only as needed. Further investigations are desirable at the country level where more specific data are available to investigate the competing explanatory hypotheses.

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[10] The two main indications for diuretics are congestive heart failure (CHF) and hypertension. For both indications, many substitutes became available. For CHF, ACE-inhibitors are now the first choice as their favourable effect on prognosis has been demonstrated in randomized trials (*e.g.* The **SOLVD** Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. NEJM 1991325:293-302). For hypertension, diuretics have also been replaced with ACE-inhibitors and with calcium channel blockers (CCB). There is evidence that ACE-inhibitors are superior for selected patients, such as those with renal failure. CCBs are sometimes preferred because they are better tolerated, especially in the elderly, but they have not shown to be superior to diuretics with respect to mortality. But they are patented, expensive and widely marketed. For more detail, see also: *Sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National High Blood Pressure Education Program/National Heart, Lung, and Blood Institute (U.S.). 1997 Nov. 33 pages.*

Serum lipid reducers

113. The high rate of growth in the statin subgroup (C10-AA) of the serum lipid reducer category (C10) has been discussed. From a policy perspective there are two utilisation related issues. Effectiveness of the statins in reducing cholesterol blood levels is accepted, but it also is important to ask whether the most appropriate agents are being used to achieve the desired reduction in cholesterol. For example, if a modest reduction in serum lipids is the goal and there is evidence that drug A can achieve this goal, then there is no need to use a more expensive product (*e.g.*, drug B) even though it has a demonstrated ability to achieve greater reductions. Matching drug therapy to clinical needs has economic as well as medical benefits. However, medical professional guidelines for what is considered a "normal" lipid level have been lowered in recent years (See footnote 8). As the "normal" level is moved downward, more of the population are considered for treatment with lipid lowering agents.

114. In the serum lipid reducer group there is also the issue of substitution. In this case, the nicotinic acid derivatives (C10-AD) are much less expensive than the statins, but have a much lower utilisation rate. The justification is that side effects are much worse for nicotinic acid than for the statins at levels necessary to achieve the same level of lipid reduction. This is true for some patients, however, many who could benefit from the less expensive nicotinic acid derivatives may not be tried on these agents first. It appears that the decision starts and stops with the statin group.

Oral vitamin K antagonists

115. These are relatively inexpensive drugs that require careful monitoring. Much of the cost of using these drugs is in the monitoring of patient blood clotting times. Since virtually all of the agents in this group have similar effectiveness and monitoring costs, the prescribing decision becomes a question of cost-minimisation. There are generics available. However, prescribers generally avoid switching patients among compounds to save drug cost because of the potential for adverse consequences and the need for additional monitoring. Because of the risks and relatively low drug costs there is an understandable reluctance to impose policies that would encourage or mandate substitution among generically or therapeutically equivalent compounds.

CONCLUSIONS

116. The countries represented in this study have used many different cost containment policies in an effort to control pharmaceutical expenditure. These include setting specific product prices, reference pricing, limits on profitability of pharmaceutical companies, price review boards, patient cost sharing, and encouraging competition through generic substitution and competitive bidding, to name a few approaches. Nevertheless, prescription drug expenditure continues to rise due to the usual mix of forces that include new therapies, increased prices, increased volume of use, and changes in the mix of products used. However, unit expenditure remains relatively flat which suggests that volume of use is rising faster than expenditure. Inspection of the individual therapeutic categories shows that much of the increase in expenditure is due to the serum lipid reducers (C10), and especially the statins. However, unit expenditure for serum lipid reducers decreased between 1997 and 1999 while expenditure for traditional antihypertensives increased. As noted earlier, the increased in the use of traditional antihypertensives may be for non-cardiovascular uses.

117. The results suggest associations between use of diuretics (C03) and beta blockers (C07) with IHD mortality, the latter variable being understood as a proxy for the burden of disease. However, it is well to remember that drug use is the consequence of many forces. This finding suggests the need for the development of multivariate models of drug use in cardiovascular disease and the need for improved measures of burden of disease, in terms of prevalence (morbidity), in addition to mortality.

118. Associations of drug use and total health expenditure as a percentage of GDP are, perhaps, a bit more straight-forward. The results show that use of "newer" pharmaceutical agents (calcium channel blockers, ACE inhibitors, and serum lipid reducers) is higher among those countries that spend a greater percentage of GDP on health. Since newer agents tend to be more expensive than "older" drugs, it may be that countries that spend more on health are likely to be more open to the newer therapies. A range of factors could have contributed to these trends, including clinical judgement that the new compounds are more effective or have fewer side effects and marketing efforts concentrating on new in-patent products. A deconstruction of spending at the country level in association with health expenditure would reveal more about this relationship.

119. There are policies which are complementary to the cost containment mechanisms described above. These approaches are seen by some observers not as replacements for expenditure control efforts, but as an approach to increasing the value received for the money spent. Of the methods in use, the two most commonly encountered are "step care" and prescriber profiling.

120. Briefly, step care requires using less expensive, but proven therapies before using more expensive treatments. For example, patients requiring lipid lowering therapy of modest proportions would be encouraged to use diet, exercise, and nicotinic acid derivatives before their prescriptions for statins would be reimbursed. The second approach, prescriber profiling, comes in many forms but generally seeks to give physicians feedback on how they are prescribing with respect to professional guidelines and their colleagues. These and other attempts to rationalise drug use are based on the belief that proper utilisation will create value. Controlling expenditure without rationalising drug therapy will not accomplish this objective.

121. This study has addressed only drug treatment for cardiovascular disease and stroke prevention. The results provide a national level overview of drug therapy for these conditions and permit cross-country comparisons. As with many investigations, the results raise additional questions. In this case it would be useful to have country-specific disease prevalence data for interpretation of drug utilisation. Finally, morbidity and health outcome data would add considerable value to this and other studies of variations in treatments for specific diseases by enabling ex-post evaluation of drug use at an international level. This study may have helped to lay the foundation for further investigations at the country level.

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ANNEX A

DRUG UTILISATION MEASUREMENT ISSUES

122. This annex describes the methods used to characterise drug utilisation. It presents the criteria for including drugs in the study and describes in more detail the defined daily dose method for quantifying drug consumption.

123. Every effort was made to include all relevant drugs for treatment and prevention of cardiovascular disease (CVD) and stroke in this study. However, because of the nature of these conditions, it is necessary to define the limits of drug therapy that will be included. For example, diabetes is one of many risk factors for hypertension. Hypertension can be prevented and treated if diabetes and the other risk factors are reduced. Therefore, we might consider whether to include drugs for the treatment of these risk factors in the study.

124. One approach to resolving the issue is to include only those agents that have received government authorisation (*e.g.*, an official marketing indication) for CVD or stroke. The problem with adopting a legal definition is that the standard of care may dictate the use of agents that do have an indication for CVD and stroke. It would be inappropriate to exclude these agents. These and other issues were addressed by using an internationally recognised drug classification system as the basis for determining which drugs to include in the study. In some cases it was necessary to also use credible expert sources.

Drug inclusion and exclusion criteria

125. **The primary selection criterion for including pharmaceuticals in this study was the World Health Organization (WHO) Anatomical Therapeutic and Chemical system of classifying drugs.**[11] The ATC categories included in the study are shown in Table A1 (and in Table 2 in the main body of the report).

[11] Anatomical Therapeutic Chemical (ATC) classification index with Defined Daily Doses (DDD). WHO Collaborating Centre for Drug Statistics Methodology. Oslo, January 2000.

Table A1: ATC therapeutic categories included in the study

ATC code	ATC category name	Condition
B01AA	Antithrombotic agents (vitamin K antagonists)	Stroke
C02	Antihypertensives	CVD
C03	Diuretics	CVD
C04	Peripheral vasodilators	CVD
C07	Beta blocking agents	CVD
C08	Calcium channel blockers	CVD
C09	ACE inhibitors	CVD
C10	Serum lipid reducing agents	CVD (high cholesterol)

Inclusion criteria

126. The inclusion criteria are designed to insure that only therapeutically relevant agents are included in the study. No consideration was given to legal status (prescription or OTC) or official indication of a compound.

127. Specifically, a drug was included in the study if it met any one of the following criteria:

1. The drug was listed in the WHO Collaborating Centre *ATC Index* in a therapeutic category shown in Table A1 and had a defined daily dose (DDD) assigned by the Centre.

2. The drug was listed in the WHO Collaborating Centre *ATC Index* in a therapeutic category shown in Table A1, did not have a defined daily dose (DDD) assigned by the Centre, but there was sufficient information available to estimate the DDD.

3. The drug was not listed in the *ATC Index*, but sufficient information was available to classify it into one of the relevant ATC categories, and to estimate its usual daily dose (*e.g.*, a DDD).

Exclusion criteria

A drug was excluded from the study if it met either of the following criteria:

1. The compound is used primarily as a food, beverage, dietary supplement, or nutritional supplement.

   However, a compound was not excluded using this criterion unless it was widely regarded as belonging to one of the excluded groups. For example, caffeine was excluded because it is widely used as a beverage, although it is known to have diuretic properties. In addition, multiple vitamin products were excluded because they generally do not contain therapeutic dosages of vitamins and are not specific for the treatment of CVD and stroke.

2. The compound is not within the scope of this study as defined by the *ATC Index* criteria.

   For example, rauwolfia alkaloids and vitamin B6 are both found in the ATC index and were in use in some of the study countries. Rauwolfia is a well known herbal substance that appears in the *ATC Index*, but does not have a DDD specified. Vitamin B6 (pyridoxine) also appears as a component in some cardiovascular drugs, is listed in the *ATC Index*, but does not have direct

cardiovascular therapeutic value (it is classified by in the *ATC Index* as a vitamin). Rauwolfia was included in the study and assigned a DDD using the sources described in Annex B. Vitamin B6 was not included because it is a nutritional supplement although it sometimes appears in CVD-related combination products.

Therapeutic issues not considered in the selection process

128. Inclusion and exclusion criteria described above were used to insure, to the extent possible, that compounds included in the analysis have therapeutic value. The unintended consequences of therapy (adverse effects, sometimes called side-effects) were not used to limit inclusion in the study because these are sometimes idiosyncratic, occur at differential rates across a population, and do not negate the main therapeutic effect of the drug. They may limit the therapeutic response of an agent because of poor compliance or the inability to tolerate a therapeutic dose, but the potential for therapeutic effect still exists. Likewise, compounds that were used during the period 1989 through 1999, but were subsequently removed from the market for any reason, were included in the study. These compounds were used and should be included in the analysis even though they were later removed.

Herbal and homeopathic products

129. Inclusion of herbals and homeopathic products must be addressed because they exist in all countries and some could be considered as treatments for CVD and stroke. In many countries herbal and homeopathic products have a different legal status than prescription drugs, but that status is not consistent across all countries and can change over time in the same country. Because of these inconsistencies in regulatory treatment it was not possible to use this criterion for including or excluding herbal and homeopathic products. The difference in legal status, from traditional prescription drugs, means there are different standards of evidence for determining product indications and claims. The problem is made more difficult because many herbal and homeopathic products do not have standardised strengths used by all manufacturers (*e.g.*, mg of active ingredient). Doses are often expressed in drops, tablets, or other non-standard units rather than milligrams of active ingredient. The amount contained in 10 drops of one product, for example, may require 20 drops of another product of the same herbal substance and often the amount of active ingredient is not disclosed. Consequently, it can be difficult to compare products or determine the strength of an active ingredient. On the other hand, some of these products have a long tradition of use for CVD and stroke in some countries. Arbitrarily excluding all herbals could distort drug consumption statistics. Therefore, herbal and homeopathic products were included according to the inclusion and exclusion criteria described above. In practice this removed most if not all homeopathic products either because the amount of active ingredient was not known or was exceptionally small.

130. Where there was at least some scientific literature for establishing the therapeutic effect and a standard dosage for an herbal product it was included. However, merely being on the market was not sufficient evidence for inclusion because, as noted earlier, the standard for herbal products is much different than for traditional prescription drugs. Testimonials and advertisements were not sufficient evidence to justify inclusion. There was an expectation of some evidence of therapeutic value and usual daily dose in unbiased pharmaceutical references. For example, Allium sativum (garlic) is widely used and there have been Phase IV-type clinical trials to test its effectiveness. In addition, there has been some work to determine a usual daily dose sufficient to provide a therapeutic effect. It was therefore included. On the other hand, Olea europaea (olive leaf) which is widely available does not have this base of information on which to judge its usefulness and for establishing a standard dosage, and was therefore not included.

131. Several herbal substances were excluded from the study using these criteria. Since these products are not equally distributed across countries in the study, the exclusions are expected to have a differential affect on drug utilisation statistics. However, establishing evidence of a therapeutic effect as the criterion for inclusion insures that a compound is appropriate for treatment of CVD or stroke. The exact distribution of herbal substance utilisation for countries is difficult to determine. However, a review of the products listed shows that herbals occur with greater frequency in France, Germany, and Japan than in the other countries in the study. Herbal products are concentrated almost exclusively in the traditional antihypertensive (C02), diuretic (C03), and vasodilator (C04) drug categories.

The problem of combination products: establishing comparability

132. The therapeutic groups in Table A1 are a framework for associating active ingredients in pharmaceutical products to disease conditions. However, some products are combinations of active ingredients rather than being a single chemical compounds. For example, it is common to combine diuretics with beta blockers or antihypertensives. Combination products are based, in part, on the logic that they will simplify therapy for patients. Some clinicians are critical of combination products because they are a fixed combination of the ingredients and do not allow for separately adjusting the component parts as might be needed to optimise drug therapy. Combination products are generally not allowed in some countries. Regardless of the position taken, combination products are used extensively and must be included in the study.

133. Because combination products often represent two or more different therapeutic classes, it is necessary to reflect this when measuring drug utilisation. Either a separate category must be created for each different combination or the components of a combination must be separately accumulated as if they were single entities. If the first approach is taken it will result in therapeutic categories with only one product and a rapid multiplication of categories that will make comparisons of drug utilisation impossible. A second problem is that certain combinations may be allowed in one country and not another which means that a cross-country comparison is not possible even though the same active compounds are being used in both countries. Therefore, the second approach is used in this study.

134. For the purpose of establishing comparability across countries, the active compounds in combination products are accumulated separately. This has the effect of measuring drug consumption rather than product consumption. It means that consumption of products cannot be directly compared across countries, but that it is possible to measure the use of active ingredients. If combination products have some special value that is more than the sum of its parts, then this value is not measured. However, if a combination product is viewed as the simple sum of its ingredients then this procedure is appropriate and useful for creating cross country comparability. The active ingredient orientated approach is used in this study to enhance comparability at the therapeutic level with the understanding that it is not possible to directly compare product consumption. An example using a hypothetical combination product will illustrate the point.

135. The combination of propranolol (a beta blocker) and triamterene (a diuretic) is marketed in virtually all OECD countries under numerous names. It comes in various strengths of the two ingredients and a variety dosage forms which are not the same across countries and will be available in different presentations within a country. Direct comparisons of these product is not possible. However, if the product is divided into its two components of propranolol and triamterene, these can be compared. This method is quite similar to the "hedonic approach" followed by economists (Lancaster 1966): the purpose of this approach is to analyse multidimensional goods through those dimensions which offer utility to consumers. Here, we could make the hypothesis that each of the active ingredients can have a treatment effect for one of the ATC categories.

Quantifying drug use

136. Comparisons of drug use in this study will be made at two levels: by generic and therapeutic categories. Generic comparisons are relatively straightforward since a single compound is involved and 10mg of it from product A is equivalent to 10mg from product B with the possible exception of differences in dosage form. Therapeutic category comparisons are more difficult, because these groupings are composed of different generic substances with possibly different potencies although they are for treatment of the same condition. For example, pindolol and propranolol are both non-selective beta blocking agents. The average daily dose of pindolol is about 15mg while that of propranolol is more than 10 times greater at 160mg. In addition, different dosage forms for the same generic substance can require different quantities to achieve the same therapeutic effect. For example, hydralazine, a diuretic, has an average daily dose of about 100mg administered orally, but only 30mg when given parenterally. In general, combining pharmaceutical compounds into comparable groups requires consideration of the relative potency of the different substances and differences in the dosage forms of all compounds. A unit of measurement for drug utilisation must be responsive to both of these methodological considerations.

137. The "defined daily dose" (DDD) methodology is used to resolve these measurement issues.[12] Each of eight therapeutic categories shown in Table A1 is composed of several generic compounds. Equivalence among different compounds in the same therapeutic category is established by specifying a DDD for each of them. DDDs are set by the WHO Collaborating Centre using experts and a set of rules for making decisions. In the final analysis, a DDD is the, "average daily adult maintenance dose" for a compound given by a specific route of administration. Drug utilisation data measured by DDDs is usually presented as the number of DDDs per 1000 inhabitants per day for a defined population thus permitting comparisons across groups and time periods.

$$\text{DDDs in DDD/1000 population/day} = \left[\frac{\text{Unit}_{si} * \text{Strength}_i}{\text{DDD}_i \times 365 \text{ days/year} \times \text{population(000)}} \right]$$

138. It is important to remember that a DDD is simply a standardised unit of measurement that removes differences in potency among generically or therapeutically similar substances. The DDD is not necessarily the dose used in clinical practice and the dose may differ based on age and medical condition. However, it is a therapeutically reasonable compromise for the purpose of measuring drug utilisation across entire populations.

139. Mutually exclusive categorisation for some generic compounds is not possible because a single chemical substance can have different therapeutic effects. Where this occurs they often can be differentiated by route of administration and dosage required to achieve a specific therapeutic effect. In practice this means that a compound may be classified in more than one ATC category. When this occurs, the DDD will correspond to the particular category in which it appears.

Missing information

140. Unfortunately, not all generic compounds have been assigned a DDD by the Collaborating Centre. In general, the Centre publishes a DDD if there is a request. When a DDD is not available, the Centre advocates consulting product manufacturer information and data from available clinical reports.

[12] Anatomical Therapeutic Chemical (ATC) classification index with Defined Daily Doses (DDD). WHO Collaborating Centre for Drug Statistics Methodology. Oslo, January 2000.

That advice was followed in this study. Many of these sources are now available on the internet or are referenced by internet drug information services. Technical assistance also was provided by Dr. Jill Michels Assistant Director of the University of South Carolina, College of Pharmacy, Drug and Poison Information Center and her staff. The complete list of sources is found in Annex B.

141. Combination products were a particular problem because the strength of each ingredient was sometimes not available. Since combinations are popular in some countries and not others, eliminating them would introduce a measurement bias. Also, removing combination products would underestimate drug utilisation for those classes that are frequently combined. To avoid such a bias, extensive effort was made to include products using reasonable judgements about strengths of ingredients. Much of this information was assembled from manufacturer sources and the sources in Annex B. This effort is made a little easier since biology and drug therapy are relatively standard across countries. Thus, if a generic compound is generally available in a 25mg dose in some countries, it was thought reasonable to apply that same strength to similar products where strength information was missing, especially if the product was produced by the same company.

142. A second principle used to assign product strengths is that the daily dose of most drugs is divided throughout the day, usually two to three times daily. Thus, if the DDD for a product was determined to be 150mg per day, for example, the strength of the product would be set at 50mg so that a patient would get the DDD amount by taking the product three times during a day. This assumption is clinically reasonable, but not perfect. However, given the somewhat arbitrary nature of DDDs, it is more important to be inclusive and consistent than absolutely correct on the dosage. Since this is a comparative study the greatest interest is in making cross country comparisons. Attention will often be focused on percentages rather than absolute levels of DDDs consumed.

ANNEX B

INFORMATION SOURCES FOR CLASSIFCATION OF CVD AND STROKE DRUGS

143. To prepare the drug utilisation data for this study it was matched to the previously described World Health Organisation Collaborating Centre for Drug Statistics Methodology electronic file of ATC and DDD codes. This linkage provided the primary means for obtaining the DDD for each product in the drug utilisation database. However, there were cases in which a product could not be matched to the ATC file. This generally occurred for certain combination and herbal products. Where a match was not obtained the products were manually coded and added to the database.

144. In some cases a match was made to the ATC file, but the latter did not include a DDD for the drug. When this occurred a DDD was created using the criteria described in Annex A, and the new DDD was added to the drug utilisation database.

145. The following publications and web sites sources were the main sources of information used, when necessary, to classify products into ATC categories and to establish a new DDD. The complete list of sources consulted is not provided because it would include hundreds of entries. Some of these were not useful or were considered less than authoritative so are not included in the list that follows. In addition to the web sites and print publications employed, the project also had the services of clinical pharmacy consultants. The primary clinical consultant for this project was Dr. Jill Michels. For a general listing of government and organisational sources of drug information see: www.pharmweb.net

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* prescription drugs

www.hc-sc.gc.ca official site of Health Canada
* Canadian prescription drug information

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* Japanese prescription drugs

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* Prescription drugs

http://emc.vhn.net/professional Electronic medicines compendium maintained by Virtual Health Network
* UK prescription and OTC drugs

www.webmd.com maintained by the WebMD corporation
* prescription drugs and herbal products

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FIGURES

Figure 1. Expenditure for traditional antihypertensives (C02)
(US$ PPP/1000 pop./day)

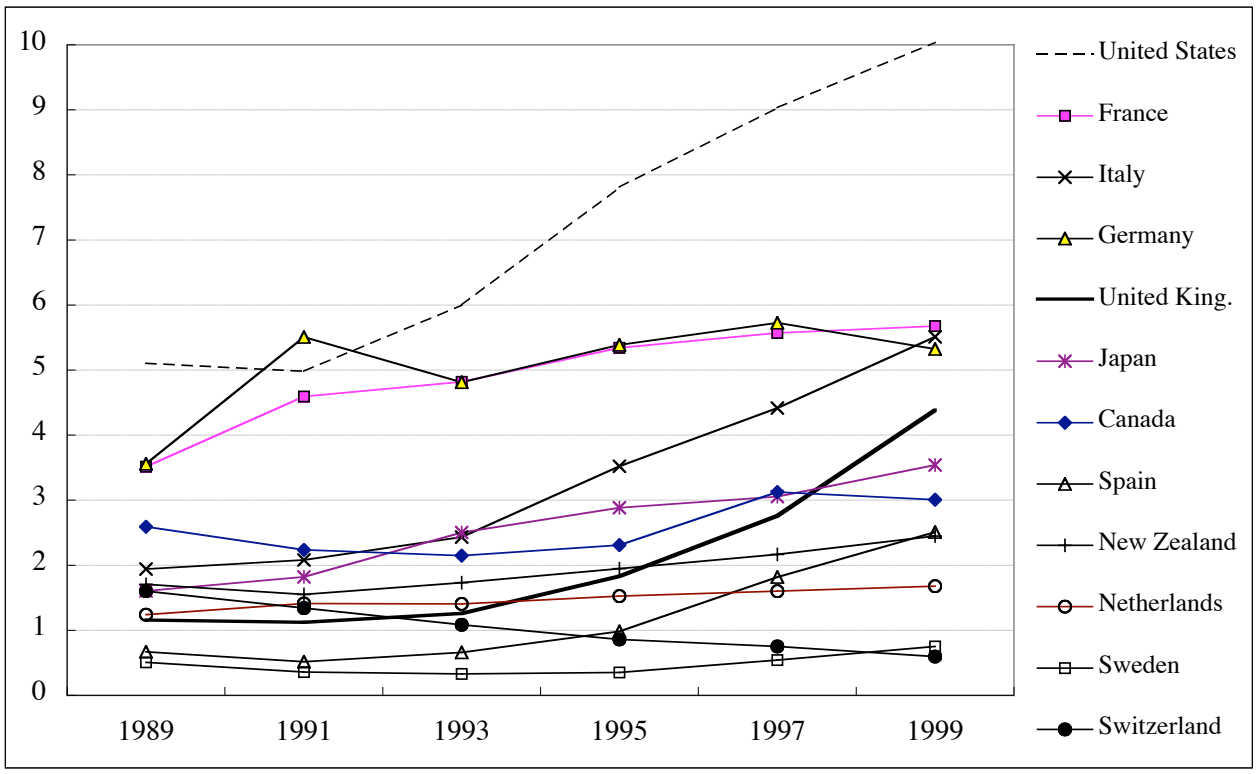


Figure 2. Expenditure for diuretics (C03)
(US$ PPP/1000 pop./day)

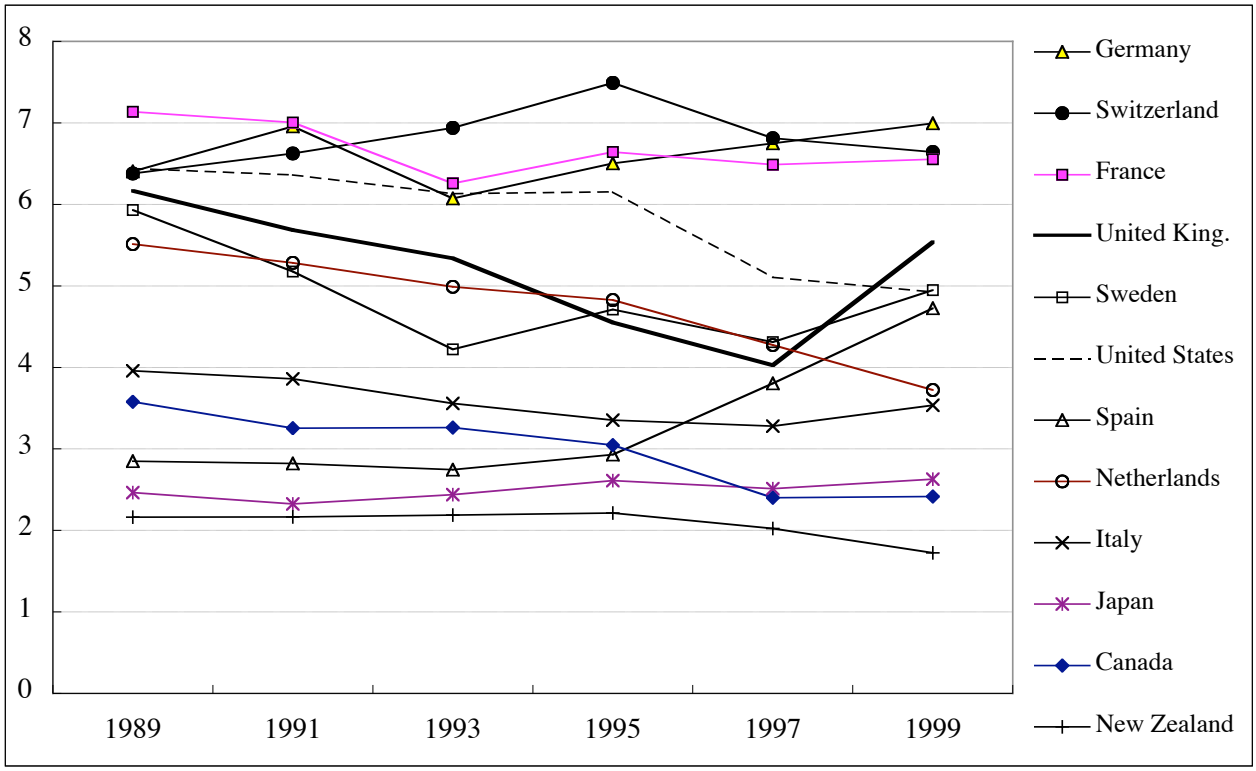


Figure 3. Expenditure for vasodilators (C04)
(US$ PPP/1000 pop./day)

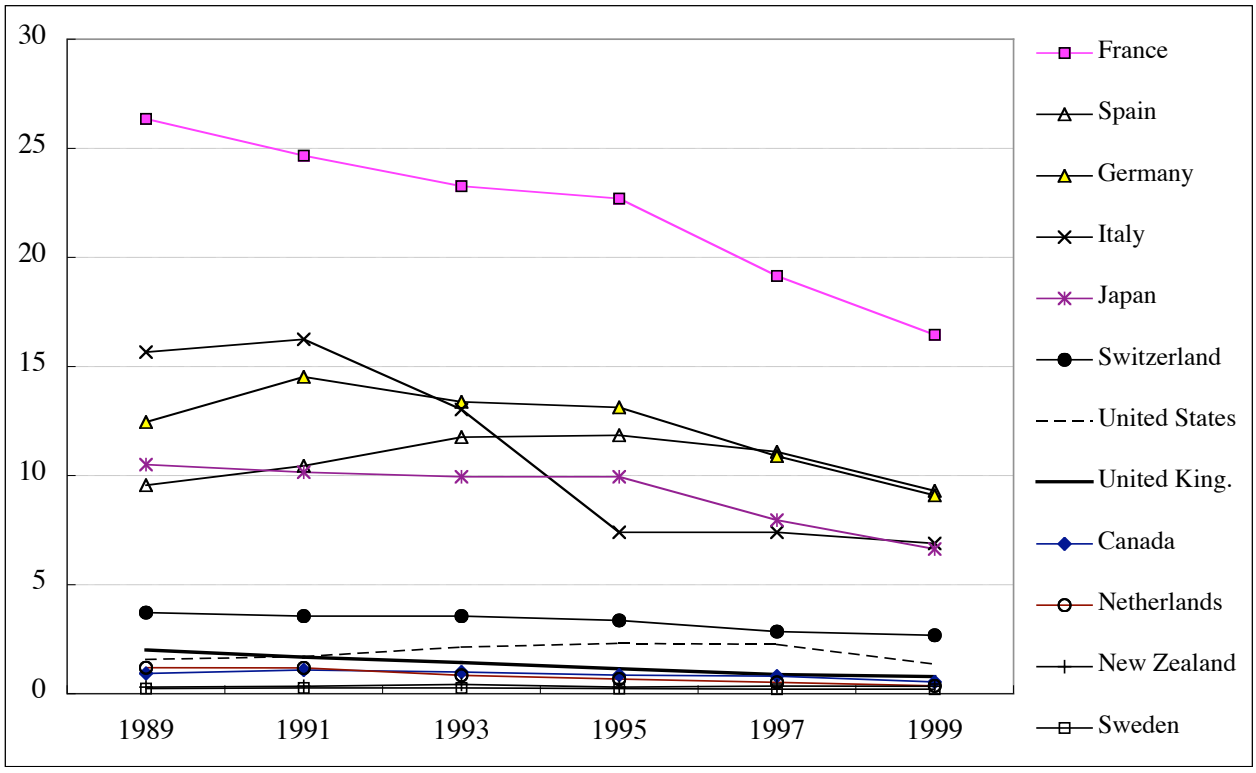


Figure 4. Expenditure for beta blockers (C07)
(US$ PPP/1000 pop./day)

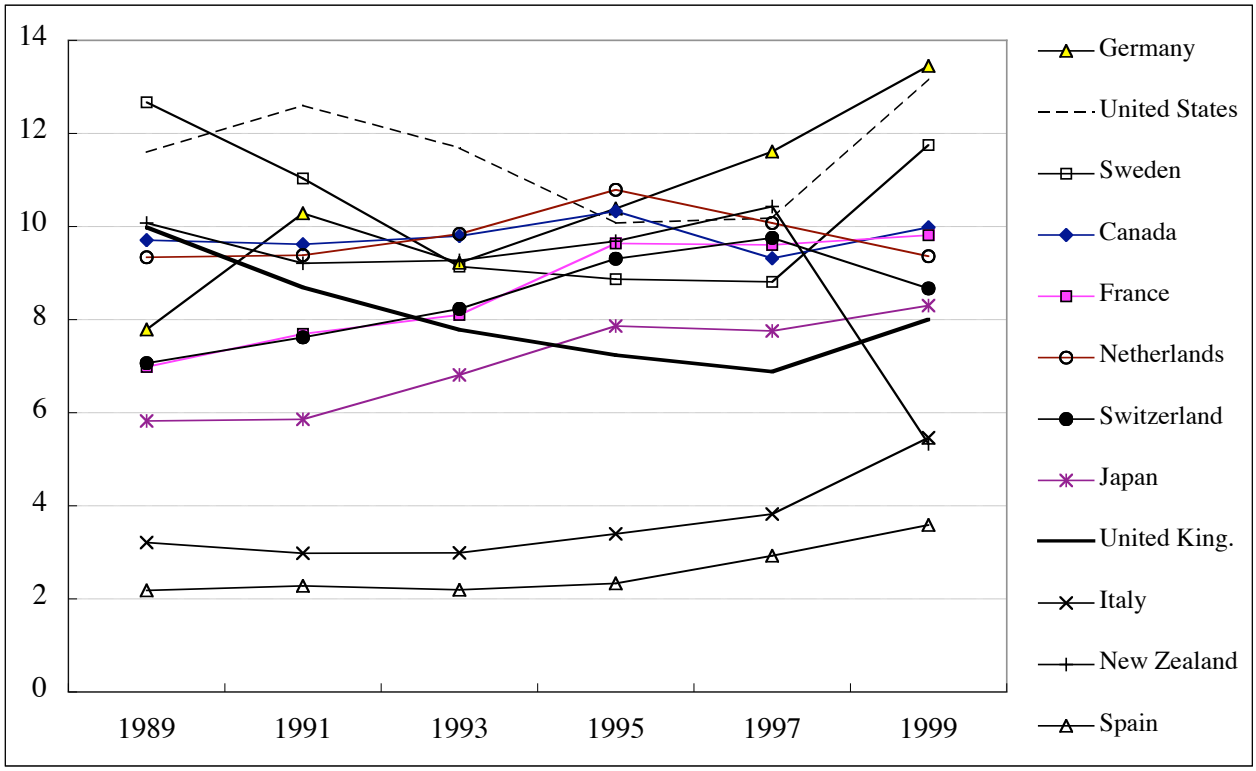


Figure 5. Expenditure for calcium channel blockers (C08)
(US$ PPP/1000 pop./day)

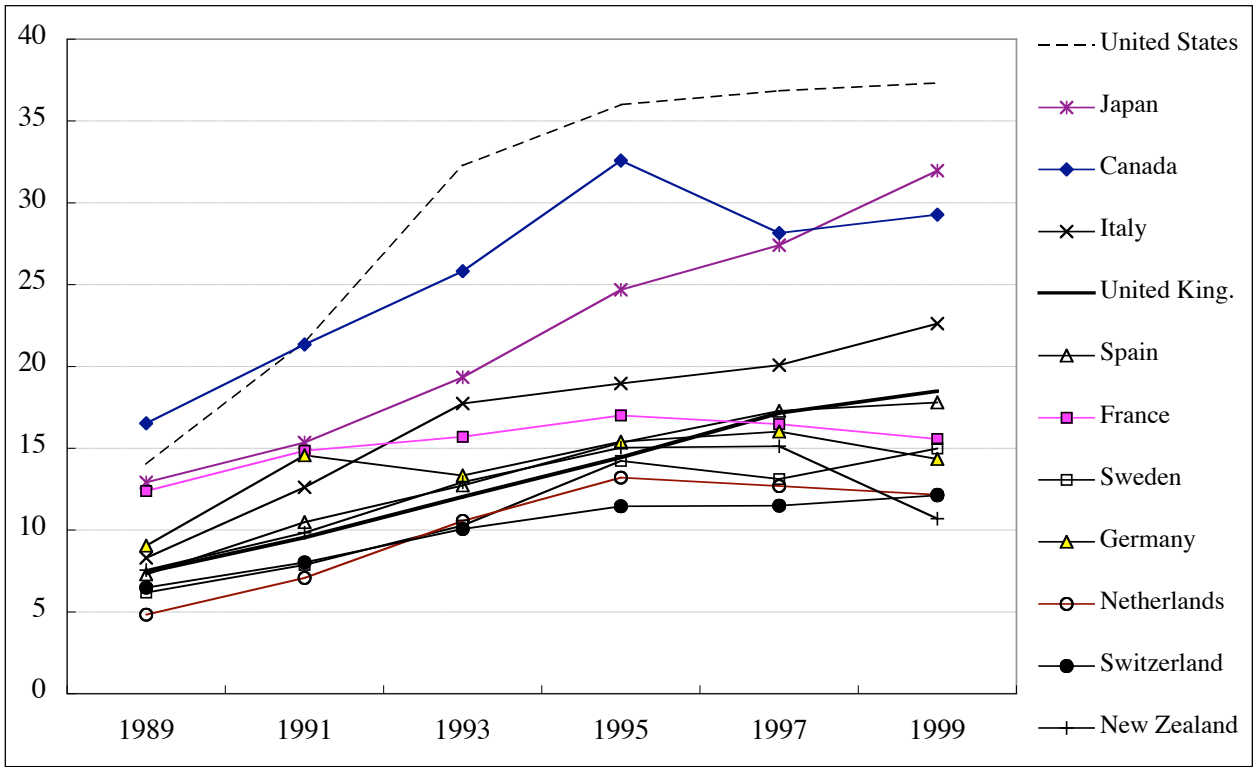


Figure 6. Expenditure for ACE inhibitors (C09)
(US$ PPP/1000 pop./day)

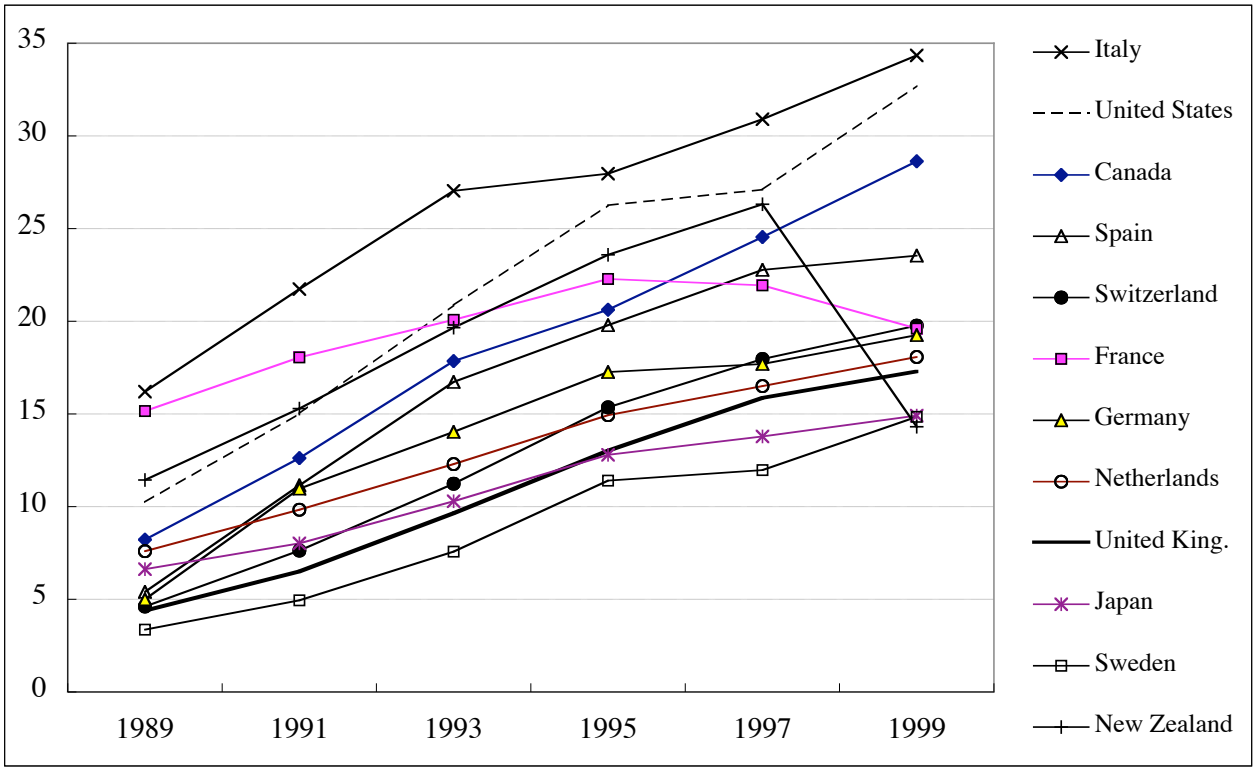


Figure 7. Expenditure for serum lipid reducers (C10)
(US$ PPP/1000 pop./day)

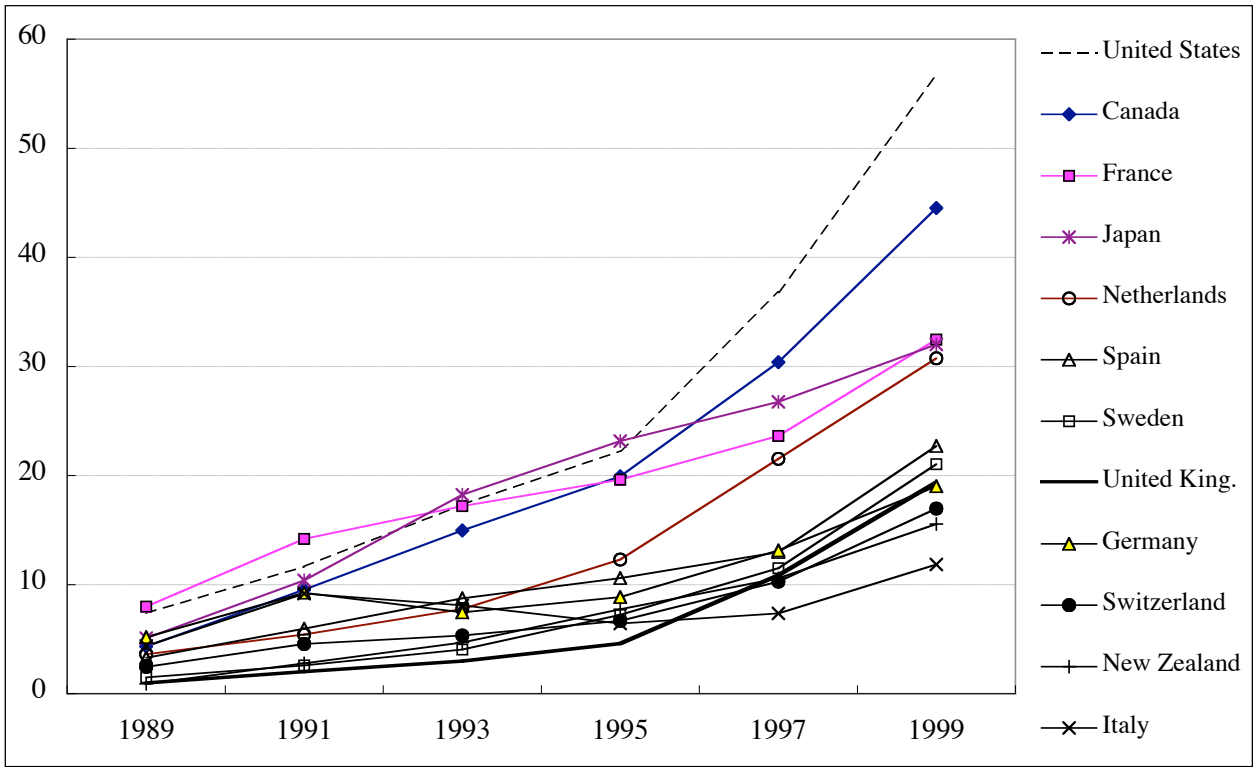


Figure 8. Average expenditure for all countries
(US$ PPP/1000 pop./day)

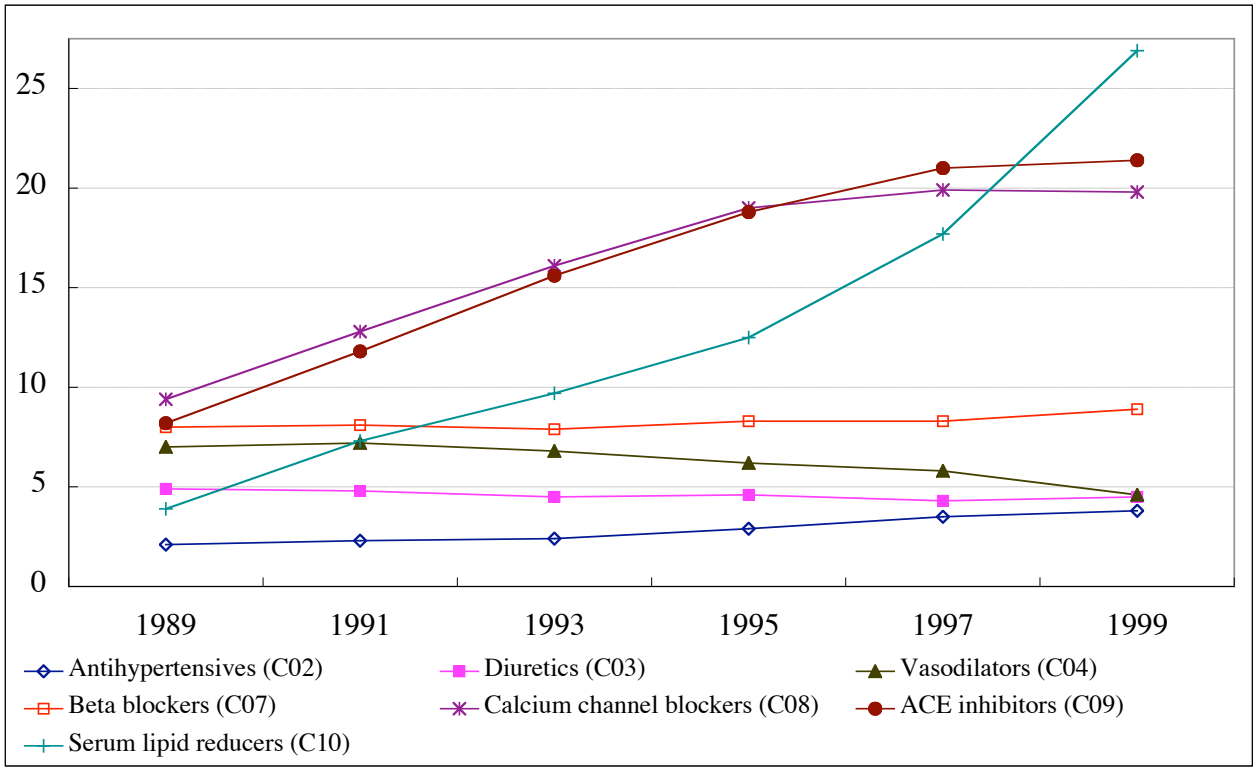


Figure 9. Traditional antihypertensive consumption (C02)
(DDD/1000 pop./day)

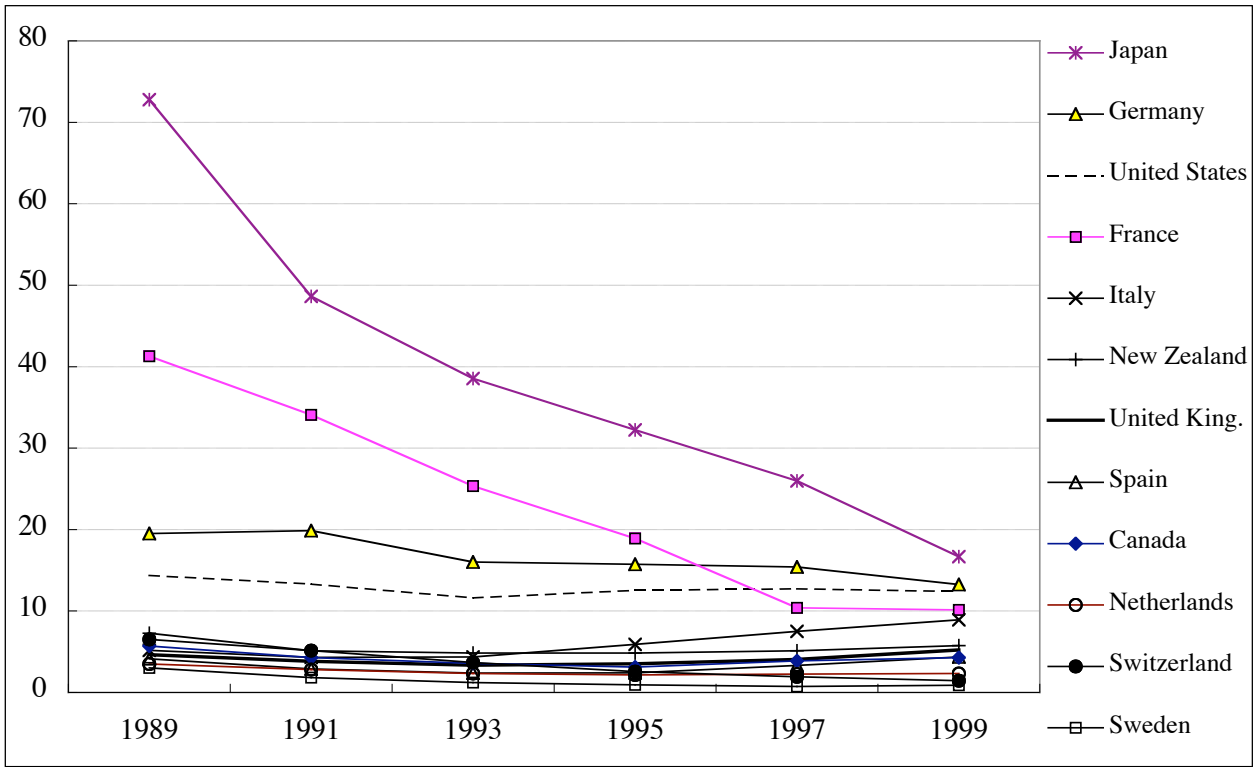


Figure 10. Diuretic consumption (C03)
(DDD/1000 pop./day)

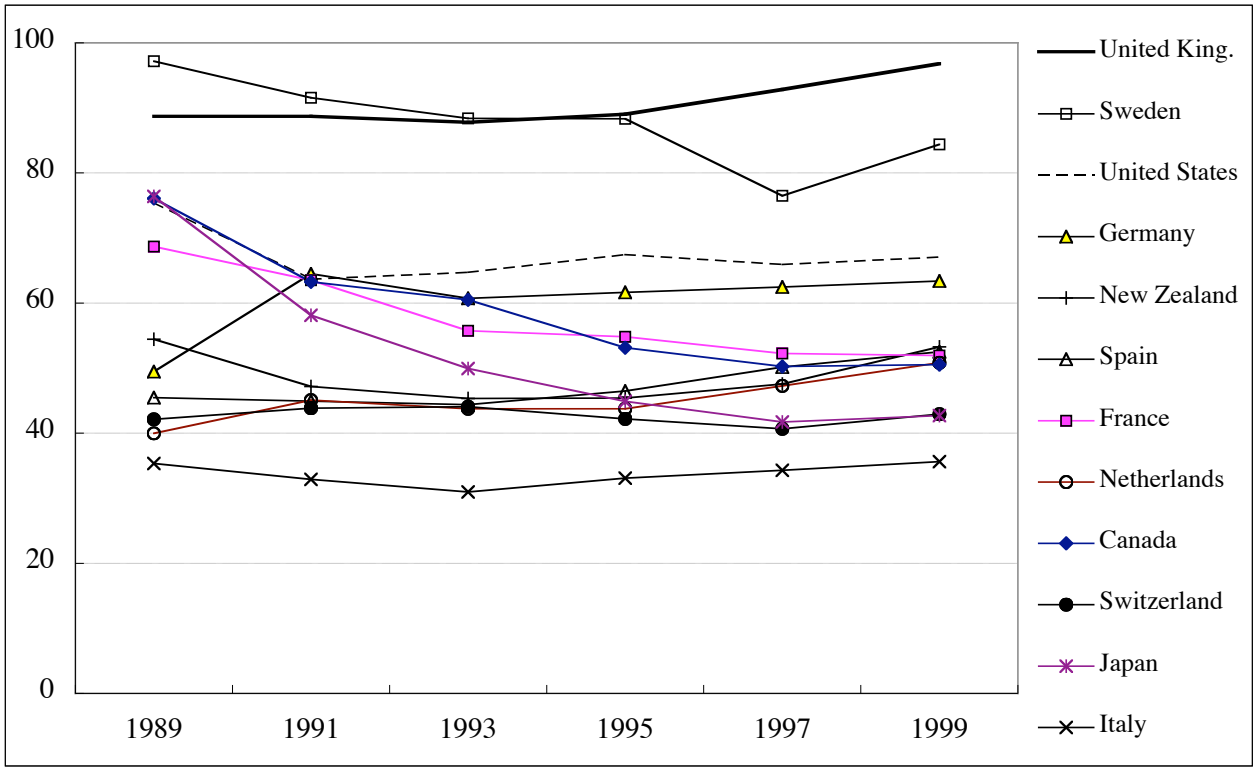


Figure 11. Vasodilator consumption (C04)
(DDD/1000 pop./day)

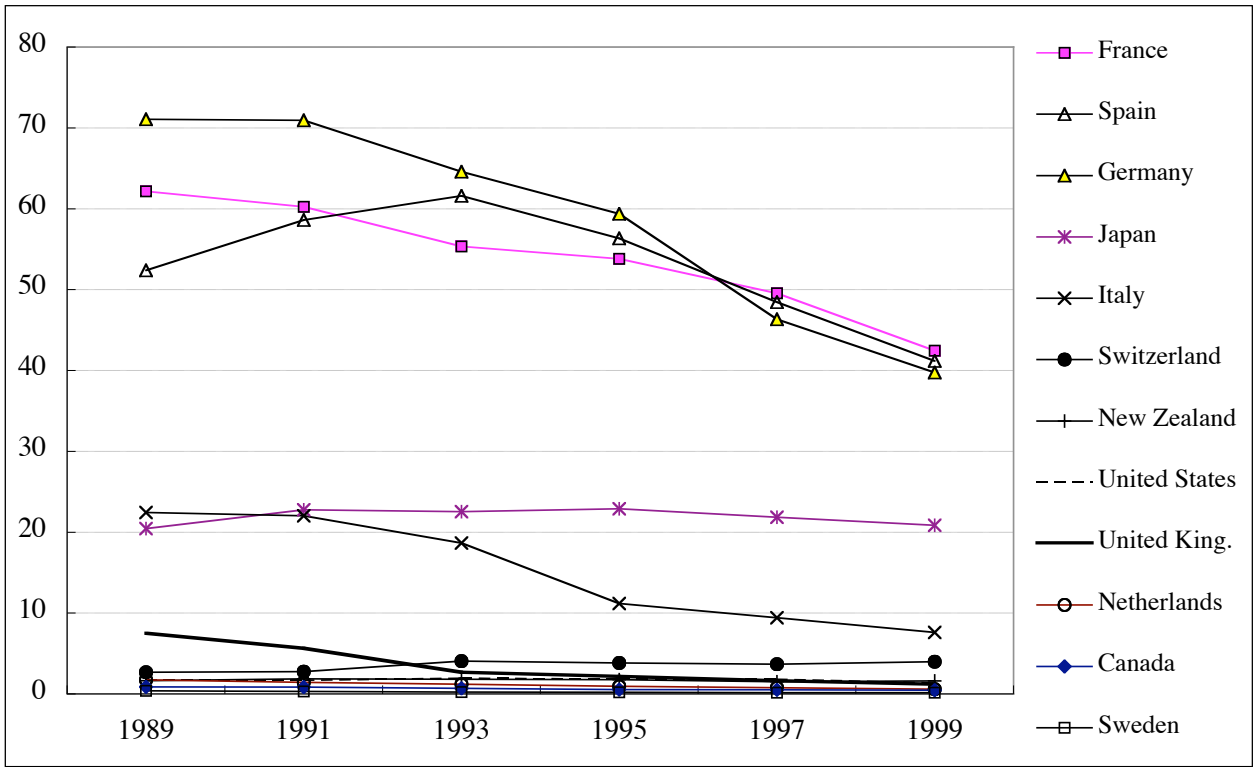


Figure 12. Beta blocker consumption (C07)
(DDD/1000 pop./day)

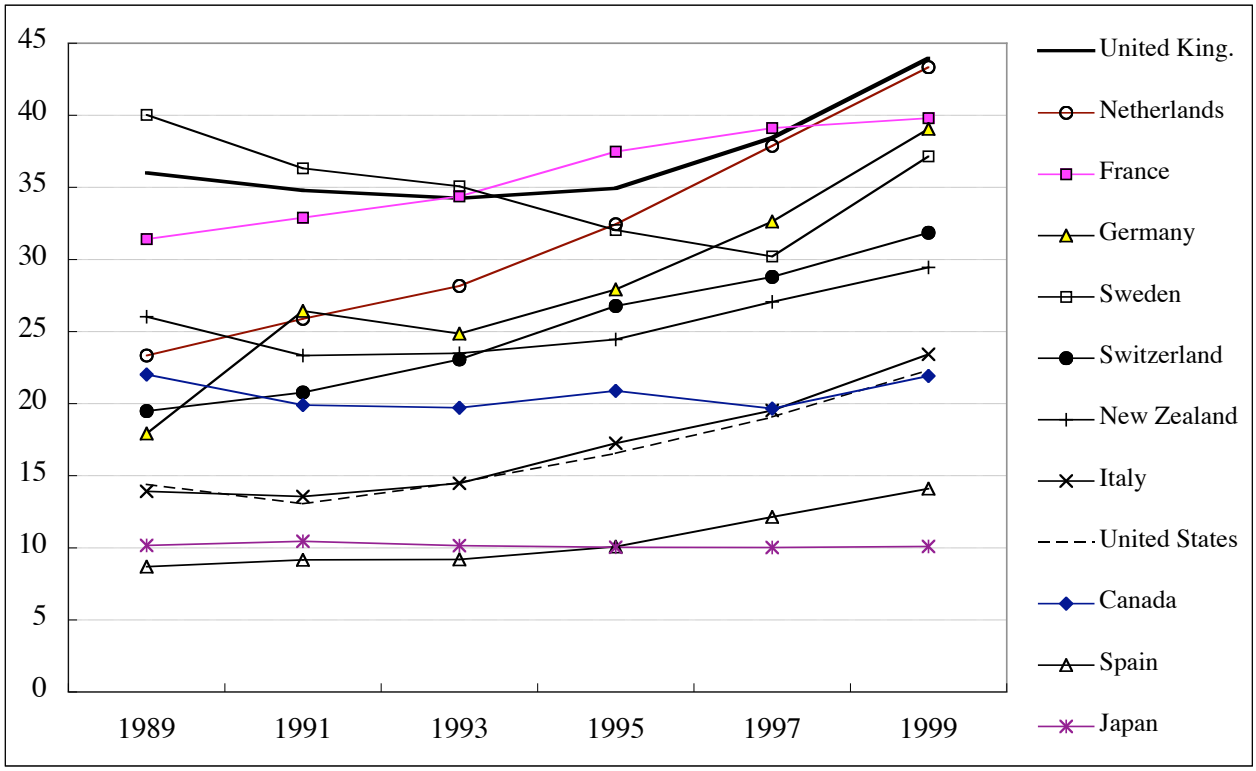


Figure 13. Calcium channel blocker consumption (C08)
(DDD/1000 pop./day)

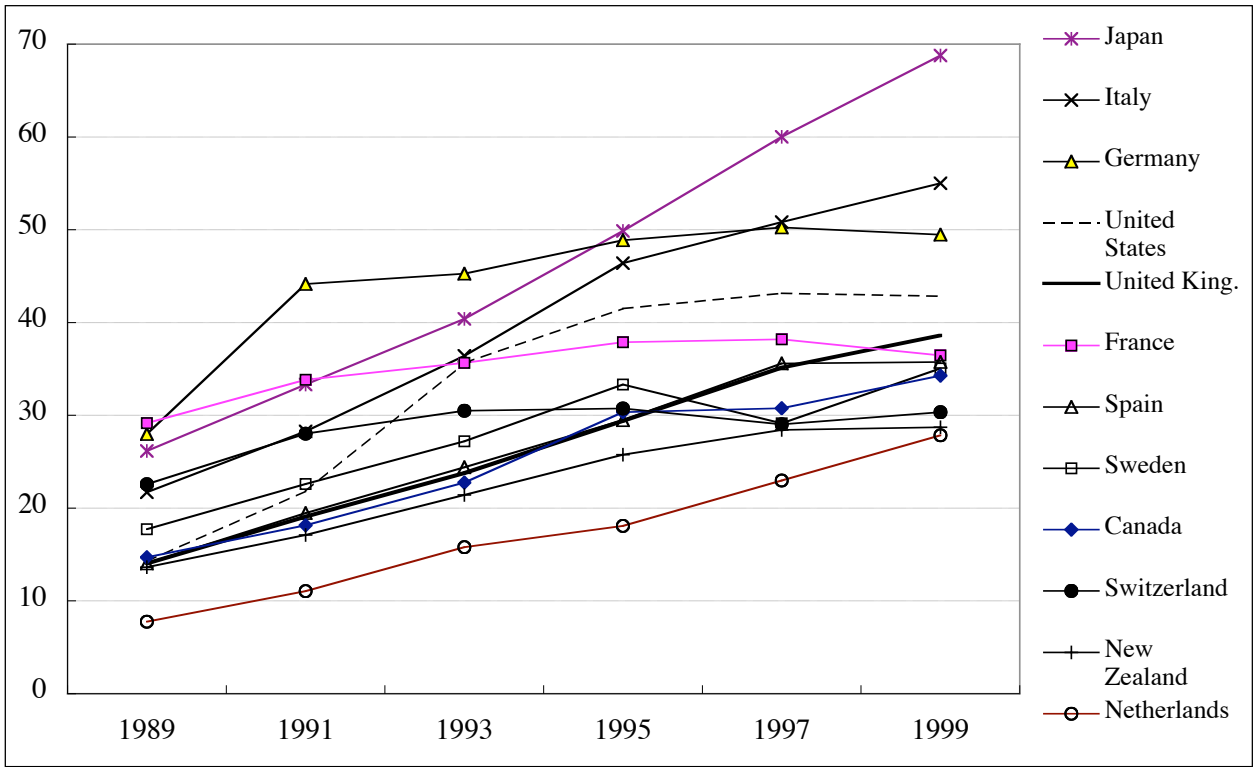


Figure 14. ACE inhibitor consumption (C09)
(DDD/1000 pop./day)

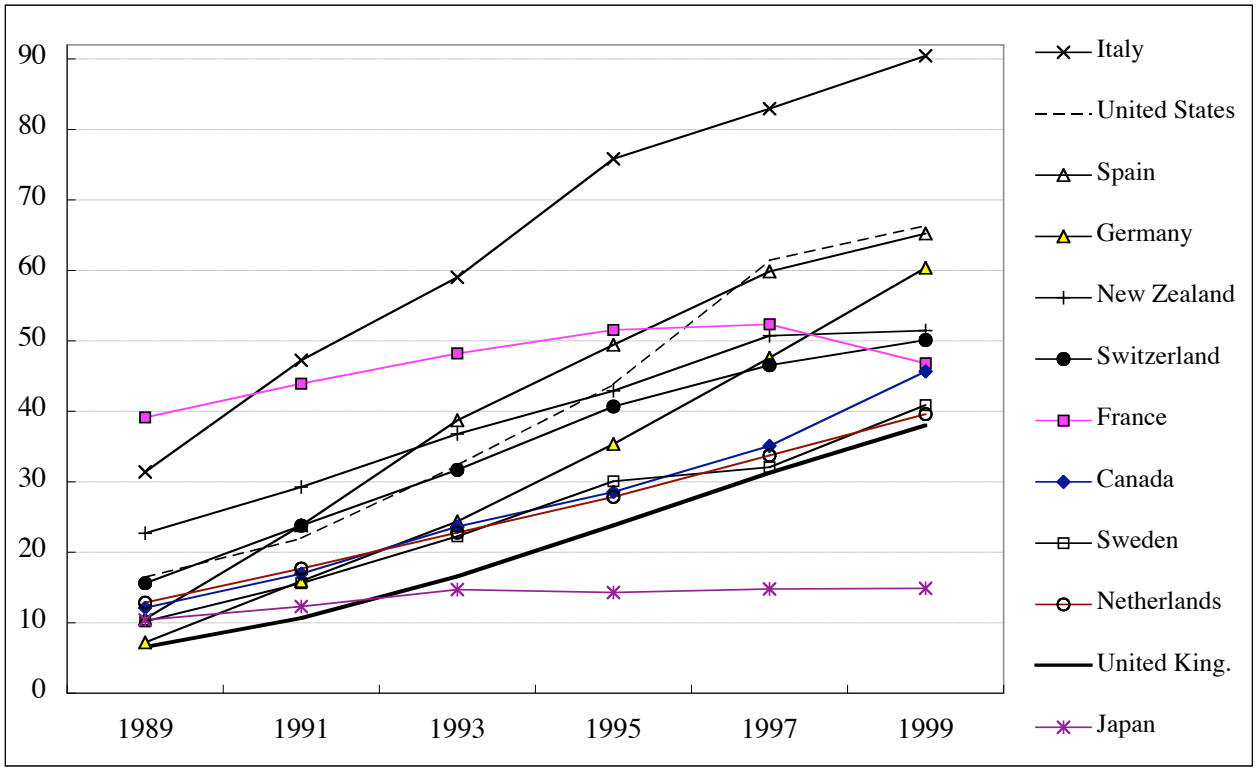


Figure 15. Serum lipid reducer consumption (C10)
(DDD/1000 pop./day)

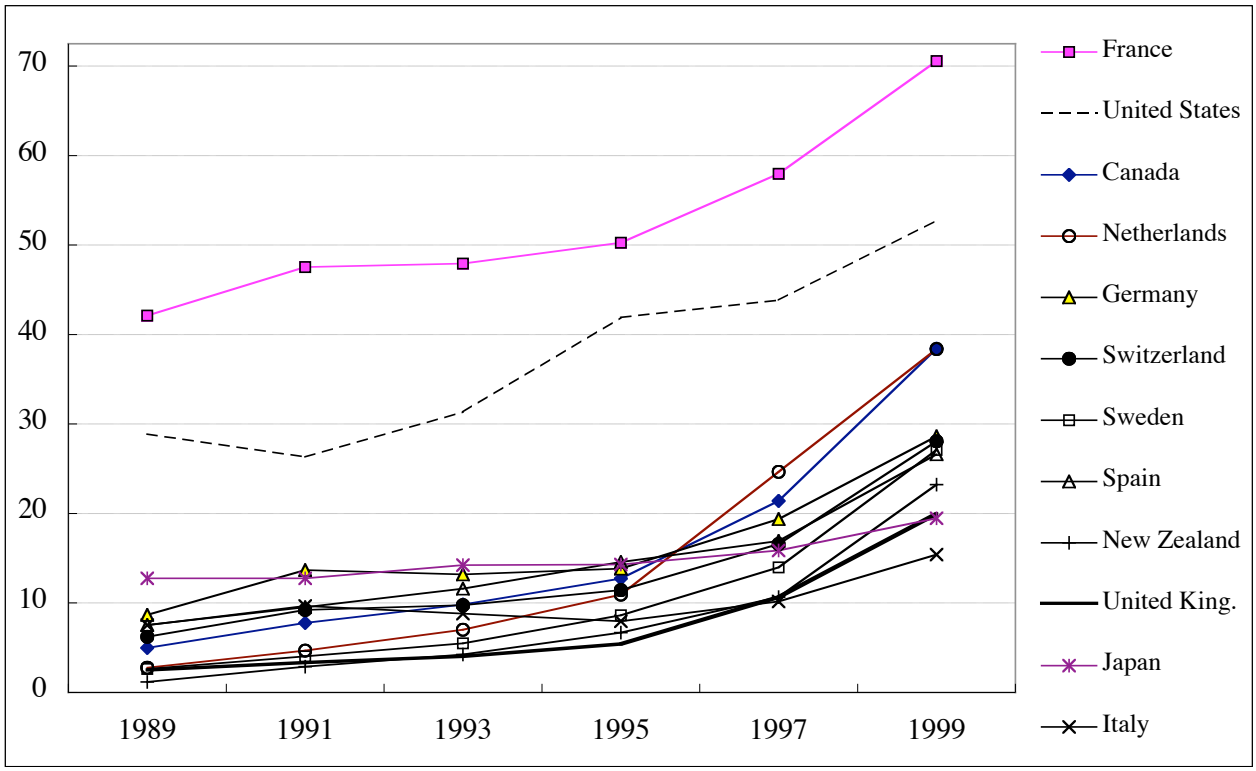


Figure 16. Average consumption for all countries
(DDD/1000 pop./day)

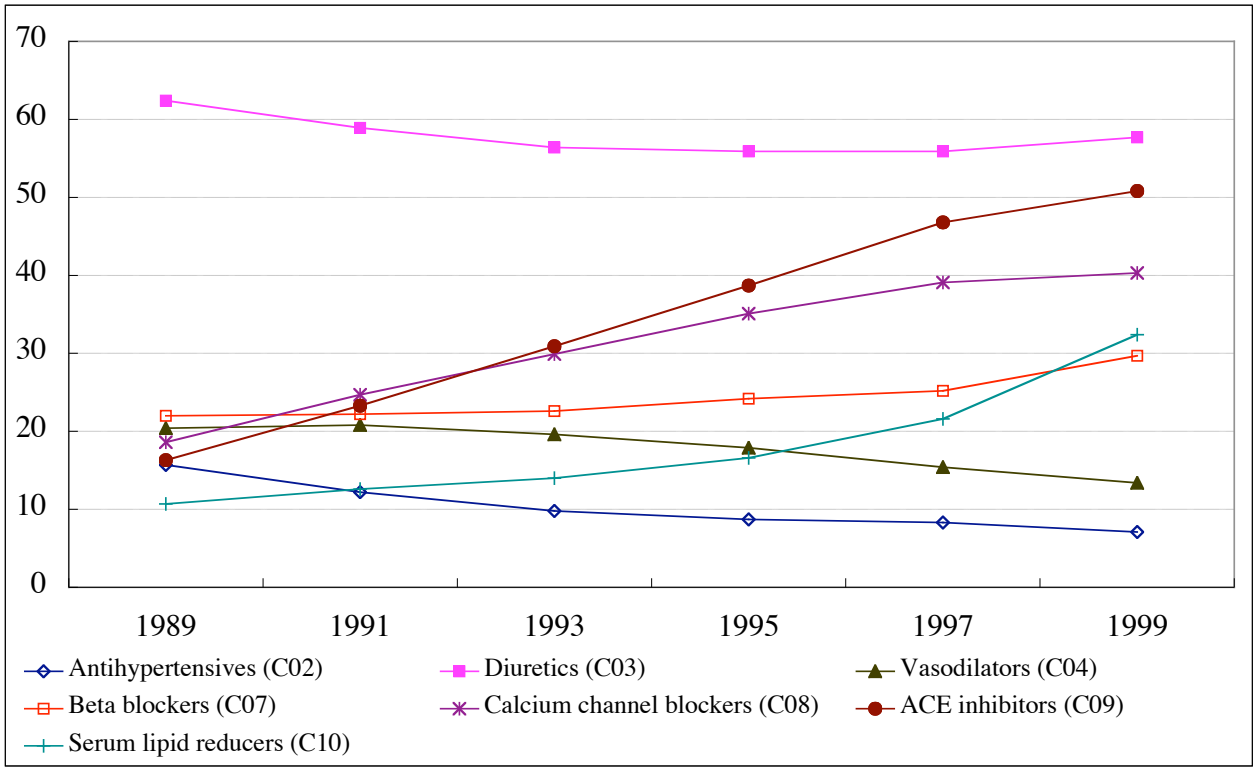


Figure 17. Unit expenditure for traditional antihypertensives (C02)
(US$ PPP/DDD)

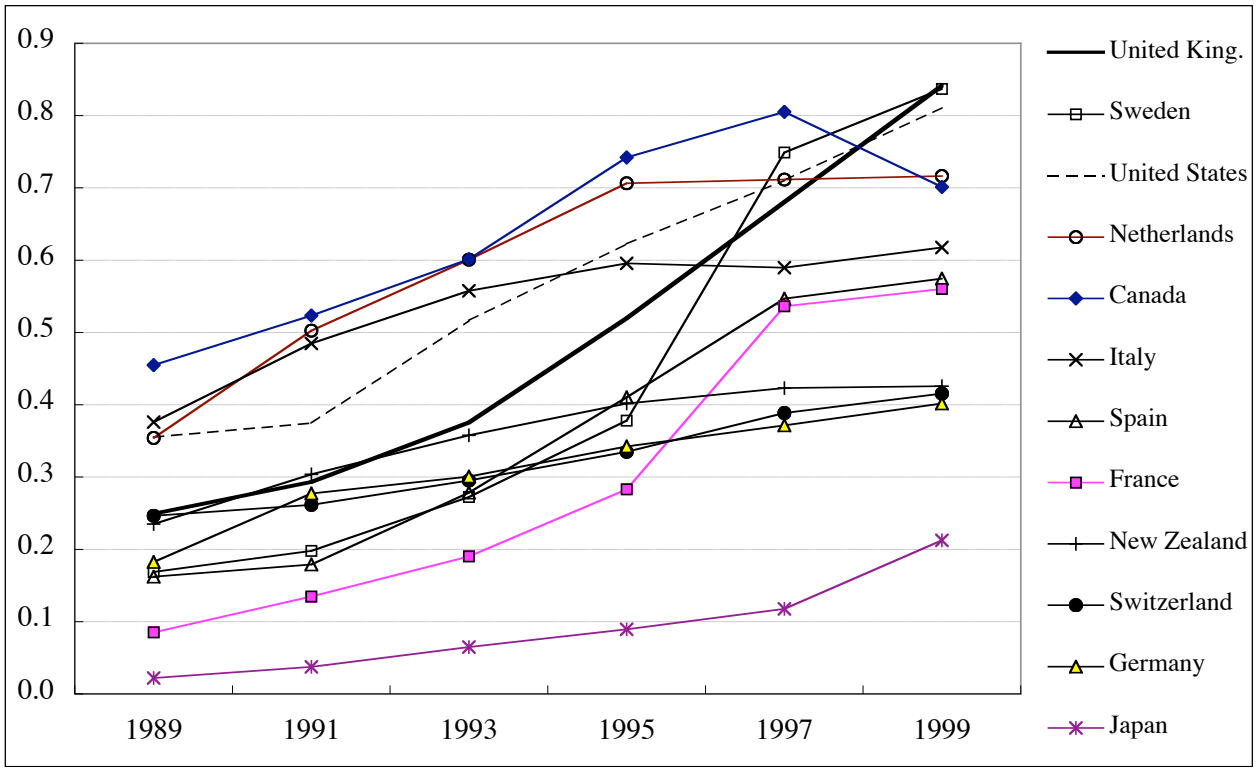


Figure 18. Unit expenditure for diuretics (C03)
(US$ PPP/DDD)

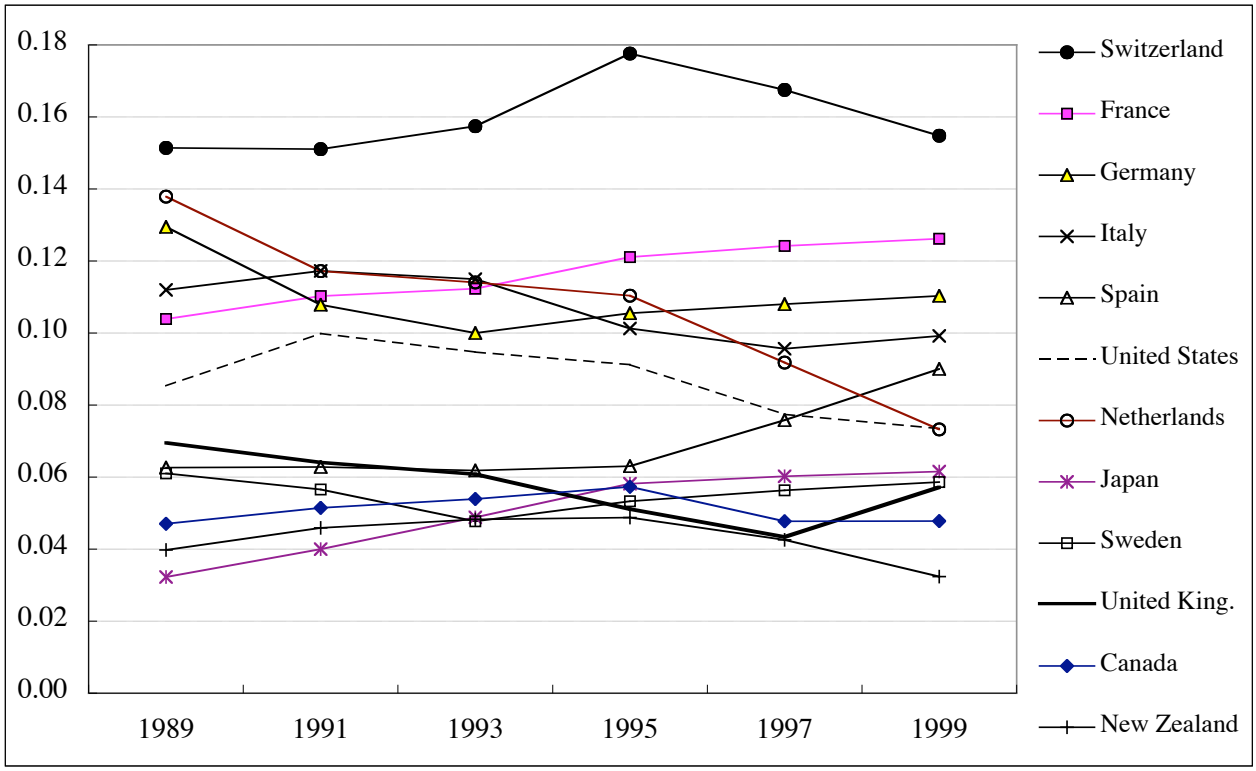


Figure 19. Unit expenditure for vasodilators (C04)
(US$ PPP/DDD)

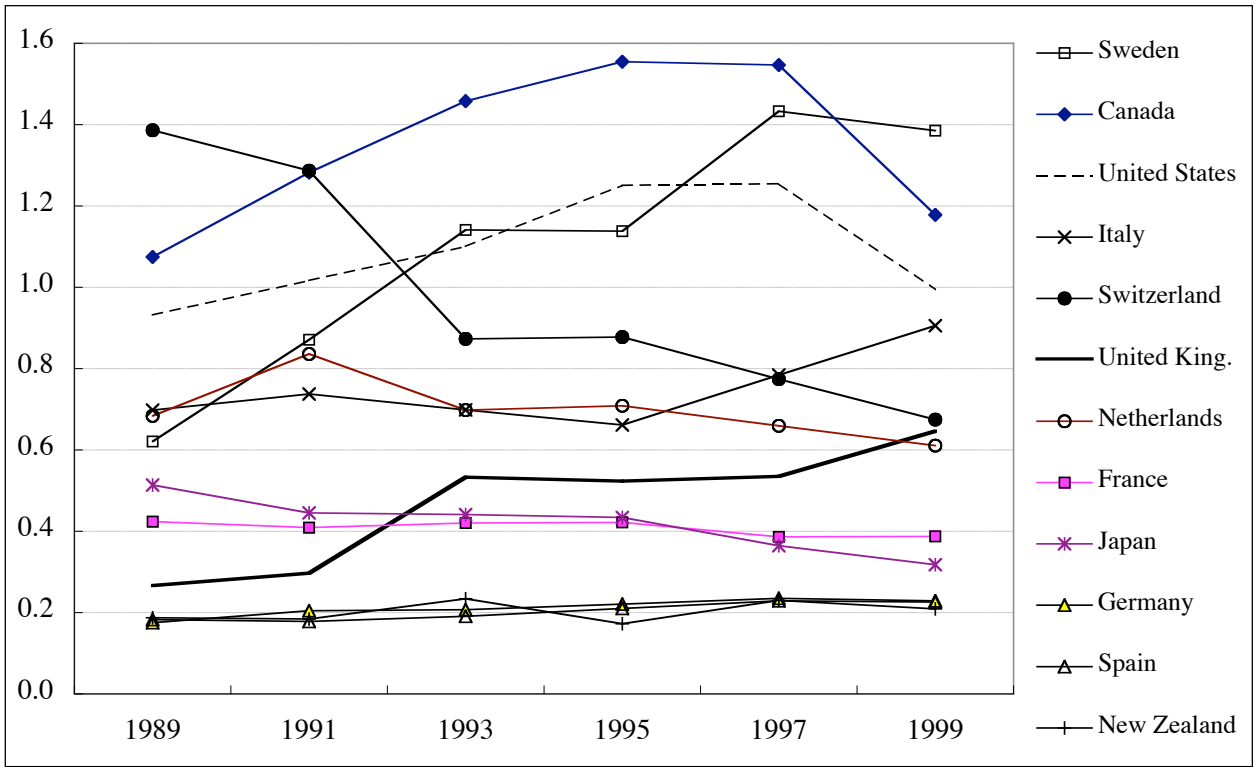


Figure 20. Unit expenditure for beta blockers (C07)
(US$ PPP/DDD)

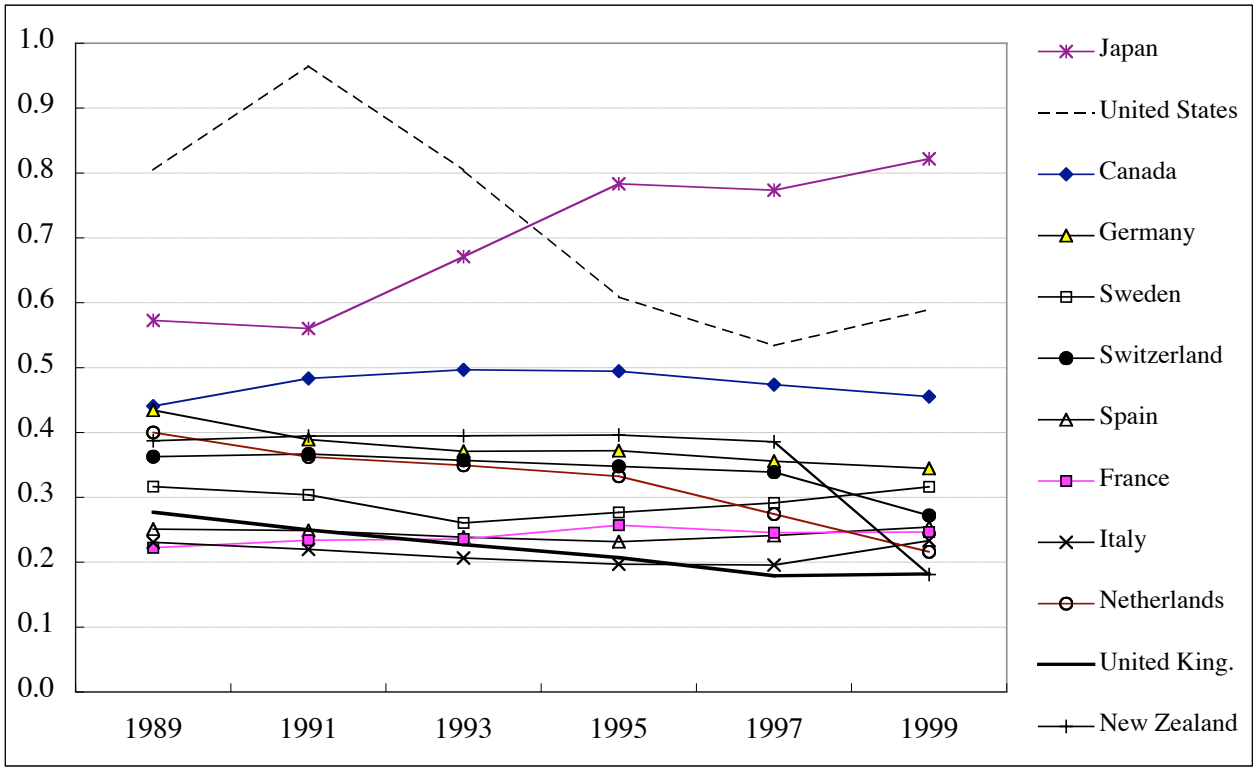


Figure 21. Unit expenditure for calcium channel blockers (C08)
(US$ PPP/DDD)

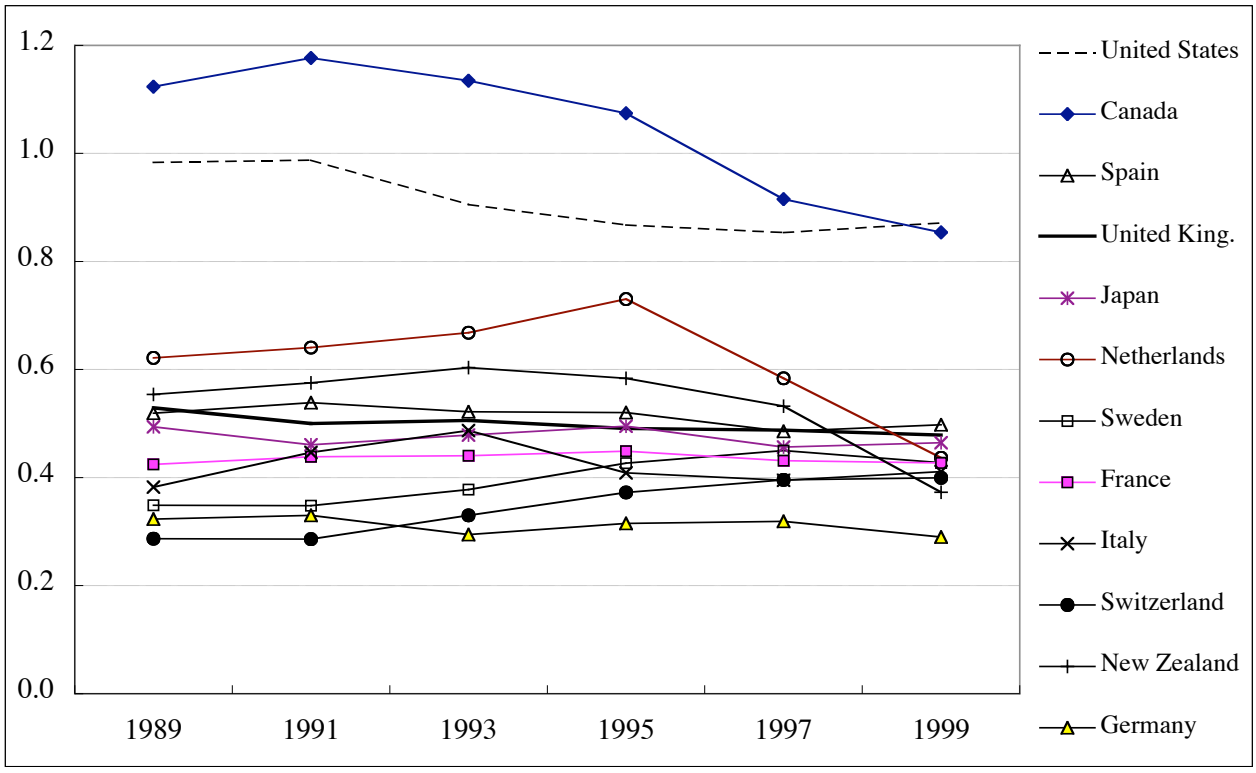


Figure 22. Unit expenditure for ACE inhibitors (C09)
(US$ PPP/DDD)

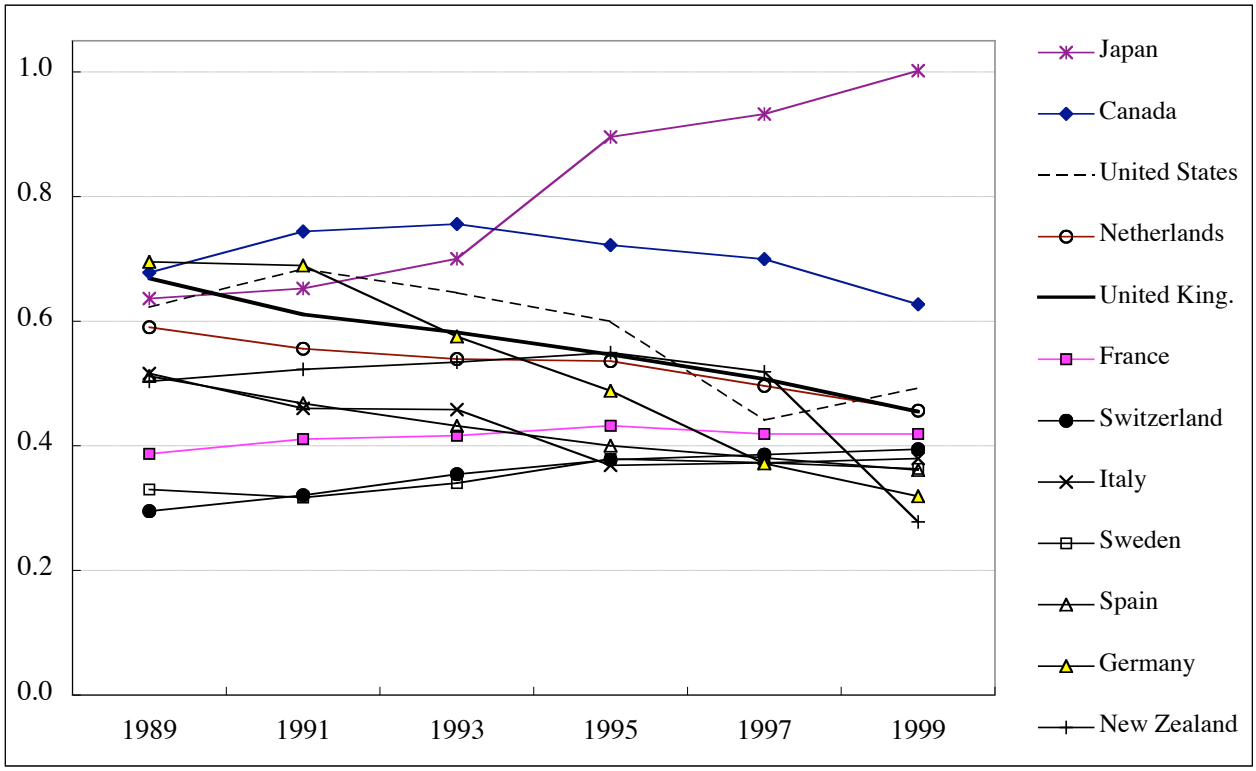


Figure 23. Unit expenditure for serum lipid reducers (C10)
(US$ PPP/DDD)

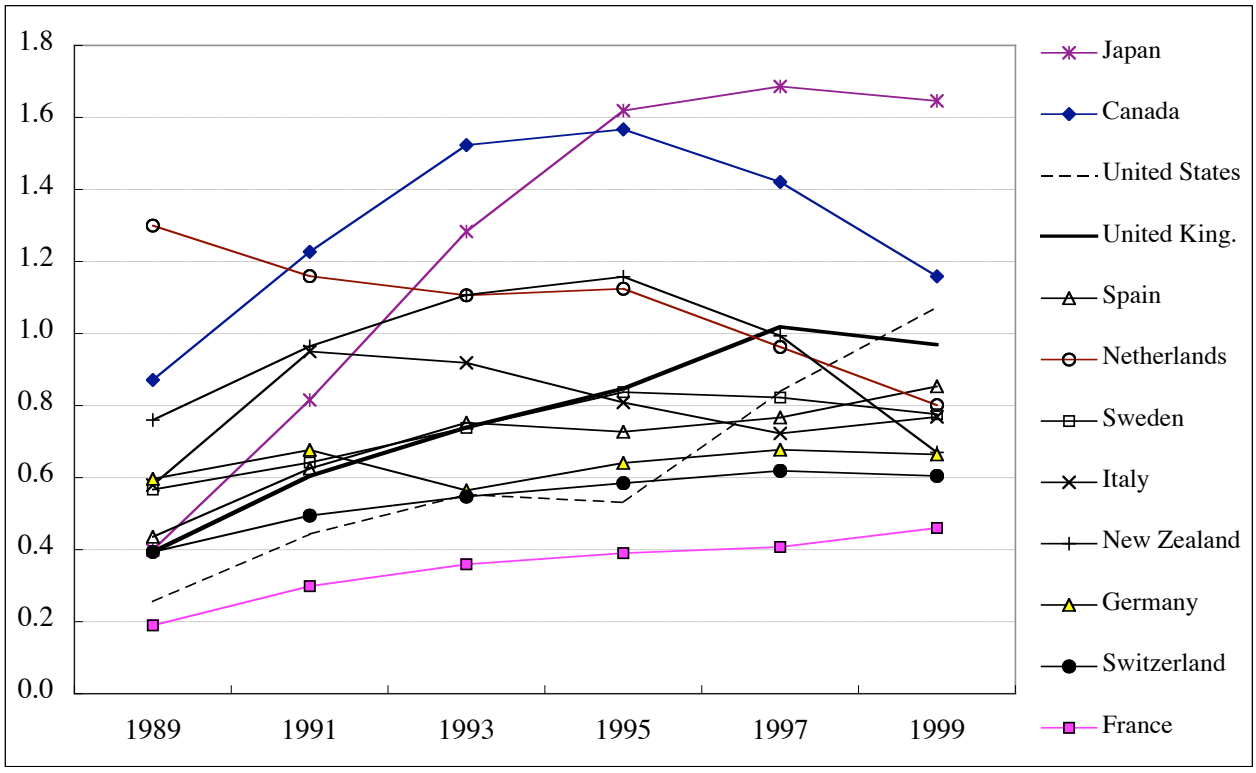


Figure 24. Average unit expenditure for all countries
(US$ PPP/DDD)

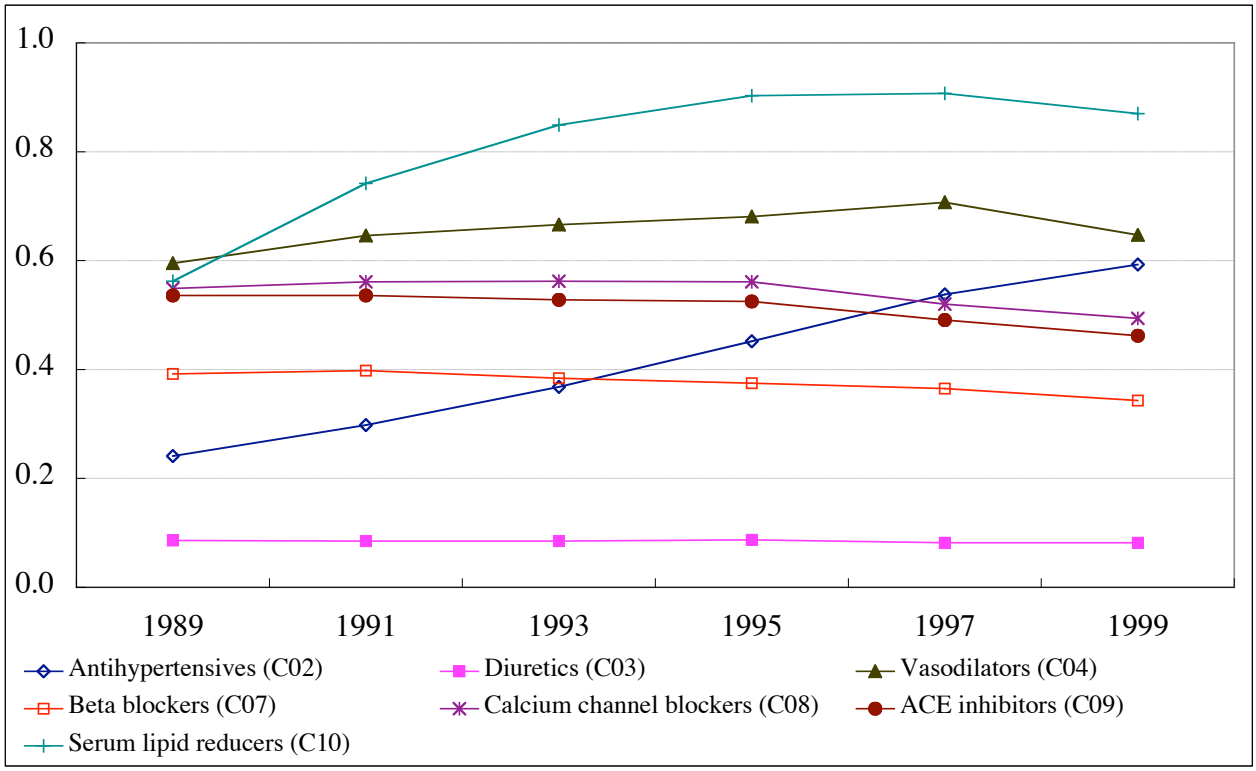


Figure 25. Aggregate trend in consumption and expenditure

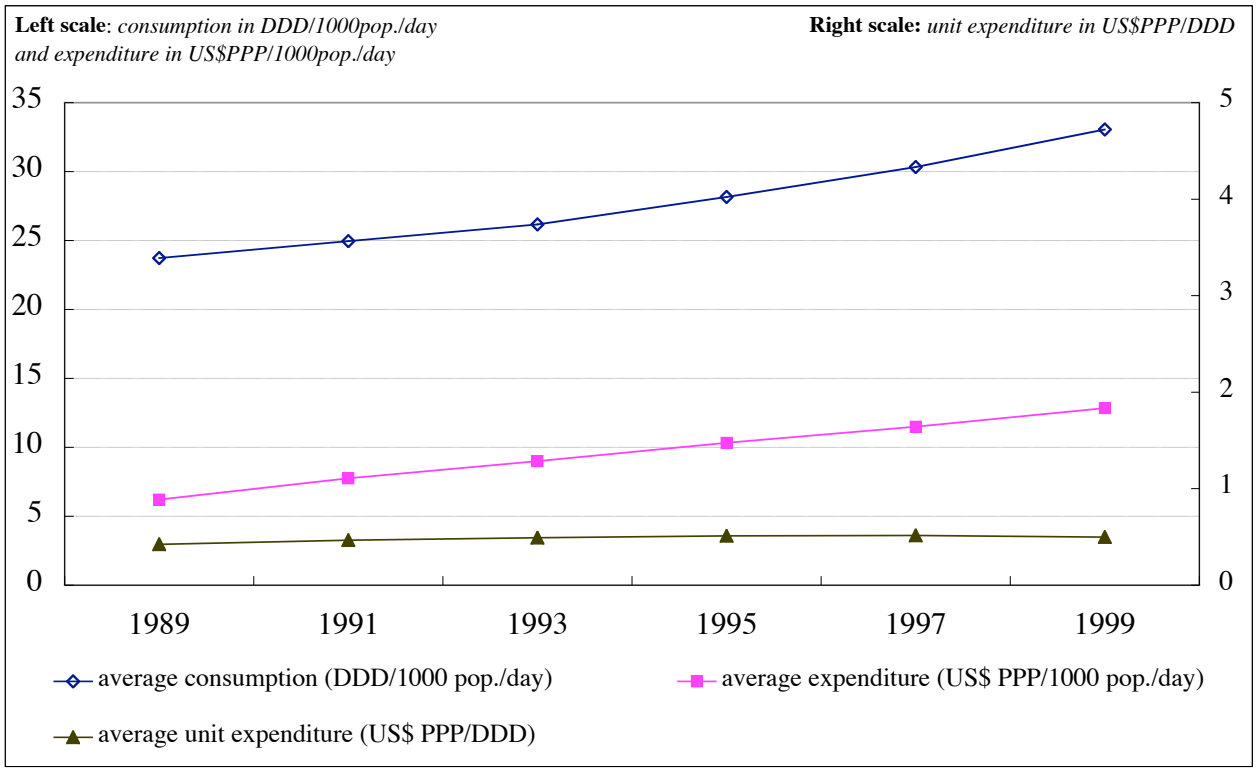
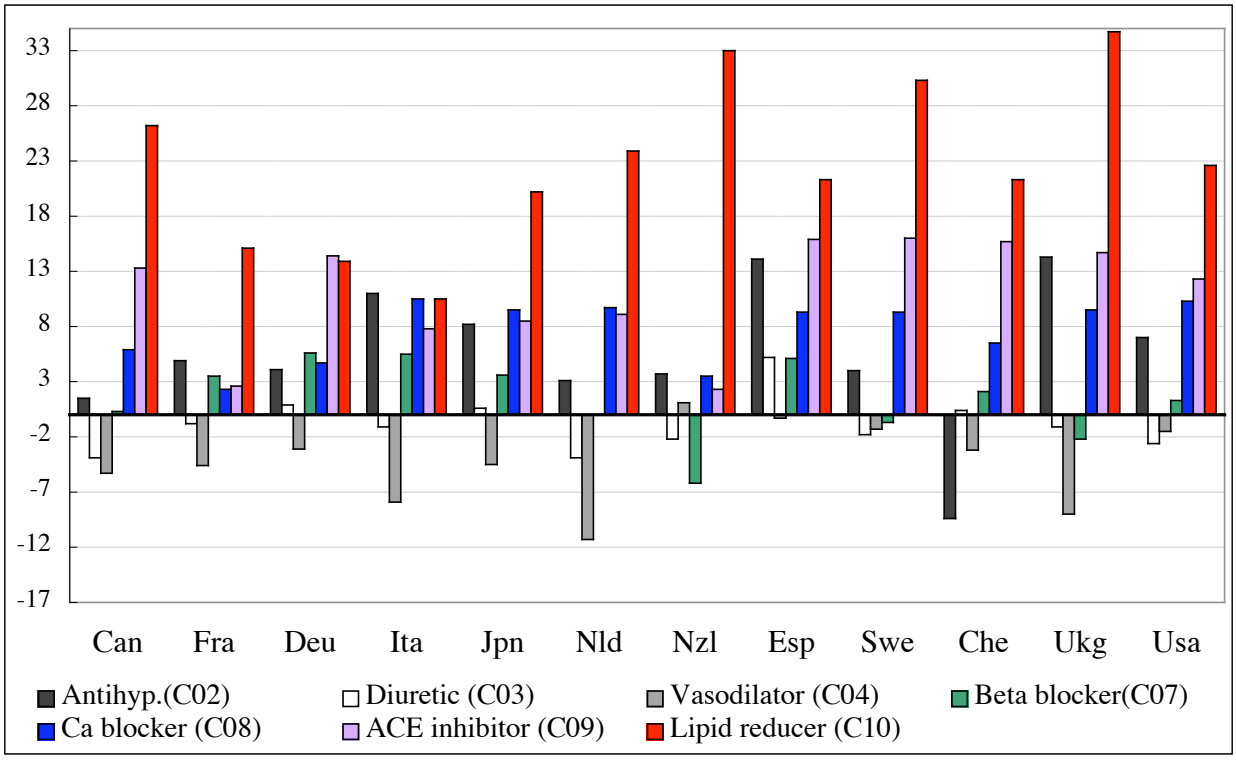
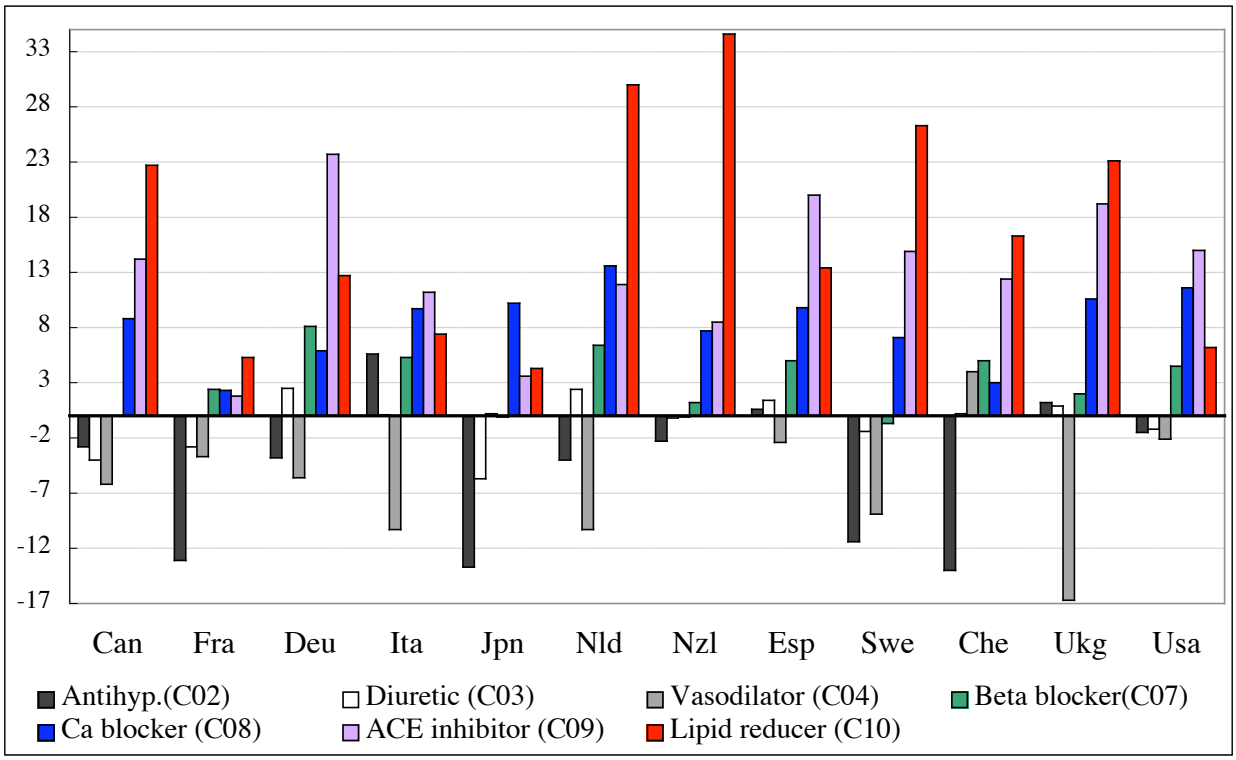


Figure 26. Trend in expenditure by drug category (1989 to 1999)
(average annual growth rates in percentage)



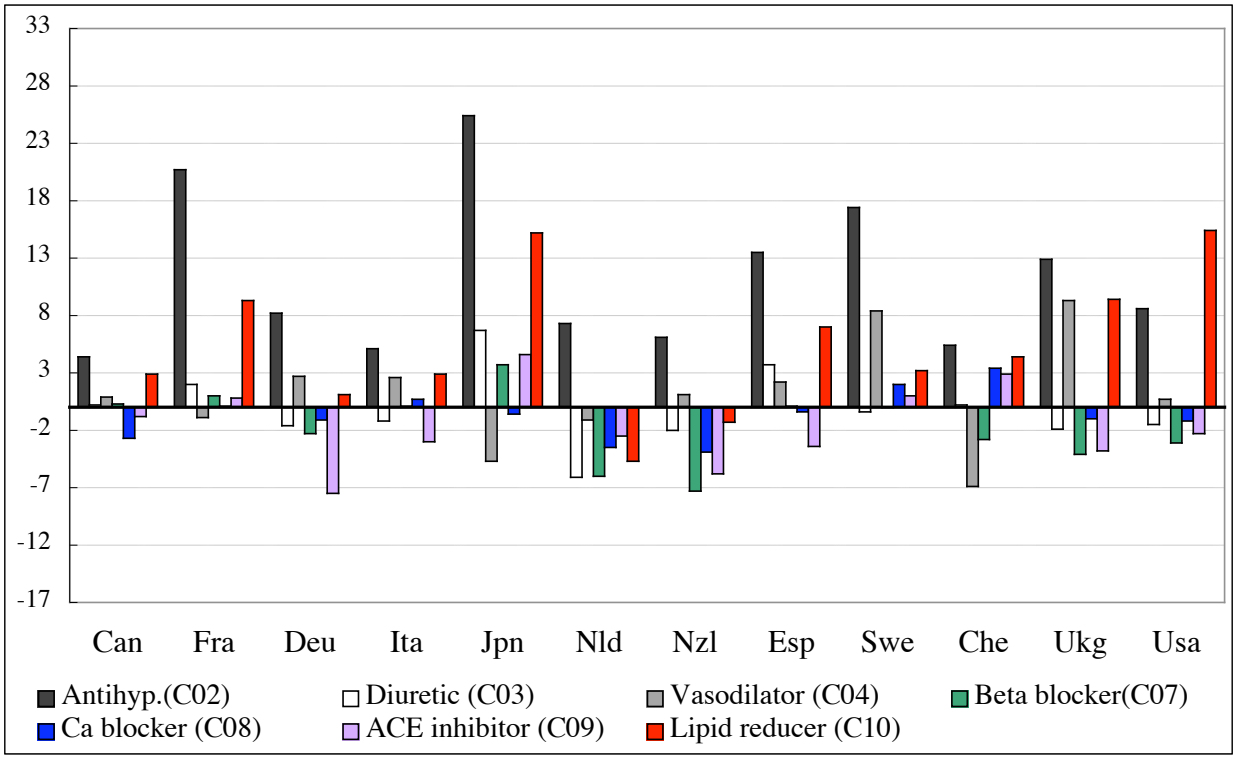
Note: Expenditure is expressed in US$ PPP/1000 pop./day.

Figure 27. Trend in drug consumption by category (1989 to 1999)
(average annual growth rates in percentage)



Note: Consumption is expressed in DDD/1000 pop./day.

Figure 28. Trend in unit expenditure by category (1989 to 1999)
(average annual growth rates in percentage)



Note: Unit expenditure is expressed in US$ PPP/DDD.

Figure 29. Trend in drug characteristics (1989-1999)
(average annual growth rates in percentage)

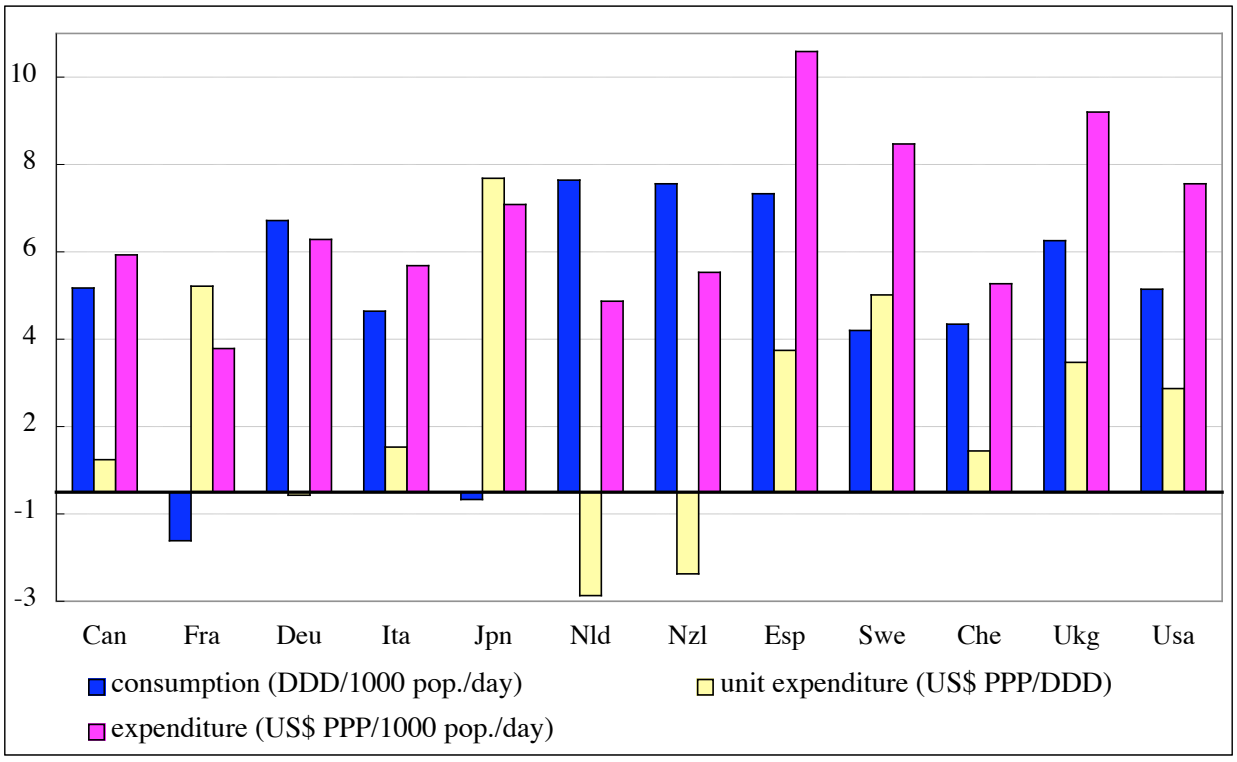


Figure 30. Traditional antihypertensive (C02) consumption by subcategories
(DDD/1000 pop./day)

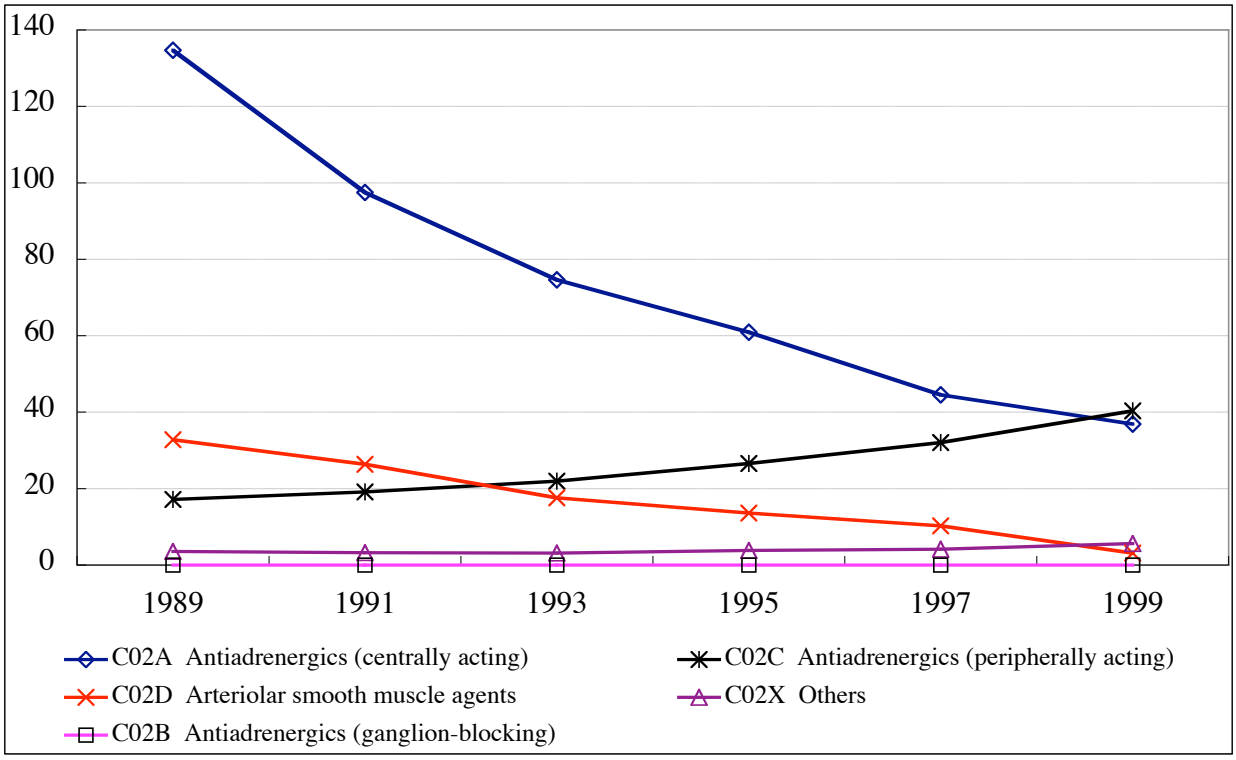
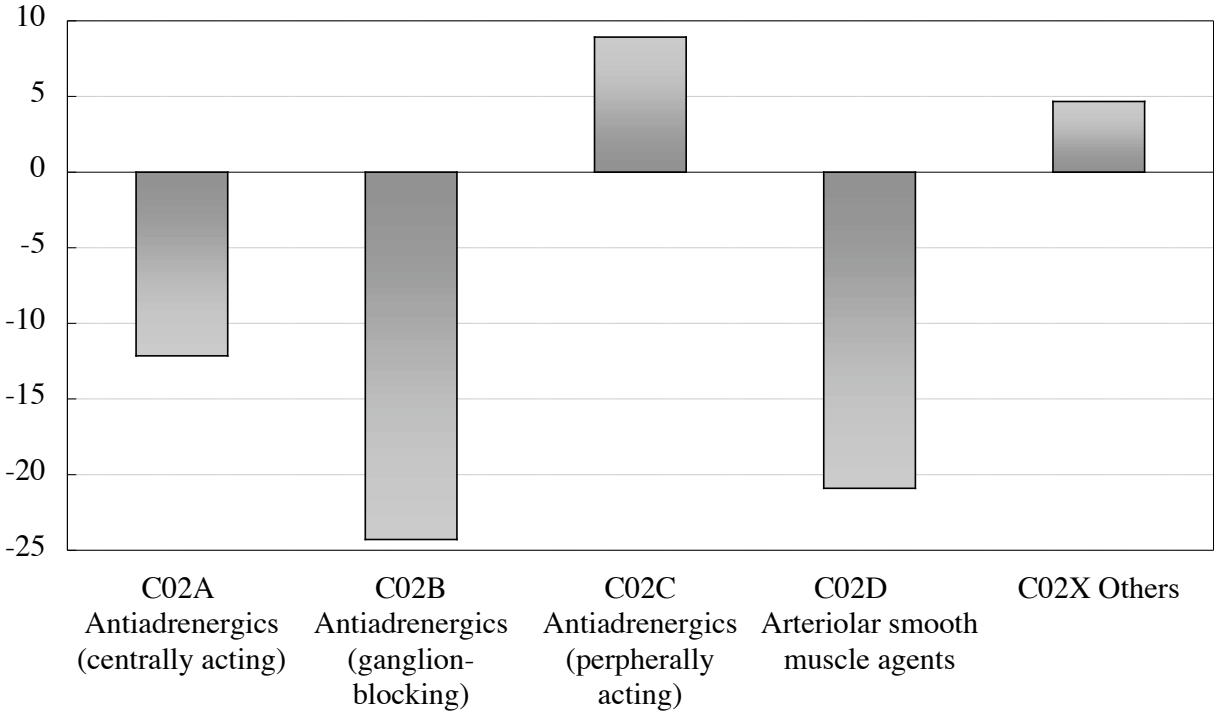


Figure 31. Trend in consumption for traditional antihypertensive (C02) subcategories (1989-1999)
(average annual growth rates in percentage)



Note: Consumption is expressed in DDD/1000 pop./day.

Figure 32. Serum lipid reducer (C10) consumption by subcategory
(DDD/1000 pop./day)

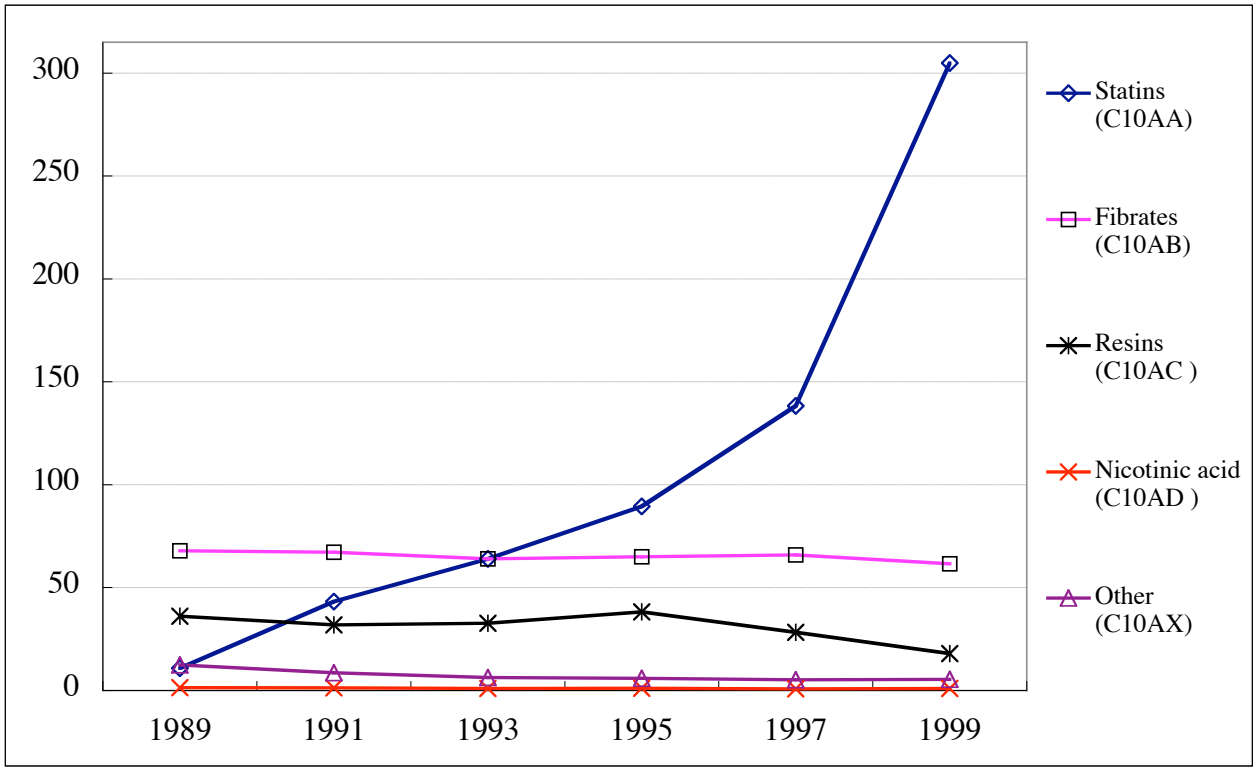


Figure 33. Statin consumption by country
(as a percentage of the serum lipid reducer consumption)

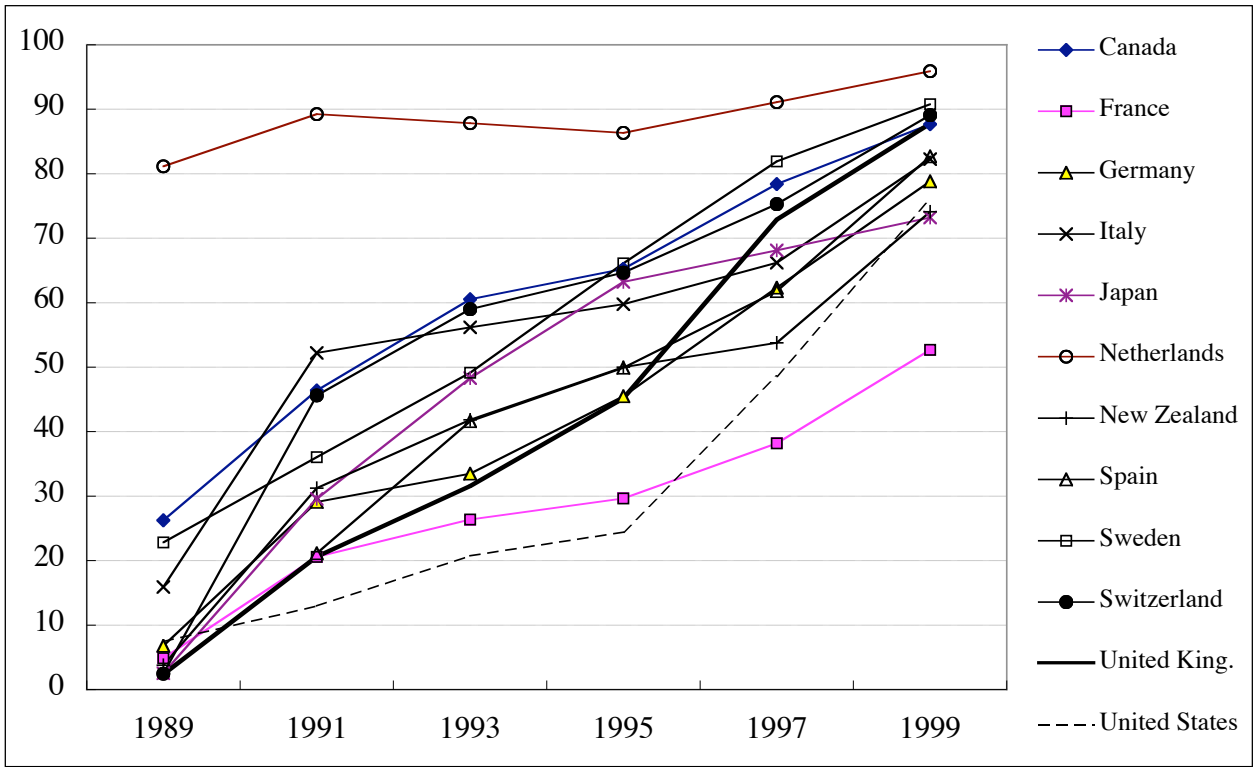
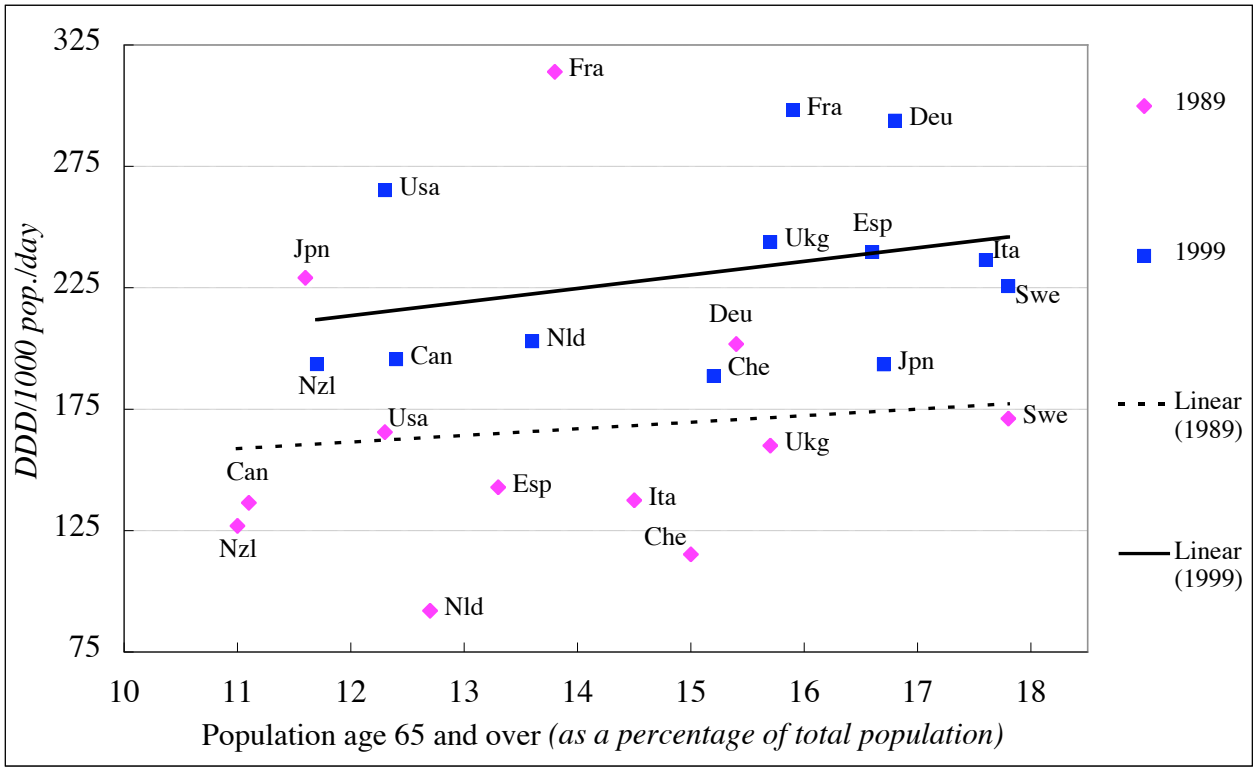
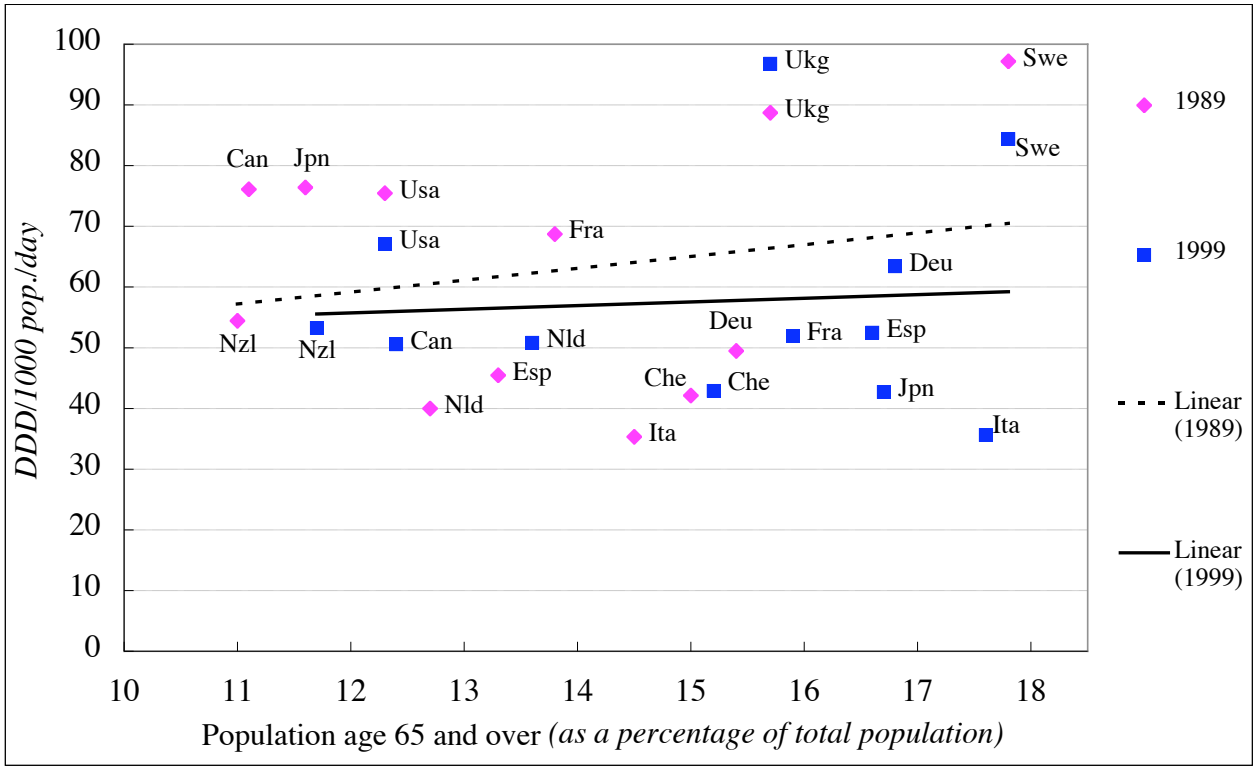


Figure 34. Cardiovascular drug consumption and population age structure *(1989 and 1999)*



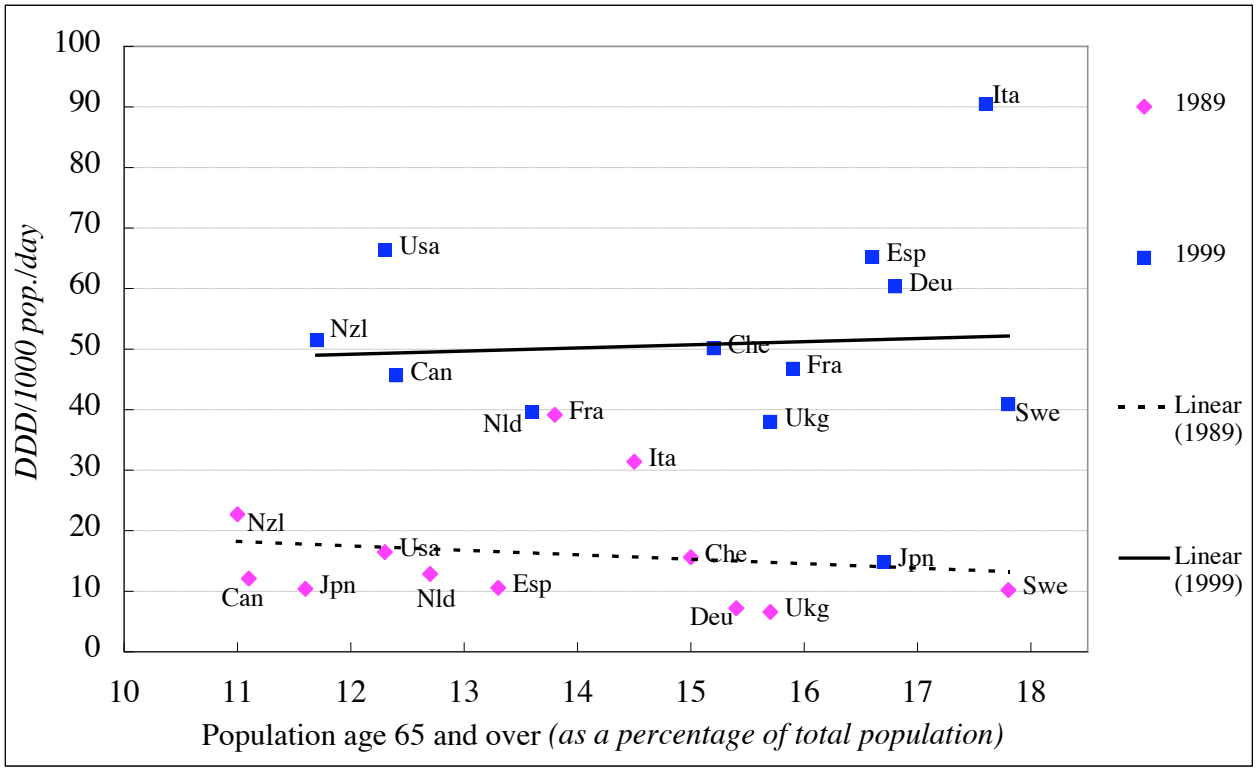
Note: 1989, R^2= 0.9 % 1999 R^2= 9.6 %

Figure 35. Diuretic (C03) consumption and population age structure *(1989 and 1999)*



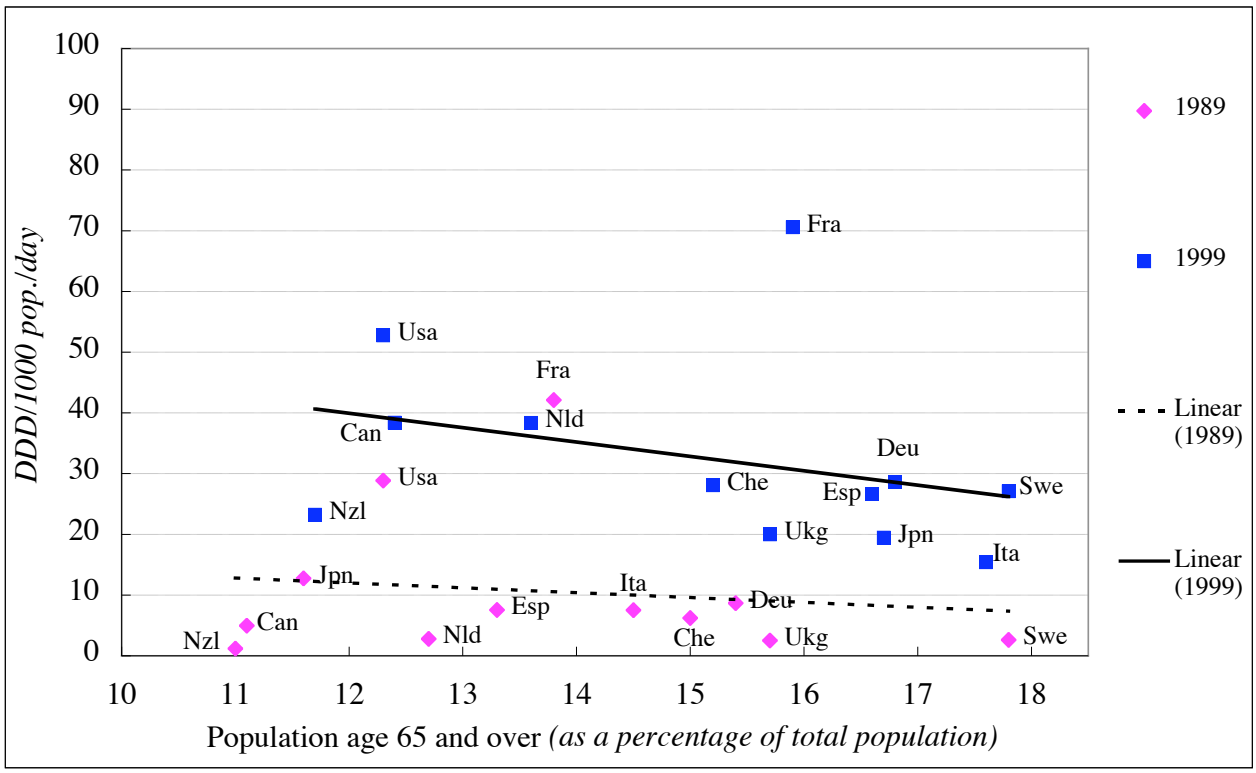
Note: 1989, R^2= 3.9 % 1999 R^2= 0.5 %

Figure 36. ACE inhibitor (C09) consumption and population age structure *(1989 and 1999)*



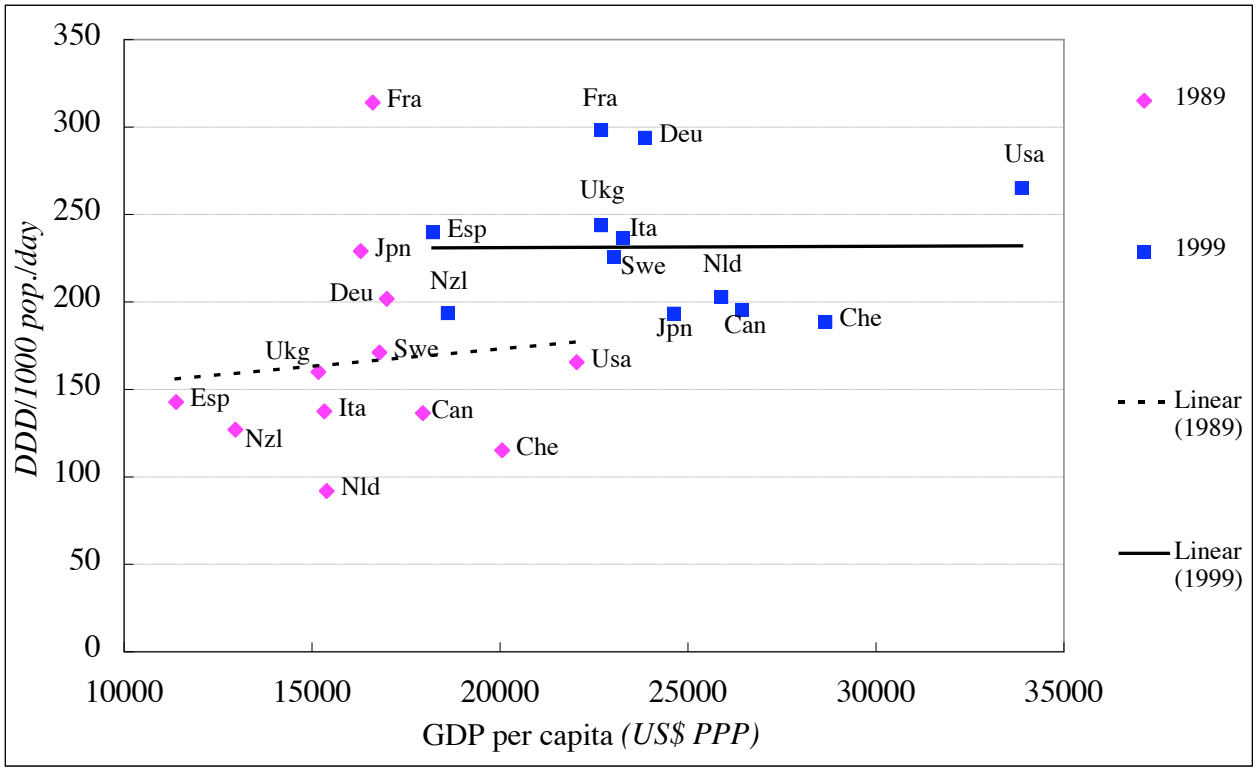
Note: 1989, R^2= 2.3 % 1999 R^2= 0.6 %

Figure 37. Serum lipid reducer (C10) consumption and population age structure *(1989 and 1999)*



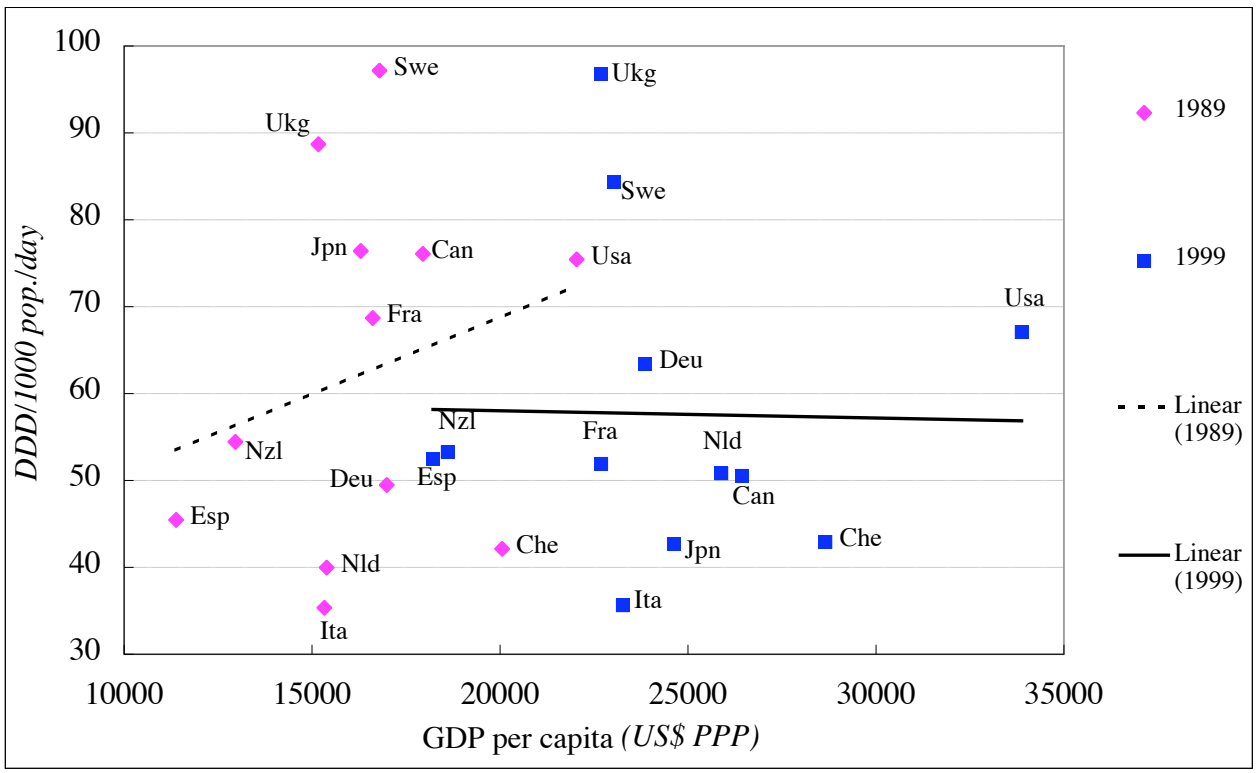
Note: 1989, R^2= 1.8 % 1999 R^2= 10.5 %

Figure 38. Cardiovascular drug consumption and national income *(1989 and 1999)*



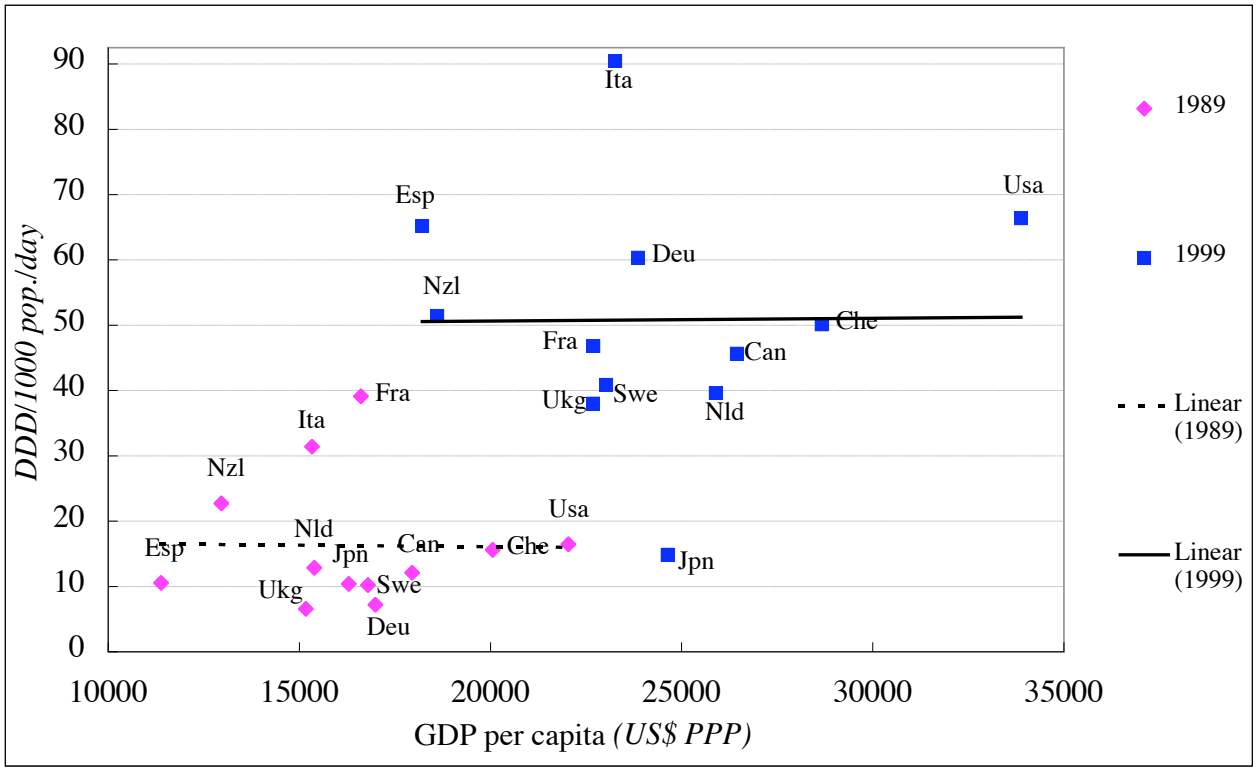
Note: 1989, R^2= 0.1 % 1999 R^2= 0.0 %

Figure 39. Diuretic (C03) consumption and national income *(1989 and 1999)*



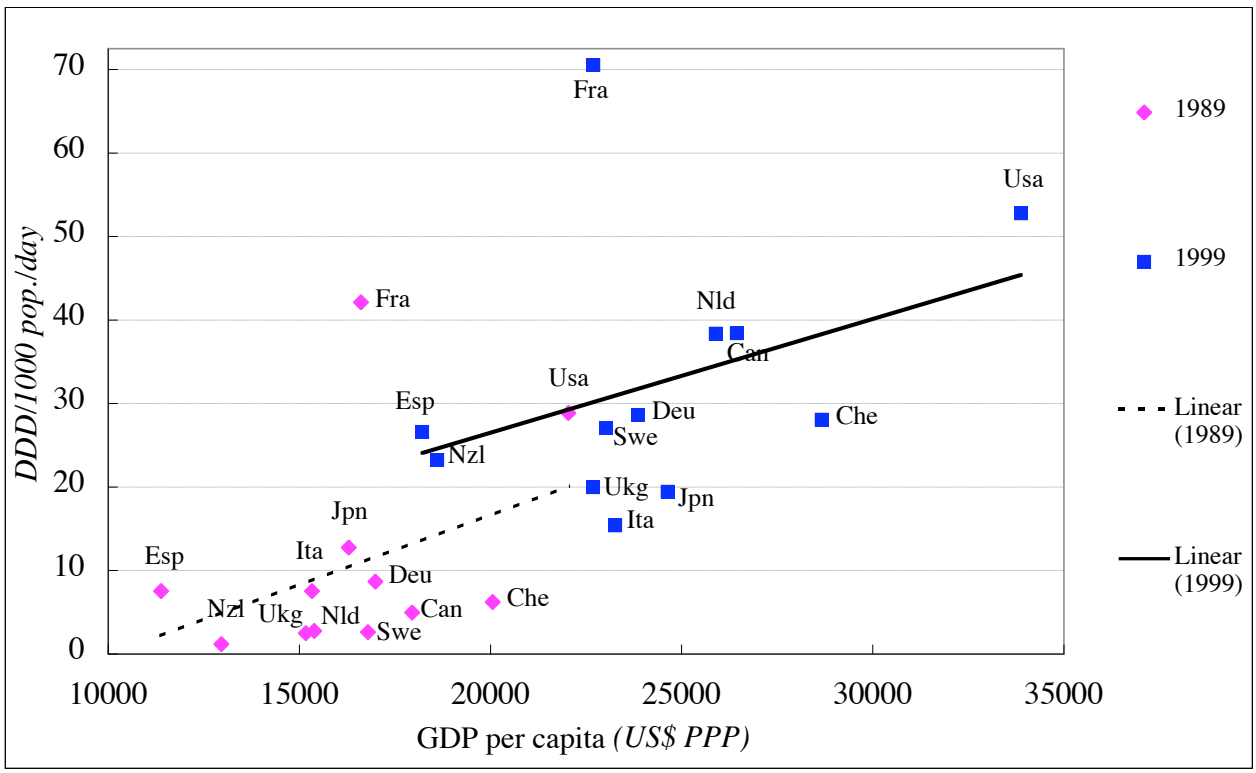
Note: 1989, R^2= 6.0 % 1999 R^2= 0.0 %

Figure 40. ACE inhibitor (C09) consumption and national income *(1989 and 1999)*



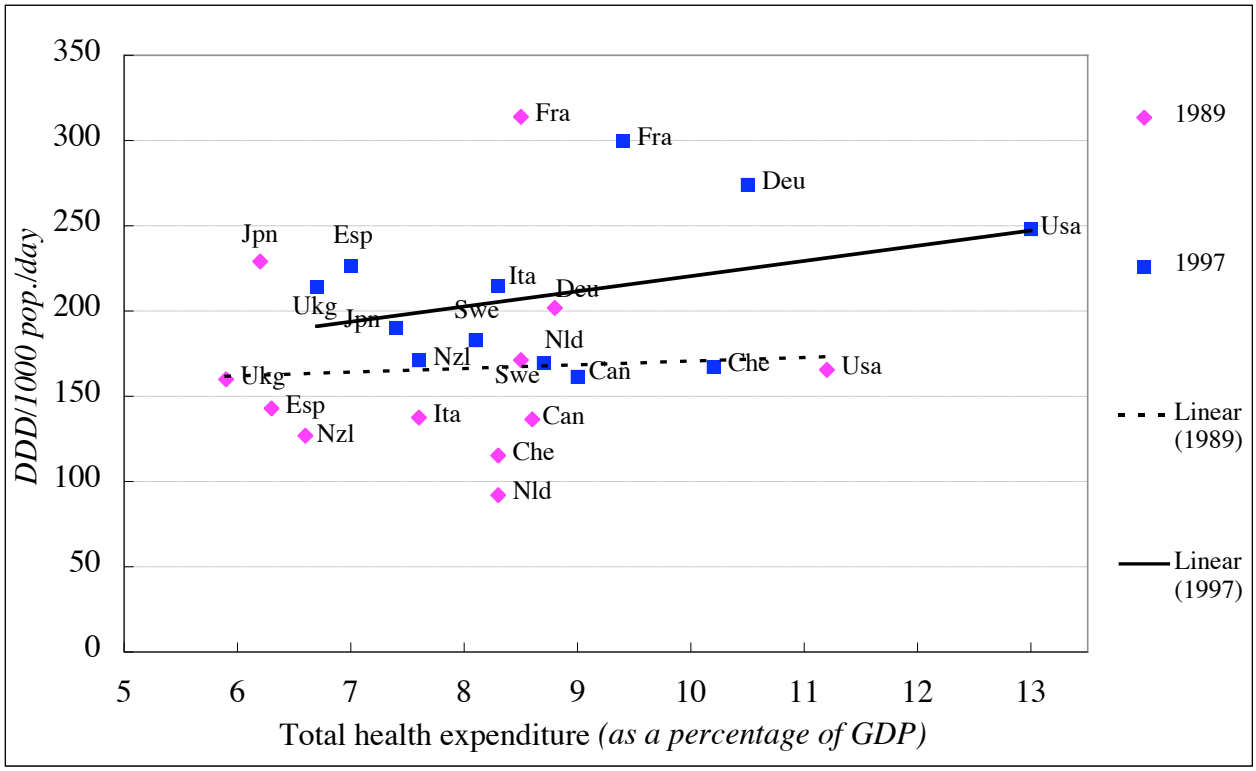
Note: 1989, R^2= 0.0 % 1999 R^2= 0.0 %

Figure 41. Serum lipid reducer (C10) consumption and national income *(1989 and 1999)*



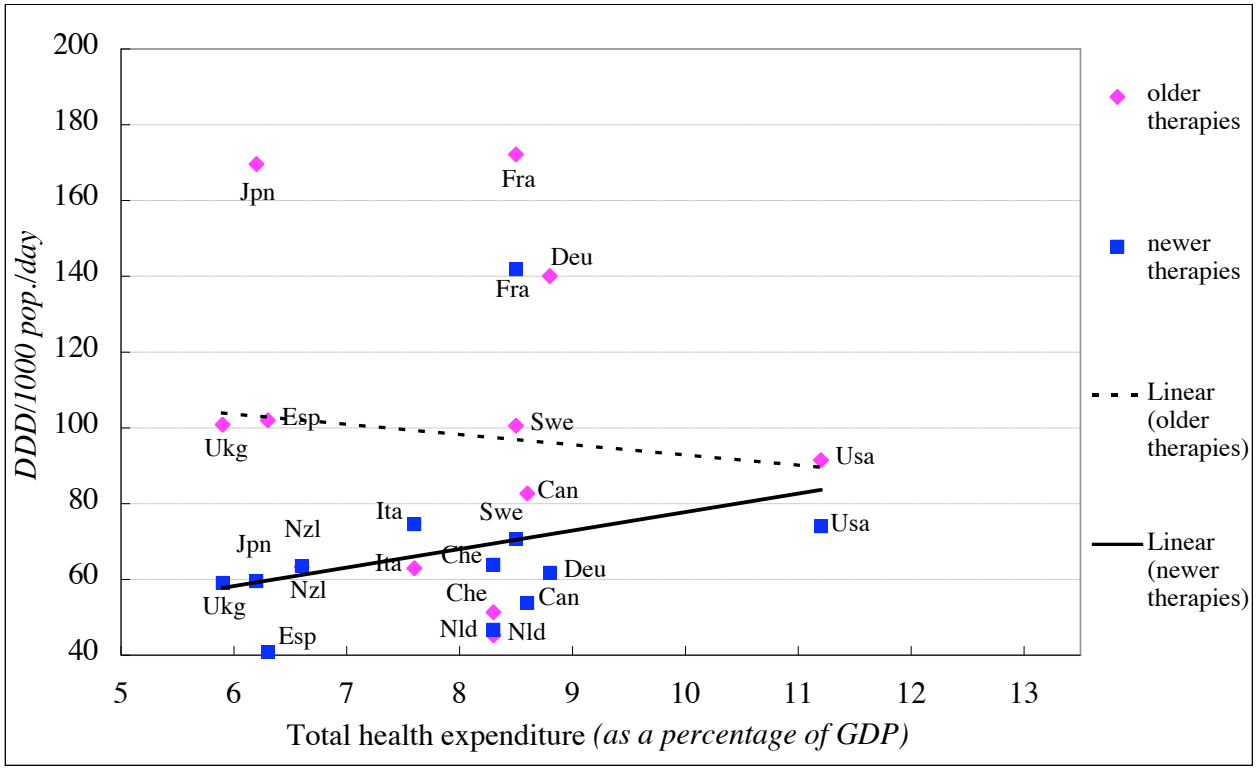
Note: 1989, R^2= 14.9 % 1999 R^2= 13.2 %

Figure 42. Cardiovascular drug consumption and health spending *(1989 and 1999)*



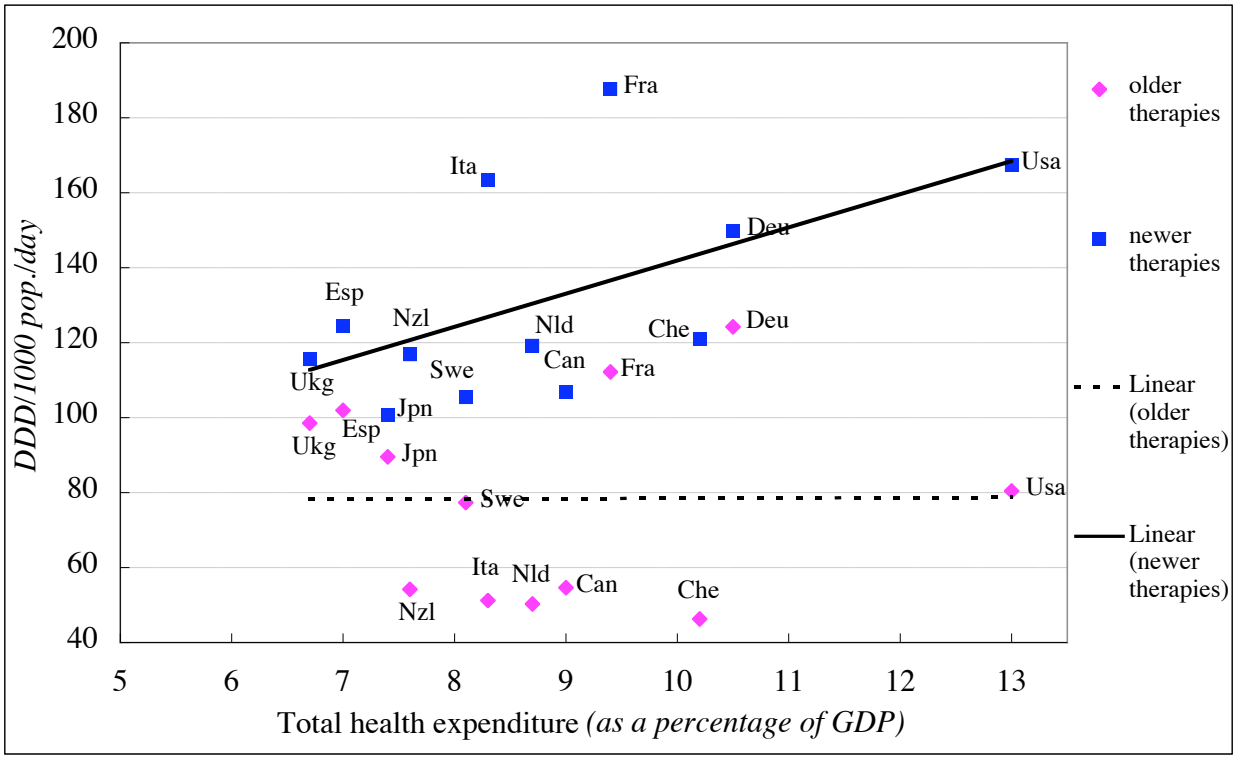
Note: 1989, R^2= 0.3 % 1997 R^2= 12.3 %

Figure 43. Cardiovascular drug therapies and health expenditure *(1989)*



Note:Older therapies, R^2= 0.1 % Newer therapies R^2= 8.2 %

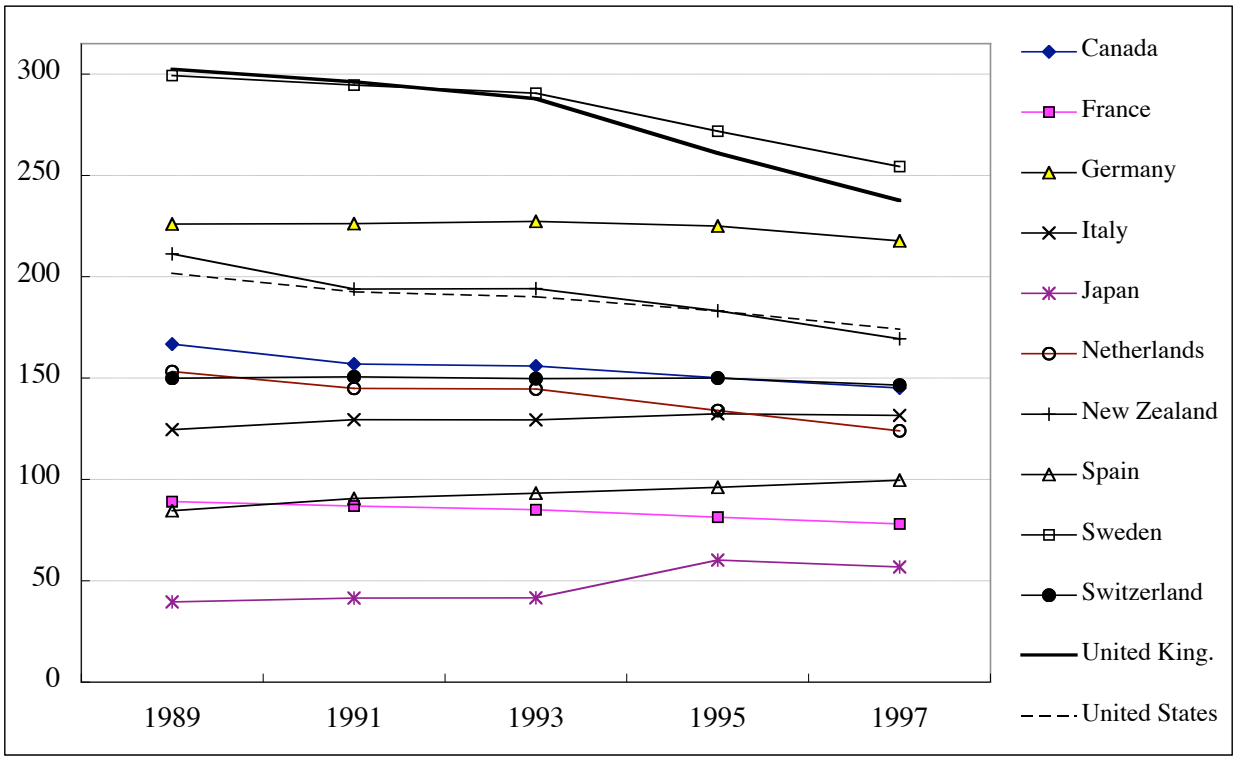
Figure 44. Cardiovascular drug therapies and health spending *(1997)*



Note:Older therapies, R^2= 0.0 % Newer therapies R^2= 30.7 %

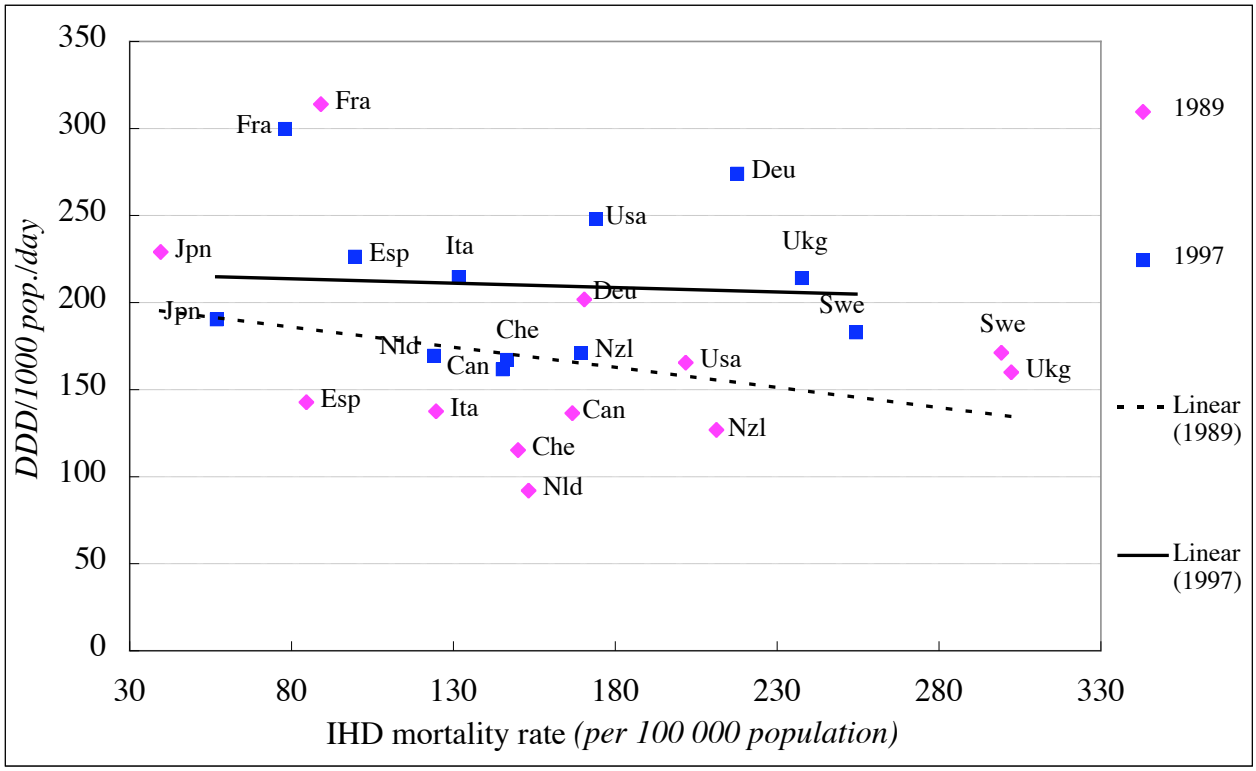
Figure 45. Mortality rate

(number of deaths due to ischaemic heart disease per 100 000 population)



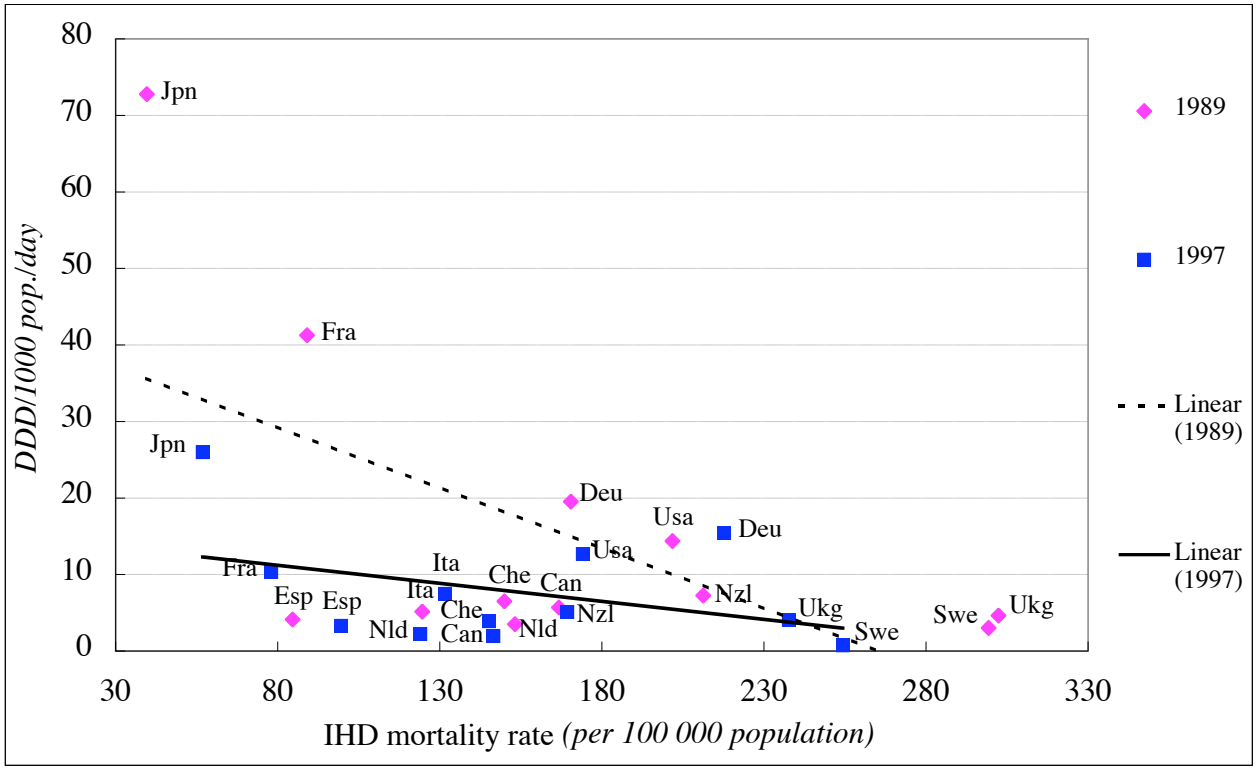
Source: OECD Health database (2001).

Figure 46. Cardiovascular drug consumption and mortality *(1989 and 1997)*



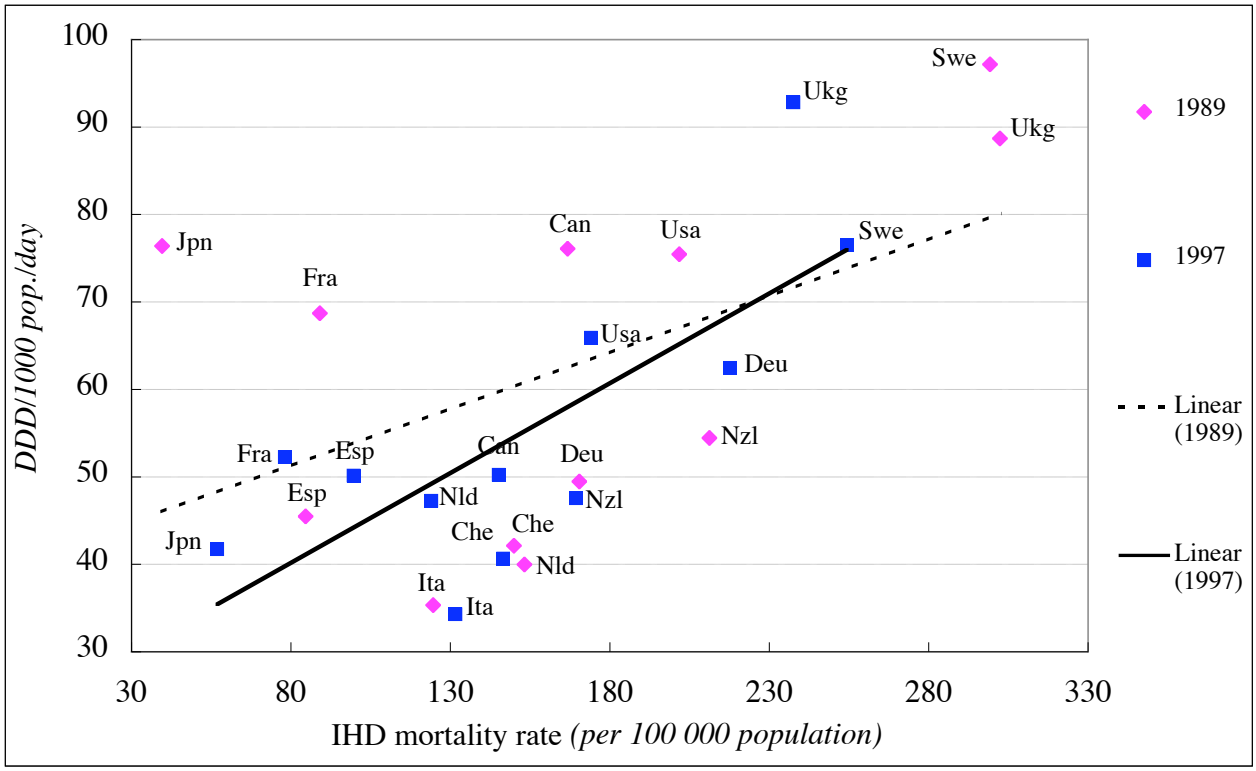
Note:1989, R^2= 9.7 % 1997 R^2= 0.0 %

Figure 47. Antihypertensive (C02) consumption and mortality *(1989 and 1997)*



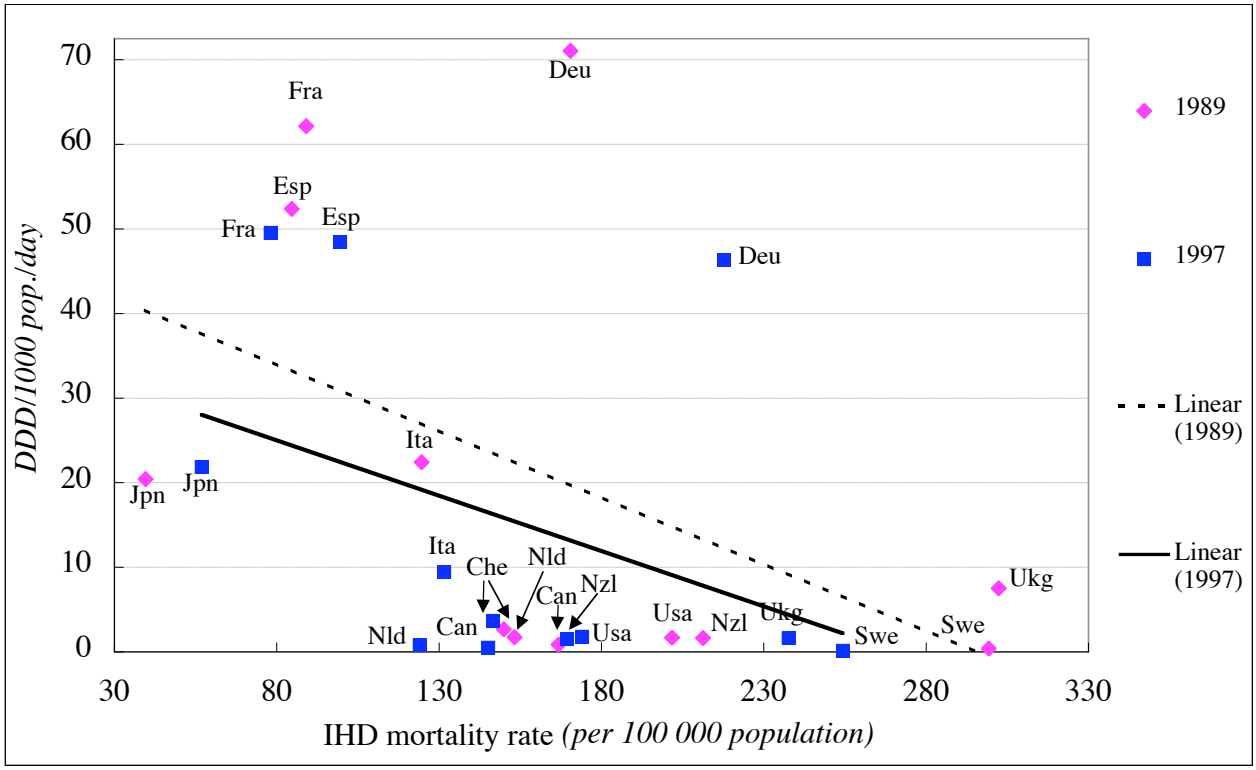
Note:1989, R^2= 36.1 % 1997 R^2= 15.7 %

Figure 48. Diuretic (C03) consumption and mortality *(1989 and 1997)*



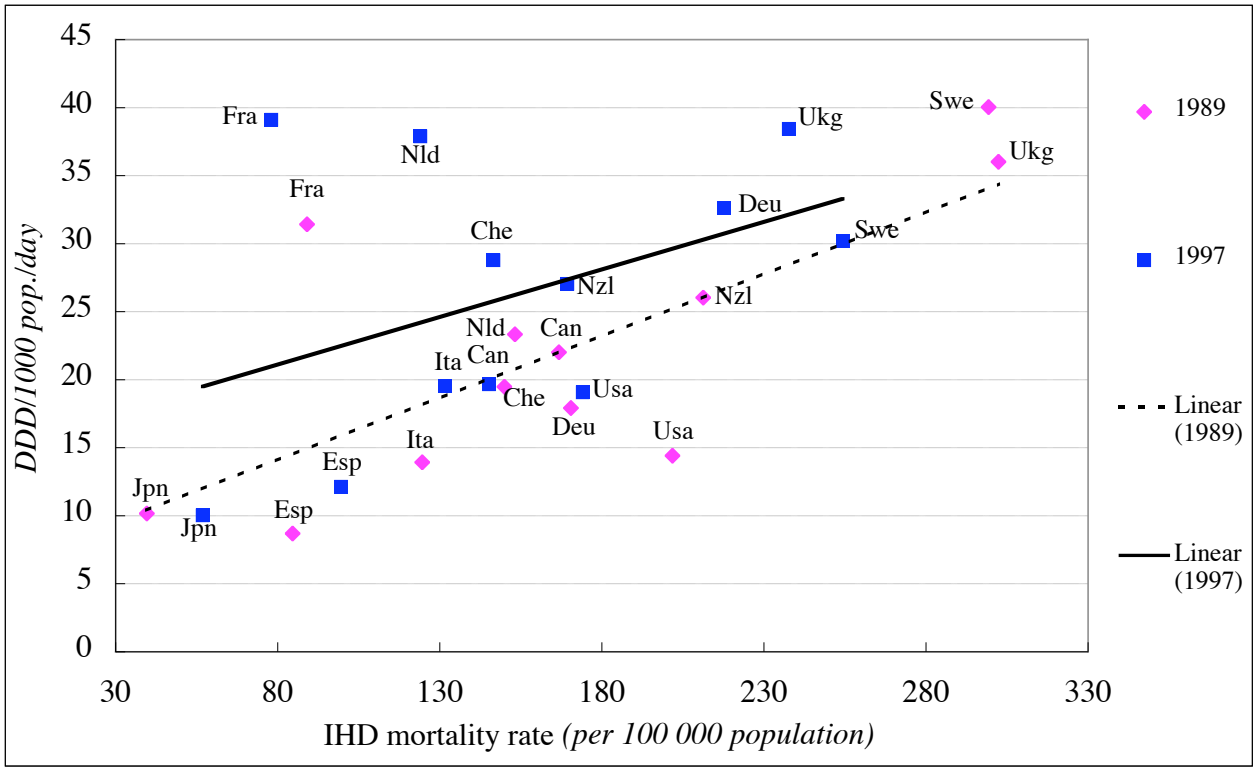
Note:1989, R^2= 25.5 % 1997 R^2= 57.3 %

Figure 49. Vasodilator (C04) consumption and mortality *(1989 and 1997)*



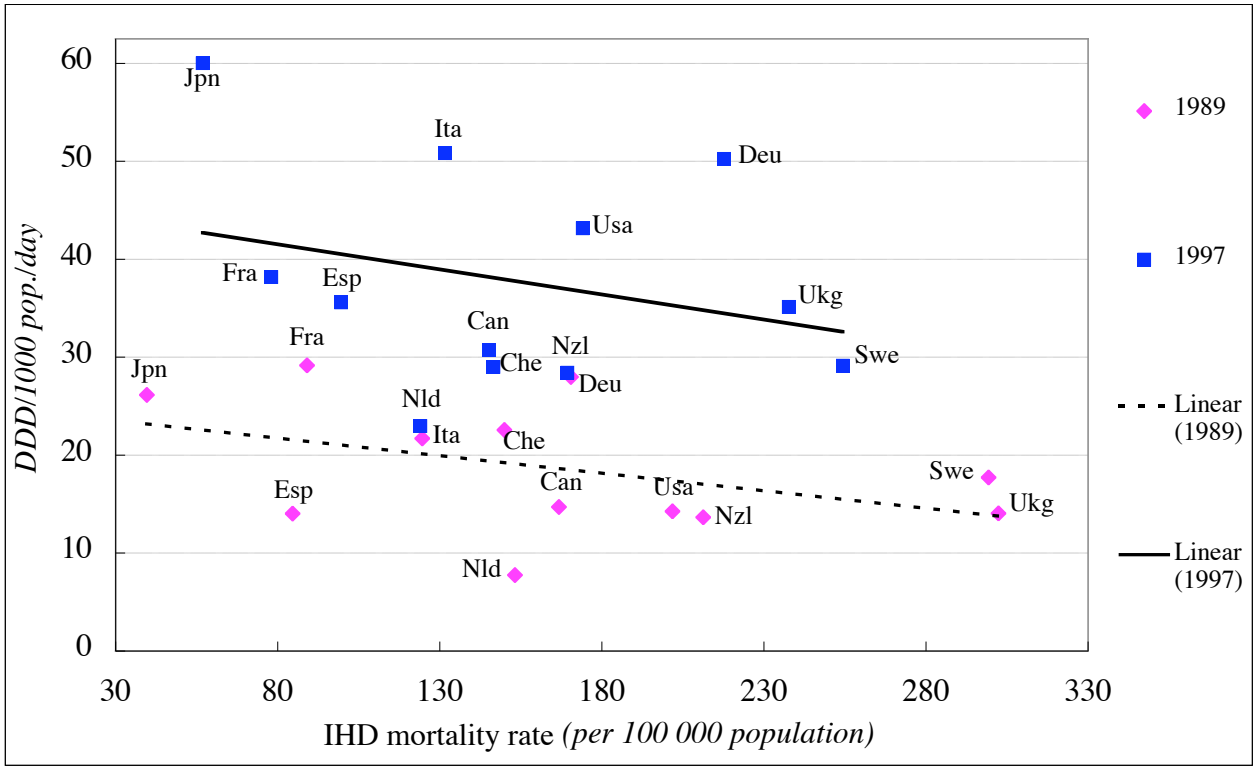
Note:1989, R^2= 23.0 % 1997 R^2= 15.2 %

Figure 50. Beta blocker (C07) consumption and mortality *(1989 and 1997)*



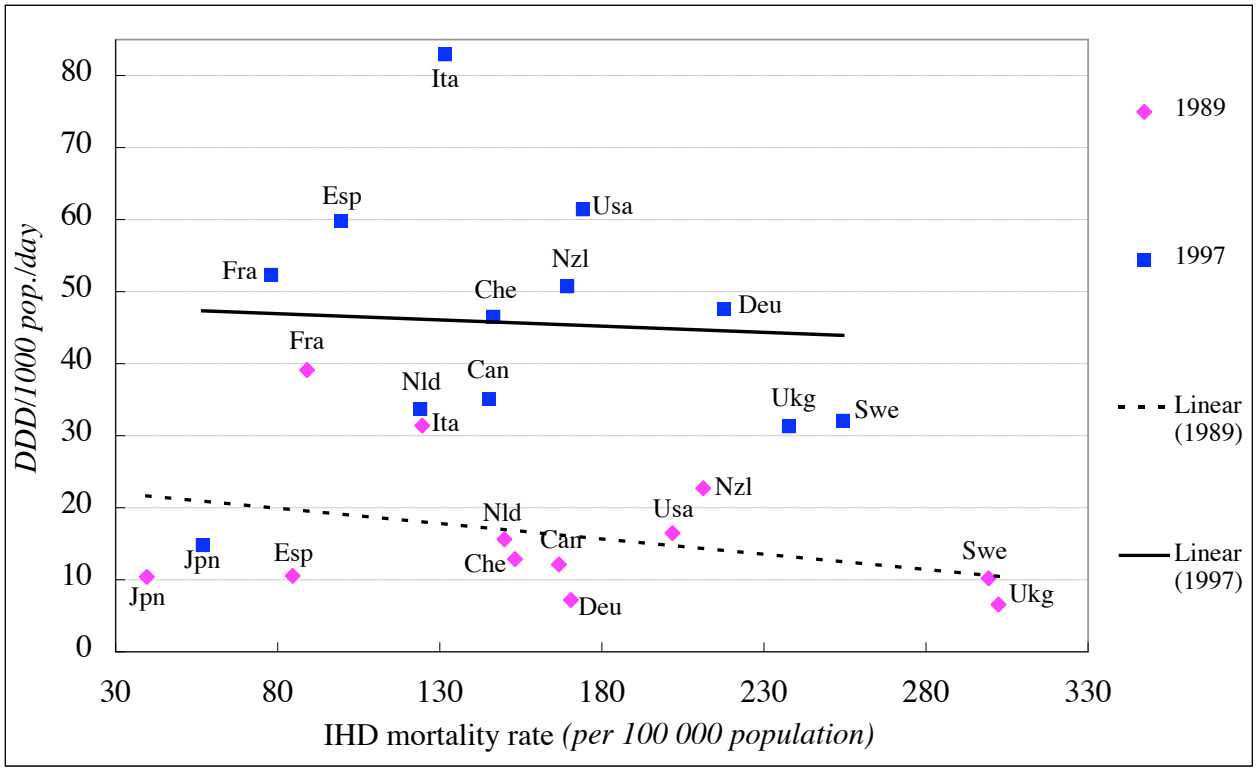
Note:1989, R^2= 53.7 % 1997 R^2= 18.2 %

Figure 51. Calcium channel blocker (C08) consumption and mortality *(1989 and 1997)*



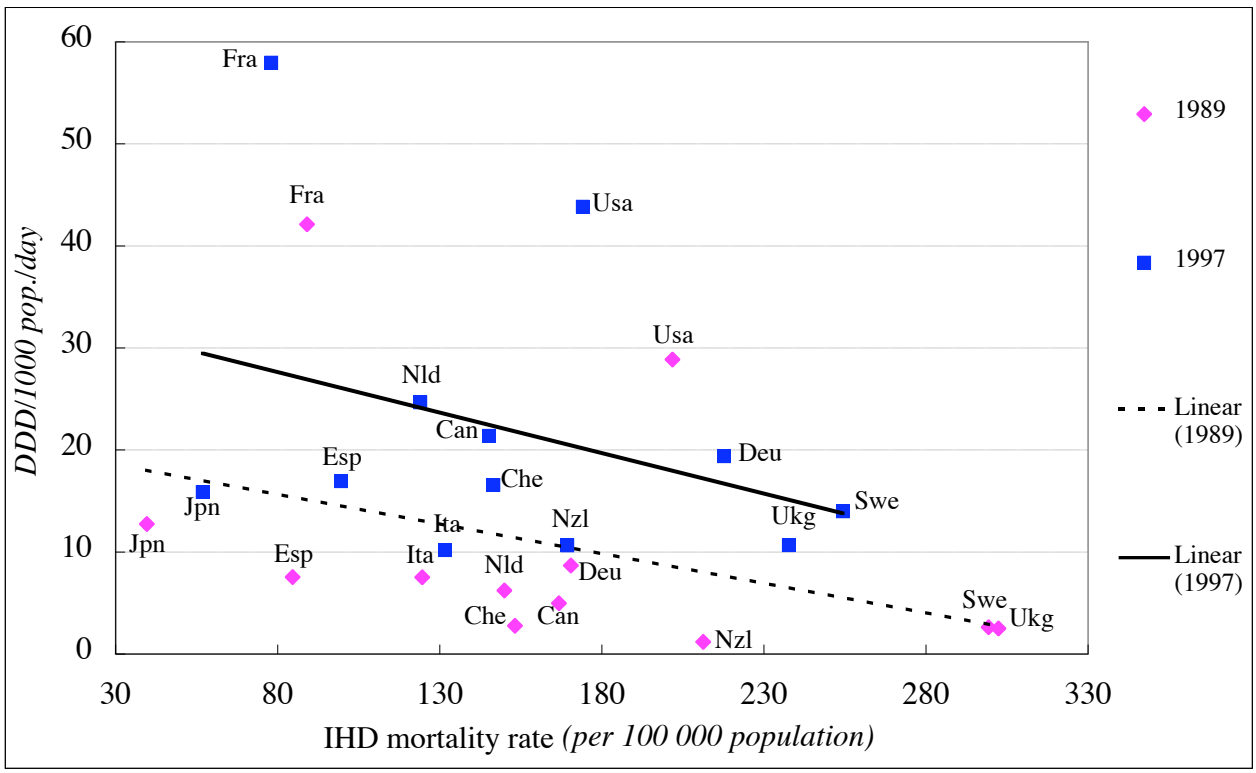
Note:1989, R^2= 18.2 % 1997 R^2= 7.9 %

Figure 52. ACE inhibitor (C09) consumption and mortality *(1989 and 1997)*



Note:1989, R^2= 11.6 % 1997 R^2= 0.4 %

Figure 53. Serum lipid reducer (C10) consumption and mortality *(1989 and 1997)*



Note:1989, R^2= 14.2 % 1997 R^2= 11.2 %

Figure 54. Expenditure for vitamin K antagonists (B01AA)
(US$ PPP/1000 pop./day)

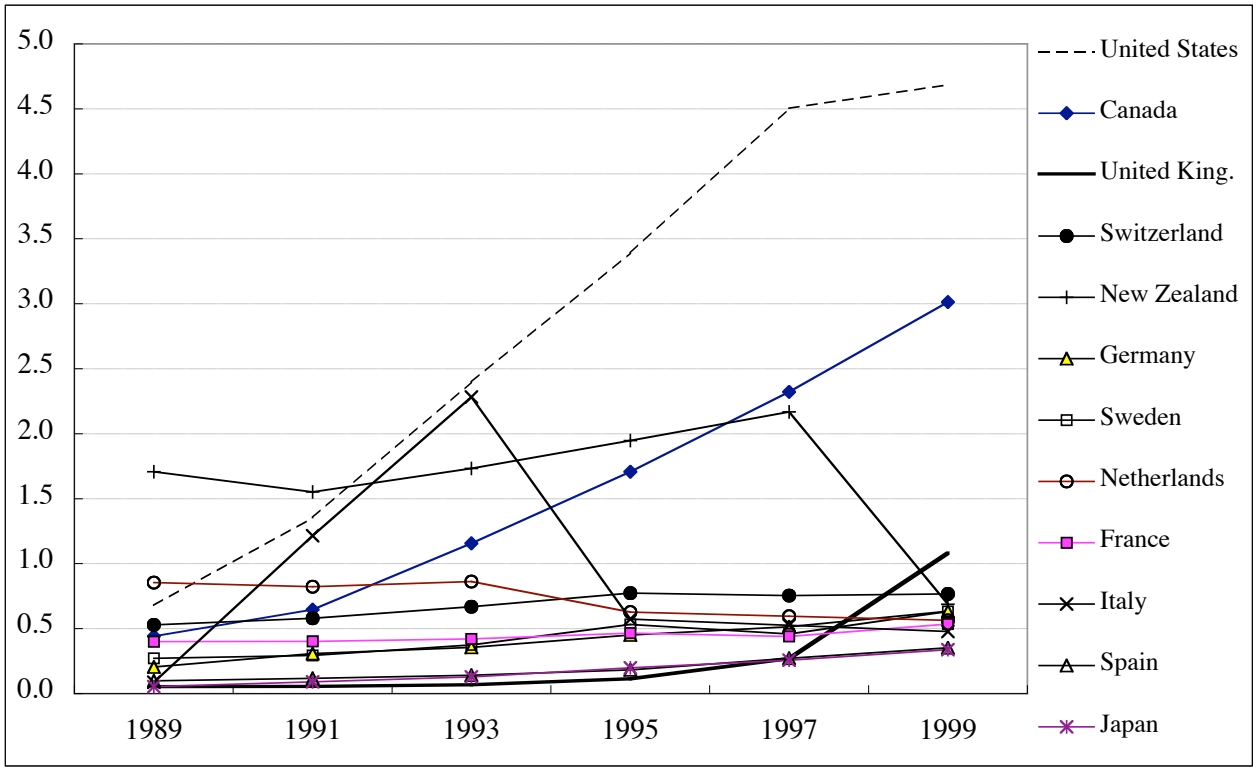


Figure 55. Vitamin K antagonists consumption (B01AA)
(DDD/1000 pop./day)

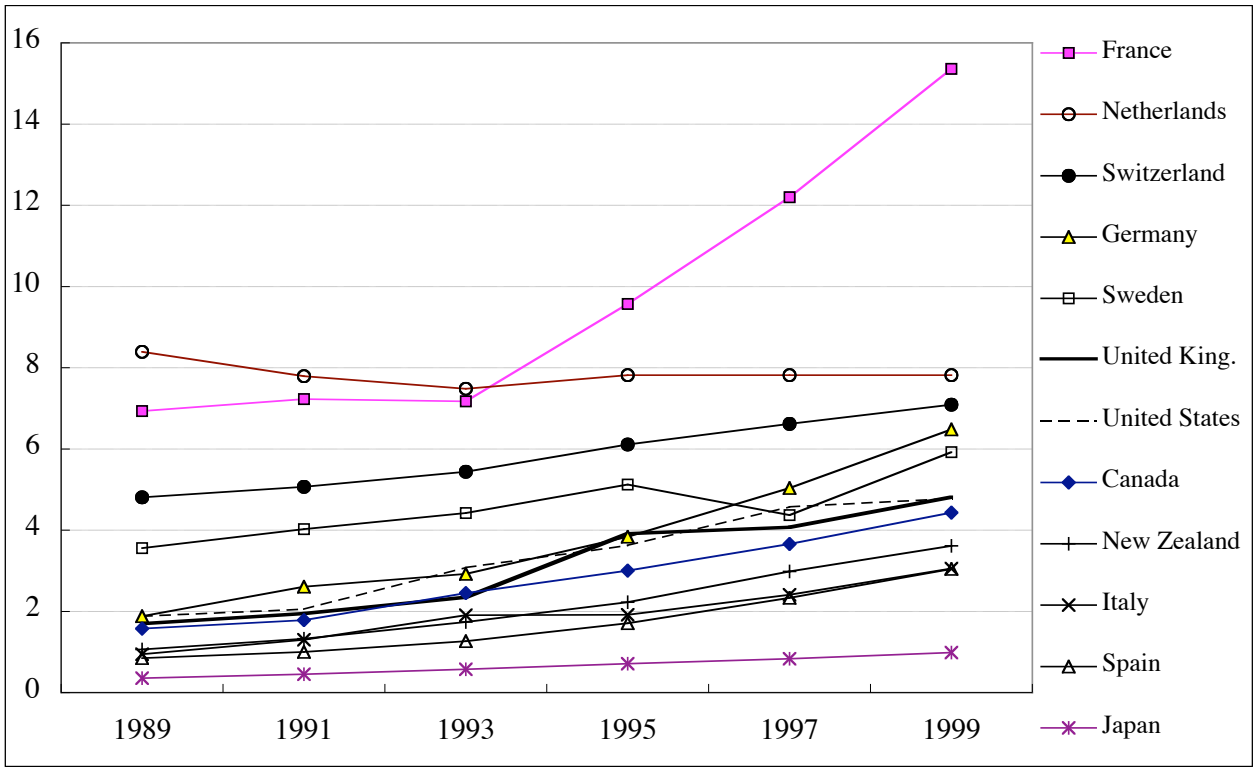


Figure 56. Unit expenditure for vitamin K antagonist (B01AA)
(US$ PPP/DDD)

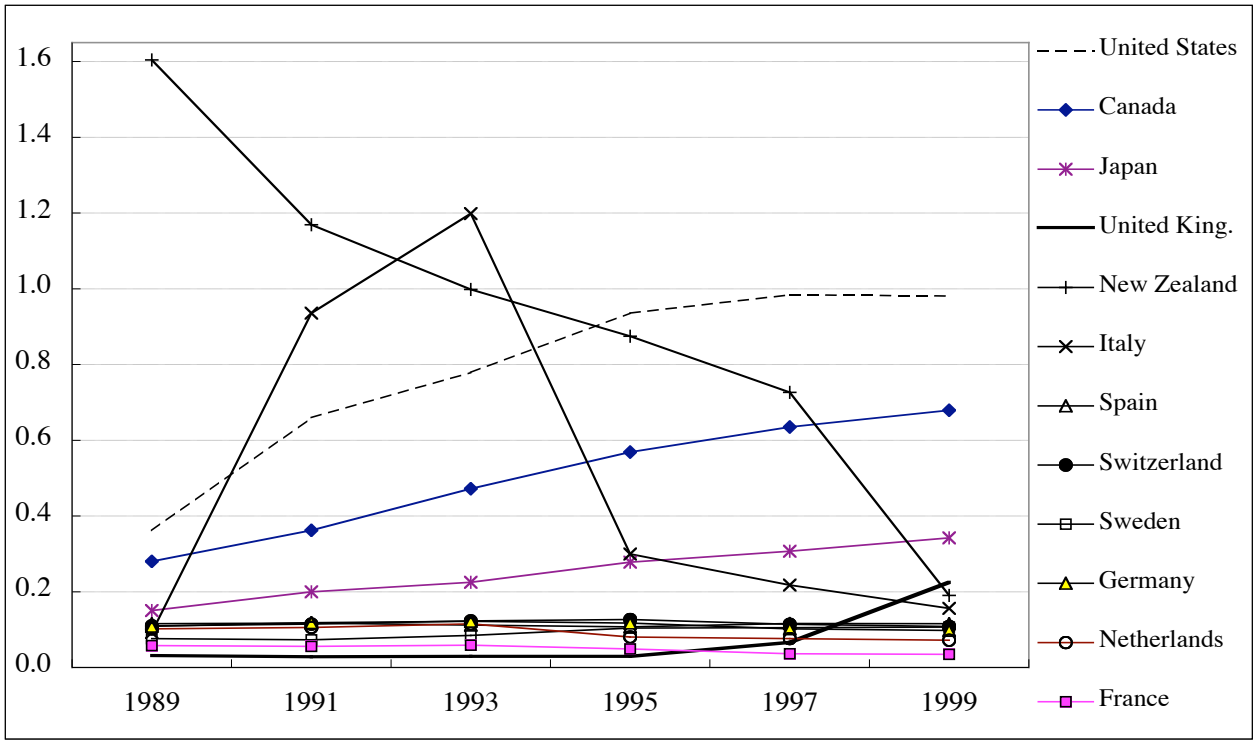
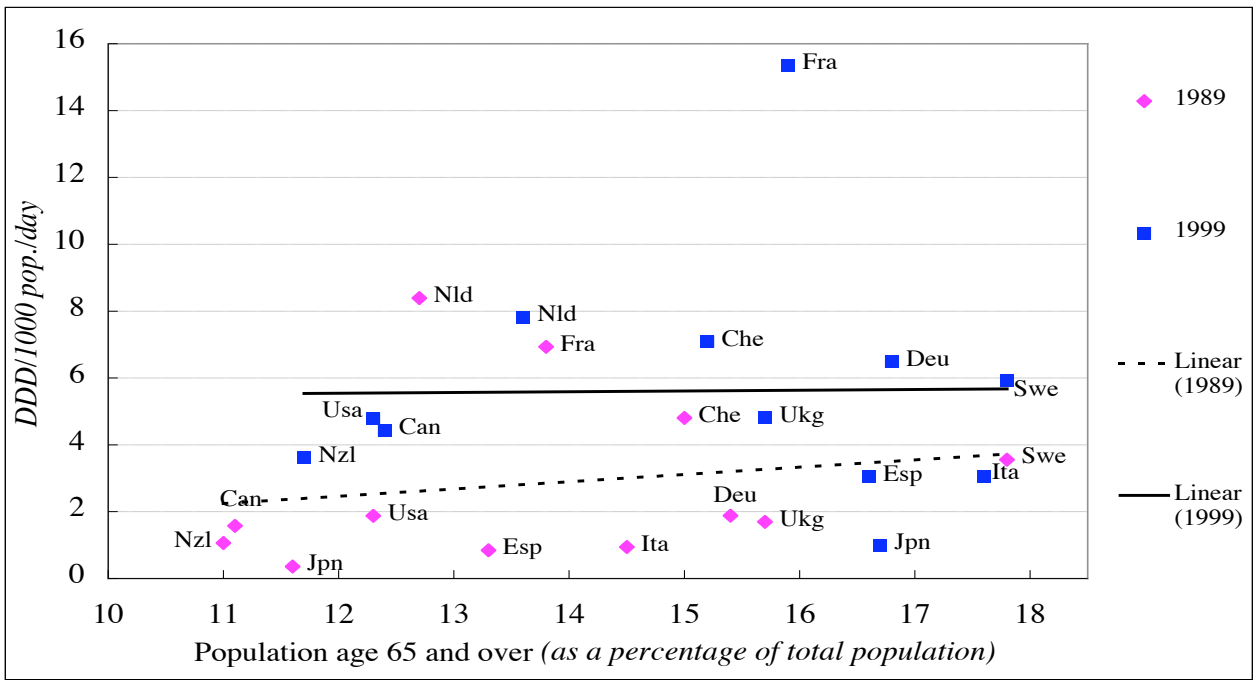
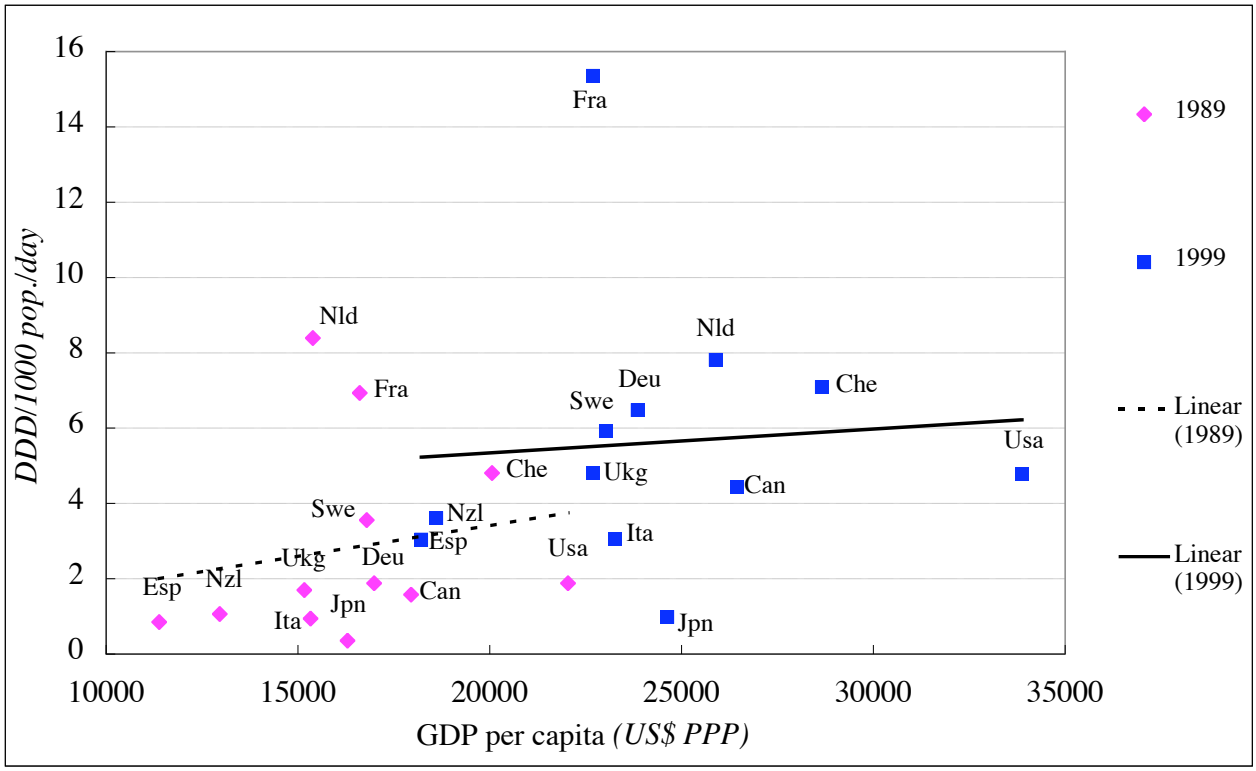


Figure 57. Vitamin K antagonist (B01AA) consumption and population age structure *(1989 and 1999)*



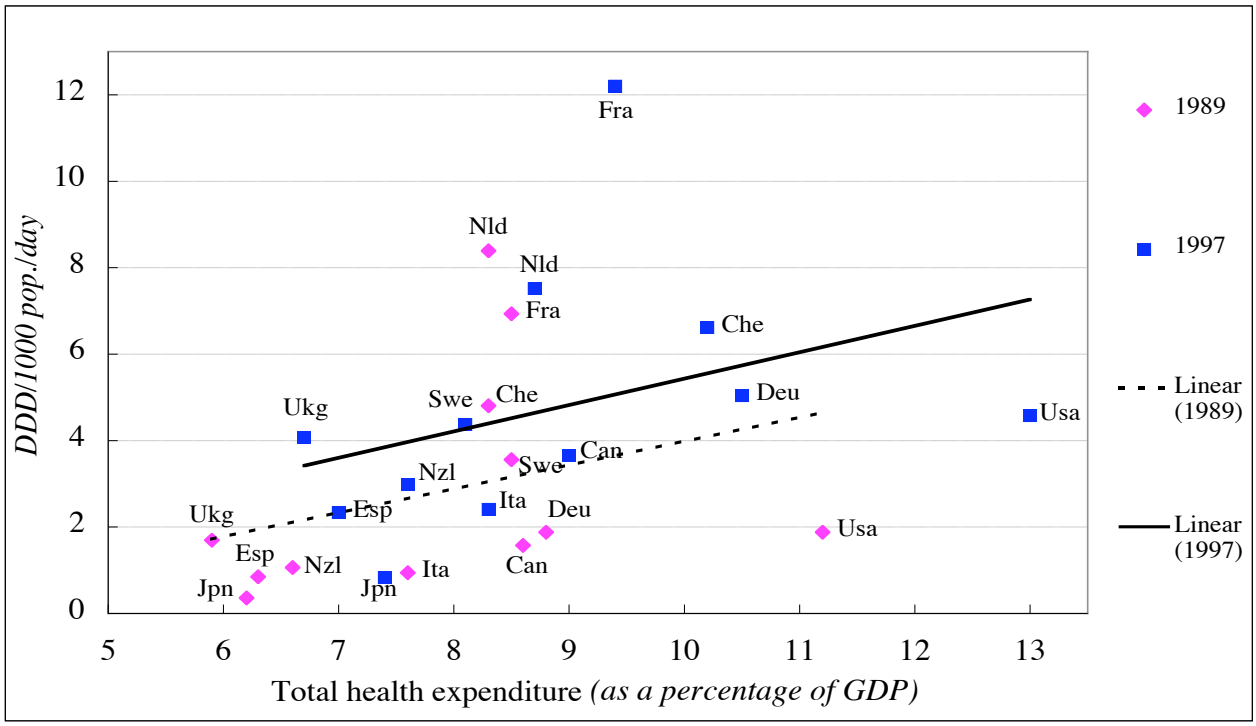
Note:1989, R^2= 3.8 % 1997 R^2= 0.0 %

Figure 58. Vitamin K antagonist (B01AA) consumption and national income *(1989 and 1999)*



Note:1989, R^2= 3.3 % 1997 R^2= 0.1%

Figure 59. Anticoagulant (B01AA) consumption and health expenditure *(1989 and 1997)*



Note:1989, R^2= 10.2 % 1997 R^2= 13.2%

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