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COMPARISON OF THE CASE-TIME-CONTROL AND THE CASE-CROSSOVER DESIGN IN ESTIMATING RISK OF INJURY FOR PRESCRIPTION MEDICATIONS USING POPULATION DATABASES

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Résumé

L'objectif de l'étude était de comparer les analyses de cas chassé-croisé (CCO) et de cas-contrôle du temps (CCT) afin d'évaluer la relation entre l'usage de prescriptions et le risque de blessures traumatiques en utilisant des bases de données populationnelles incluant les données du Registre de Traumatisme de Québec, d'hospitalisation du MED-ECHO et la RAMQ. Les cas ayant rapporté une blessure entre janvier-2000 et décembre-2000 ont été inclus dans l'analyse. Pour chaque cas, un contrôle a été apparié sur l'âge, le sexe, le niveau du centre de traumatologie et la date de sortie de l'hôpital. 2,417 cas et 2,417 contrôles ont été appariés dans l'étude. Les résultats ont démontré que l'analyse de CCO est 1,5 fois plus susceptible de produire une association négative pour le risque de blessure comparativement à l'analyse CCT. Un faible niveau d'accord (62.4%) sur les estimations des risques a également été évalué par les deux méthodes.

Abstract

The aim of the current study was to compare the case-crossover (CCO) and case-time-control (CTC) analyses for assessing the relationship between the use of prescription medications and the risk of traumatic injury using population databases. Analyses were based on data from the Quebec Trauma Registry, the MED-ECHO hospitalization database, and the RAMQ database in case subjects who reported an injury between January 2000 and December 2000. For each case, one control was matched based on age, gender, level of trauma care center, and date of discharge from the hospital. There were 2,417 cases and 2,417 matched controls included in the study. The results showed that the CCO analysis is 1.5 times more likely to produce a negative association for the risk of injury compared to the CTC analysis. A low level of agreement (62.4%) in the direction of the risk estimates was also assessed by the two methodologies.

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To my two loves Kosta and George who are my world,
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who inspired and encouraged me
to never give up and
always believe
in myself

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Chapter 1: Introduction

Traumatic injury is a serious public health concern with a major impact on the health and well-being in western society and worldwide. It is the leading cause of death and disability of children and young adults and is among the leading causes of hospitalization for children, young adults and seniors. Each year, injuries account for nearly 1 in 10 deaths worldwide.[1] In Canada alone, an estimated 4.27 million people aged 12 or older suffered an injury severe enough to limit their usual activities in 2009-2010.[2] Traumatic injury can represent a significant burden in terms of mortality and morbidity on individuals, as well as health resource utilization. Such utilization has considerable economic cost implications for the health care system as well as societal costs affecting those injured and their families. [3]

Extensive epidemiologic investigations have demonstrated that the use of prescription medications is associated with an increased risk of traumatic injury.[4-17] The use of these medications have shown to affect the nervous system by impairing psychomotor and sensory functions, thus reducing the ability to perform functional tasks accurately.[18,19] Most epidemiologic studies up to date have evaluated the use of psychotropic drugs namely benzodiazepines which are known to cause motor vehicle and occupational accidents. Studies performed in the elderly patients have also identified that these and several other medications are significantly associated with the risk of falls.[20,21] Because the use of prescription medications is increasing at a growing rate, it is important to assess the impact of these and other medications on the potential for injury.

Epidemiologic studies which have assessed benzodiazepine (BZD) use have shown the most consistent increase in risk of accidents. However, these studies have also shown considerable variation in the results regarding the potential for risk of injury.[17] These differences were evaluated in a study conducted by Neutel where he concluded that the quality of the exposure measure, the differentiation between new and chronic use, as well as age differences in the study populations may influence the result of the odds ratio (OR).[22] For example, in his research, Neutel showed that the risk of a hospitalization due to traffic accidents within 4 weeks after a prescription was filled had an OR of 3.9 in

subjects taking BZD hypnotics and for those taking BZD anxiolytics the OR risk was 2.5. When the window of exposure was shortened to 2 weeks, the OR increased to 6.5 and 5.6 respectively. Neutel also looked at the effect of separate time windows for time lapsed since the index prescription for BZD. The results for the use of BZD hypnotics showed a large variation in the OR for the different time window categories. The OR decreased from 9.1 for the time window of 1-7 days of elapsed time exposure to an OR of 2.7 for the time window of 22-28 days.

Neutel's study was a case-control study design with BZD as the exposure to be investigated. Information collected on each case subject and control subject in the study was retrieved from health databases. The statistical methods used to assess the relationship between the risk of hospital admissions for traffic injury and BZD-exposed subjects was evaluated with the use of logistic regression analysis adjusting for the influence of other risk factors. The case-control design is typically the reference design for the analysis of rare risks, despite the limitations of this design, mainly due to biases in the definition of the control population.[23]

In the last decade, retrospective studies of case series that provide risk estimates without the need to enroll controls have emerged as an alternative method to evaluate risk estimates. The most popular and applied design is by Maclure who developed the case-crossover design for assessing the effects of brief exposures on acute events. [24] This design is particularly useful to examine the effects of drug use in subjects with diseases that vary in severity. In this study design, the relative risk estimates are based on the ratio of the frequency of exposure during a risk period just before the event, to the frequency of exposure during previous control periods. Each case serves as their own matched control, where the control periods are defined and could be included as several matched controls.[25,26] However, case-crossover studies are not free of methodological difficulties, such as time trends of the exposure within subjects. A way to remove the effect of the time trend is the case-time-control design which was developed as a method to control for confounding by indication by adding a traditional control group to the case-crossover design. Confounding by indication is a bias that may occur when a particular exposure may

be falsely associated with a certain outcome when in reality it may be the severity of the disease and not the exposure that is the cause. In this design, both cases and controls are inquired for their present exposure at the time of the event and at their past exposure in the control period. The exposure risk estimate in controls is used to adjust the exposed risk estimate in cases. Computing the exposure risk estimate among the controls will estimate the size of the time trend. The risk estimate among the case subjects is then divided by the risk estimate among the control subjects to remove the effect of the trend. If the time trend in the exposures explains all the effect among cases, the risk estimate should be similar among the case and control subjects and the ratio should therefore be one.

Because case series designs have been increasingly applied, there is a need for better knowledge of which statistical method is best suited in order to provide the most accurate and statistically valid results. The current study will therefore focus on two analytical approaches, the case-time control design and the case-crossover design, that will estimate the risk of injuries associated with exposure to specific prescribed medications.

Chapter 2: Review of the literature

2.1 The case-crossover design: an extension of the crossover design

The case-crossover design was developed as an extension of the crossover design. The crossover design represents a type of controlled clinical trial in which the study subjects are assigned to two or more treatments. Upon completion of the course of one treatment, the study subjects are then switched to another treatment. The treatment effects are estimated by comparing the treatment results within each subject. The crossover design has several advantages. First, each subject serves as his own control whereupon the influence of confounding is reduced. Second, crossover designs are statistically efficient in that they contain more power than do parallel group designs and thus could use a more limited sample size. Other advantages include more control and reliability. The limitations and disadvantages of this type of study design are the effects of treatment which may affect the outcome due to the order in which the treatment is administered. Second, there is the issue of "carry-over" between treatments which confounds the estimates of the treatment effects. This "carry-over" effect could be avoided with a sufficiently long "wash-out" period between treatments.

The case-crossover design was developed in 1991 by Maclure as a method to assess transient effects of a brief exposure on the risk of onset of an acute outcome.[24] Similarly to the crossover design; the key feature of this design is that each subject serves as its own control where the study subject alternates between exposure and non-exposure to the agent of interest. However, the only exception where they are not similar is that the investigator does not decide when and how the periods of exposure and non-exposure are assigned, and, the exposure history is obtained only for subjects who had the outcome.

2.2 History of the case-crossover design:

The development of the case-crossover design began in 1988 with the Myocardial Infarction (MI) Onset Study to avoid control selection bias.[27] At first, the aim of the study was to use a case-control design to determine why the incidence of MI peaks in the morning. However the problem was determining the choice of the control group. The idea

of using healthy subjects as the control group from the general population would be difficult to recruit and would generate a biased sample. The other idea to utilize subjects that were already hospitalized for other emergencies would also create the issue of bias by what triggered their emergency in the first place. After considering various possibilities of who would make up the perfect controls for this study, it became clear that the answer to the dilemma would be to use the cases themselves as controls because this would provide a perfect matching control for each subject. Eventually it also became apparent how for the same study there were multiple control days for each subject by the possibility to record exposure frequency during the entire week, month or year before.

With this extension of the crossover design to observational studies, the study subjects could represent a large population rather than a limited sample size as we find in clinical trials. Also when comparing this design to other observational studies such as the case-control design and the cohort design, the major advantage is that the cases and controls represent the same study subjects and are instantly matched on all subject characteristics that do not change within individuals.

2.3 Methodology and statistical analysis of the case-crossover design

The first step in a case-crossover design is to define the case window and the control window. Each case contributes one case window and one or more control windows. The case window is defined as the "at risk" period preceding the event. The control windows are periods of the same length as, but not overlapping with, the case window that provide an estimate of the expected frequency of exposure for each case. The case window and the control windows are derived from the same subject at different times; thus the case-crossover design represents a sample based on matched-pair subjects.[24] The case window must be defined according to the characteristics of exposure and outcome. Originally the case-crossover design was intended to study brief exposures that have immediate and transient effects such as drug use, and acute outcomes that have abrupt and obvious onsets. For example, in a study pertaining to alcohol consumption and the risk of road traffic crashes[28], the time window was defined as 6 hours. However some investigators have used case-crossover methods to study exposures with more prolonged effects as well as

outcomes with delayed or insidious onsets such as the study about hemorrhagic fever with renal syndrome that used two time windows of 7-34 days and 35-60 days before disease onset.[29] The size of the case window and control window is an important consideration since it is arbitrarily chosen by the researchers. If the time period chosen is large, such as 1 year, there is the possibility of bias due to temporal changes during the period. In cases like this, studies have applied a sensitivity analysis by repeating the analysis with varying sizes of the exposure window to assess whether the results will change. [27,30-33] Another important consideration is the number of control time periods sampled per case. Mittleman et al.[25] found that the precision of the effect size improved with the number of time periods selected, where the greatest efficiency achieved was by using the whole year prior to event.

Once the case window and control windows are defined and we have determined whether the outcome occurs when under exposure, the subsequent step is to measure the frequency with which the subject was under exposure. Maclure proposed that the case-crossover design, where the cases and controls represent the same subjects, should be estimated with the Mantel-Haenszel method of the relative risk and a corresponding estimator of the variance of its logarithm of relative risk.[23,34]

In 1993, Marshall proposed a maximum likelihood method to analyze the case-crossover design.[26] This method is based on a proportional hazards model that can be used to analyze the joint effects of several transient exposures. This method cannot only be used for binary exposure variables like the Mantel-Haenszel approach, but can also be used for continuous exposure variables. He also discussed a mixed distribution model when the distribution of exposure is mixed, consisting of a discrete probability at zero and a continuous part with a normal distribution.

Marshall demonstrated that when the exposure is measured as a single binary variable, for example X, and $P_i=f_i(1)$ is the probability for case i that X=1, then the formula proposed by Maclure as the Mantel-Haenszel estimator is derived as the approximation to the maximum likelihood solution. Maclure interpreted the P_i as an estimation of the relative risk, but the Mantel-Haenszel formula is an approximation to the maximum likelihood solution as long

as P_i represents the prior probability of the event X=1. For example, if a case is asked about frequency exposure, λ_i, in units of time $^{-1}$, a response of once a day is $\lambda_i=1/24$. Then, assuming that occurrences of the exposure happen at random, that is, as a Poisson process with intensity λ_i, the probability of at least one occurrence in a period t_0, is:

$$P_i=1-\exp_{(-\lambda_i t_0)} \qquad (1.1)$$

However, the value used by Maclure in calculating this equation is:

$$P_i= \lambda_i t_0 \qquad (1.2)$$

If t_0 is short the equations above are approximately the same. However, when t_0 is long, the difference between the equations is significant as Marshall demonstrated with the Auckland Heart Study data.[35] This Auckland Heart Study was a case-control study of acute heart disease where alcohol consumption associated with myocardial infarction was analyzed. Under the probability that a case would have drunk alcohol in a 24 hr time window before the event, the relative risk is 1.87 (95% CI, 1.35-2.58) when P_i is calculated with equation (1.1). However, when the P_i is calculated with equation (1.2), the relative risk is 0.48 (95% CI, 0.27-0.84). Therefore one of the method calculations showed a harmful effect while the other showed a protective effect for alcohol consumption associated with myocardial infarctions. The author suggested that the problem in the difference between the two calculations may lie in the 20 cases who said they drunk "once a day" with an assigned probability of one, when in fact they did not drink in the last 24 hrs before their myocardial infarction. Their contribution outweighed the effects of other cases. It was therefore suggested that an instrument to elicit the prior probability distribution be carefully developed where instead of choosing among "once a day", "every 3 or 4 days", "once a week", once a fortnight" categories, they should be asked how many times did they drink on average in a fortnight, month or year. In pharmacopedimiology studies, this problem is ruled out because the exposure is based on the exact records of prescribed medications.

2.4 Advantages and disadvantages of the case-crossover design

Advantages of the case-crossover design include the following:[36,37]

1. When dealing with a time-varying or intermittent exposure, this design is valuable because the time window of interest can be easily varied. Therefore, its main potential in pharmacoepidemiology lies in assessing acute transient events following intermittent drug exposure.
2. In a crossover design the same person is both the case and control. This means that cases and controls are comparable regarding their known and unknown confounders except for intermittent exposures; therefore control selection bias is eliminated as the cases act as their own controls.
3. The problem of difficult and time consuming control sampling processes observed in case-control studies is eliminated. The other advantage is the saving in resources since there is no need to collect information on a separate group of controls.

Disadvantages of the case-crossover design[36]:

1. Within-person confounding by transient factors including variations in disease severity or co-morbidities such as confounding by acute indication is still possible. For example patients taking nifedipine might take an additional dose if they experience worse than usual angina.
2. Even though selection bias of a control person is not possible since each case serves as his own control, there is still the possibility of selection bias regarding the control time window(s). For example, a study that proposes to use, as one of several control days, the most recent day on which there was at least one exposure event would cause an underestimate of the relative risk assuming an increased risk.[25]
3. Time trend bias may occur if the case and control time windows are very long. Only in rare situations where the outcome is believed not to affect future exposure, it is possible to use future periods as control times which would reduce the problem of time trend bias.
4. In this type of design it is not possible to study death as an outcome since a detailed retrospective drug exposure assessment obtained by proxy interviews are likely to be prone to extensive errors.

5. The chance of misclassification and measurement error of the exposure is increased due to the fact that the exposure is retrospectively assessed. For example, ascertaining drug use from a very long time ago can lead to exposure misclassification since cases are more likely to remember their medication use immediately before an event rather than their historical control period.
6. The use of administrative data may only be reporting dispensed information on a particular drug as opposed to whether a prescription drug was actually taken.

Since the introduction of the case-crossover design in 1991, the design has been used in several different fields of research such as injury epidemiology, occupational epidemiology, environmental epidemiology and pharmacoepidemiology. A medline search was conducted from 1991 to 2010, with key-word "case-crossover" and "pharmacoepidemiology". The results obtained from the Medline search showed that there are a limited amount of pharmacoepidemiological studies that have applied this study design. The type of outcomes that have been reported using the case-crossover design in pharmacoepidemiologic studies tended to be acute events such as motor vehicle accidents[11,12,14], death[38,39], and myocardial infarction[40]. Exposures have typically been a pharmacological agent for short time periods, such as vaccines, antibiotics, and psychotropic medication prescriptions. The challenges that were faced using the case-crossover design were due to the properties of the case-crossover design as well as the issues with properly classifying drug exposures as discussed in the disadvantages above.

2.5 The case-time-control design: an extension of the case-crossover design

The case-time-control design was a methodology developed by Suissa in 1995 as an extension of the case-crossover design where exposure varies over time and can be measured at two or more timepoints.[41,42] This design addresses the problem of confounding by indication such as disease severity. Suissa stated that by using subjects from a conventional case-control design as their own controls and adjusting for natural time trends in drug utilization, the case-time-control design would allow the separation of the effect associated with the drug from that of disease severity, even if the severity is not measured.

The example that was used to describe this study design was the use of inhaled β-agonists and the association with asthma deaths. In their previous work, Suissa et al. showed an increase in the risk of asthma deaths with the use of inhaled β-agonists. [43] However, the investigators argued that one potential explanation for the increase in deaths may have been a natural increase in the use of β-agonists over time and not necessarily the drugs themselves. In order to adjust for this potential confounder, they used a separate control group from the original cohort. By obtaining information on the use of inhaled β-agonists from the controls, they were able to adjust for time-dependant changes with respect to β-agonist use.

With no natural time trends in drug utilization, the case-time-control design can be reduced to the case-crossover design, except when longer time windows are considered. The case-crossover design deals with exposures that are transient and with such brief duration that the length of exposure period is not an issue in the design. However Suissa used a longer and more accurate length of exposure period (1 year) to validate the analysis of the asthma study. More importantly he wanted to distinguish the contribution of the drug to the risk of fatal or near-fatal asthma from that of disease severity with the case-time-control design.[41] The results of his study showed that the estimate of the relative risk using a conventional case-control design for high vs. low beta-agonist use was 3.1 (95% CI: 1.8-5.4), which included the confounding effect of unmeasured severity. The risk estimate using the case-time-control design was 1.2 (95% CI: 0.5-3.0), which excluded the confounding effect of unmeasured severity. These results demonstrated that the class of beta-agonists may not be the leading cause in the risk of fatal or near-fatal asthma, and therefore offers a solution to the problem of confounding by indication[44], which is a major obstacle in pharmacoepidemiology when assessing the known or intended effects of a drug using non-experimental designs. [41]

2.6 Methodology and statistical analysis of the case-time-control design

The case-time-control design includes both case and control subjects. Cases and controls are inquired for their present exposure use at the time of event and at their past exposure in the control period. Within each case subject, exposure frequencies from the case window

and the control windows are compared through a matched odds ratio, similar to the approach applied in the case-crossover design. By observing two time periods in the group of control subjects, a time trend of exposure in the source population can be estimated through a trend odds ratio. Suissa demonstrated that the case-time-control odds ratio is the case-crossover odds ratio divided by the time trend odds ratio. This in turn produced an odds ratio adjusted for time trend and controlled between-person confounding.[41]

2.7 Advantages and disadvantages of the case-time-control design

Advantages of the case-time-control design include the following:

1. No within subject confounding since the case subjects and control subjects act as their own controls.
2. This study design permits adjustment for trends in exposure over time.

Disadvantages of the case-time-control design include the following:

1. If severity which is associated with drug use, also increases within subjects over time and does so differently for case and control subjects, the residual effect associated with the drug could remain confounded to some extent. If the odds ratio is near one then this effect may not be significant. Therefore it is important to have a good understanding of disease mechanisms when applying these designs and to match case and control subjects on disease duration or similar factors.
2. Selection bias unlike the case-crossover design can be problematic since the control subjects play a key role in this design. It is therefore important to consider that exposures must be measured at the same time points as their respective case subjects. Information bias may be less of a concern if exposure measures are obtained in the same way for case and control subjects.
3. An accurate measure in the length of the control and reference periods is fundamental.

This design has a very limited amount of publications in the field of pharmacoepidemiology which have assessed in depth empirical comparisons.[38,45-48]

2.8 The impact of injuries

Injuries are among the most serious of all major health problems,[49] and it is estimated that 90% of them are preventable.[50] Injuries are the third leading cause of death in Canada, the United States, and they are the leading cause of death for individuals between the ages of 1 and 44.[51,52] Between 2008-2009, there were a little over 205,000 people admitted to hospital in Canada because of injuries.[53] Injuries are a major cause of premature mortality and disability in Canada. Fatal and disabling injuries often strike adolescents and young adults. In 2003, injury, was the second leading cause of potential years of life lost (PYLL) before the age of 70; the first leading cause was cancer.[51] Despite the importance of injuries as a public health problem, the National Research Council of the Institute of Medicine reported that for every dollar spent on cancer research only 11 cents were funded by the federal government for injury research.[54]

The National Academy of Sciences Committee of Trauma revealed the degree to which injuries were affecting our society in a report depicting accidental death and disability as the "neglected disease of modern society".[55] The report identified the problem of injury outcome as: the early death among the young, the burden of disability, and the expenditure of billions of dollars in health care costs. Consequently, the report made recommendations to help improve the care of seriously injured patients by stating that optimal treatment begins in the pre-hospital phase.

2.9 The incidence of injuries

According to Health Canada Statistics, about 218,000 Canadians are admitted into acute care hospitals for unintentional injuries every year.[56] Injury admissions on average involved 10 days of hospital stay and while the majority (77%) was discharged home, 3% (6,382) died in the hospital. The remaining patients (20%) were transferred to a rehabilitation center or a nursing home. These deaths did not include those who died at the scene of the event or en route to the hospital.

The age-standardized rate of hospitalization for injury in Canada between 2008-2009 is 534 per 100,000 persons.[57] The rate of injury hospitalization varies substantially from one province to the next. Saskatchewan and Alberta have the highest rates of hospitalization due to injury with 805 and 715 per 100,000, respectively, following the Northwest Territories with 1,285 and Yukon with 1,232 per 100,000 persons. The province of Ontario with 420 per 100,000, the province of Nova Scotia with 504 per 100,00 and the province of Quebec with 531 per 100,000 persons have the lowest rates of hospitalization due to injury.[57]

Unintentional falls accounted for the majority (61%) of injury admissions for all ages. Injury admissions due to unintentional falls also accounted for 64% of all hospital days due to injury and 75% of all in-hospital injury deaths. The second most common cause of injury admissions was motor vehicle collisions (9%), followed by being struck by objects, persons, or falling objects (5%), injury purposely inflicted by another person (5%), and self inflicted injury, excluding poisoning (2%). All other causes accounted for 18% of injury admissions, including admissions due to overexertion and strenuous physical movements.[57]

2.10 Interventions against injuries

2.10.1 Injury control and injury prevention

Although injuries are often described as "accidents" or other terms that imply a random nature or unavoidability, research has demonstrated that most injuries show clear non-random patterns with identifiable risk factors. Prevention strategies to reduce injuries have been used by societies and individuals for a long time. [58] Several researchers provided a foundation for the scientific approach in comprehending injury causation and developing prevention programs.[59-64]

Prevention can be classified into three aspects.[60] The primary prevention (pre-injury phase) is the initial avoidance of the disease or harmful condition which can be accomplished by educating the public on how to initially avoid trauma. The secondary prevention (injury phase) aims to reduce the physical damages upon the occurrence of the injury, and the

tertiary prevention (post-injury phase) aims to limit the impact of injuries that have already occurred.

2.10.2 Historical aspects of injury prevention

Injury was first defined as a public health problem by Johann Frank in 1788.[65] He was one of the early proponents of public health to suggest that accident prevention activities should be part of comprehensive public health programs which is now known as injury control.[66]

The conceptual revolution in the field of injury control began in the 1930s and 1940s by Hugh DeHaven. His research examined the causal pathway for injuries from falls and from airplane crashes and illustrated that injury severity can be reduced depending on the distribution of energy forces.[61,62] DeHaven introduced the concept of injury thresholds and provided a biomedical foundation for subsequent injury prevention work.

By 1949, John Gordon was studying the distribution and causes of injury events through the use of epidemiology. He was an epidemiologist who recognized that injuries occurred with known patterns similar to the study of infectious diseases.[63] He was also one of the first investigators to indicate that injuries were the result of the host, the agent, and the environment.

William Haddon was the visionary of injury epidemiology and injury control. Haddon was the former director of the National Highway Traffic Safety Administration and the Insurance Institute for Highway Safety. He played the leading role in bringing the principles of epidemiology to injury research and intervention programs. He recognized that all injuries resulted from rapid and uncontrolled transfer of energy to the human body and determined that such energy transfers were understandable, predictable and hence preventable. Haddon expanded on the notion of Gordon's ideas regarding the epidemiologic triad of host, agent and environment into what is known as the Haddon Matrix.[64]

In the Haddon Matrix the three factors of host, agent and environment influence the probability of injury to occur during three phases: pre-event, event, and post-event. In the pre-event phase, each factor influences the likelihood of an injury-producing event, such as a motor vehicle crash, to occur. During the event phase, the factors influence the probability that such an event will result in an injury. The severity of the injury will also be determined during this phase. In the post-event phase, the three components will further determine what consequences the injury will have. Table (1.1) provides an example of the interactions of phases and factors within the Haddon Matrix.

Table 1.1: Haddon Matrix using motor vehicle collision as an example to describe the two dimensional model

Injury Phase	Epidemiologic Factors			
	Human/Host	**Vehicle/Agent**	**Physical Environment**	**Social Environment**
Pre-Event	Alcohol	Condition of brakes	Visibility of hazards	Speed limits
	Medications	Speed capability	Weather	Running red light
Event	Failure to wear seat belt	Poorly engineered airbags	Poorly highway designed guardrails	Lack of vehicle design regulation
Post-Event	Preexisting medical conditions/physical condition	Poorly designed gasoline tanks	Poor emergency communication systems	Trauma care systems

The Haddon Matrix was monumental in changing the view of injuries from motor vehicle accidents and other injuries as well. Haddon's matrix provided the framework for the development of injury control interventions. From further elaboration of the basic principle that injuries represent energy transfer that exceeds a threshold, Haddon went on to develop a ten-strategy approach to prevent injuries through the management of energy transfer.[67] The ten methods for limiting energy transfer are the following:

Pre-Event Phase

1. Prevent the development of energy form
2. Reduce the amount of energy

3. Prevent the energy release

Event Phase

4. Alter the rate of energy release from its source or its spatial distribution
5. Separate structures from the energy release by space or time
6. Place a barrier between the released energy and susceptible structures
7. Modify surfaces that can be impacted
8. Strengthen structures susceptible to damage from energy transfer

Post-Event Phase

9. Prevent the extension of existing damage
10. Initiate intermediate and long-term repair and rehabilitation

2.11 Types of injury

Injuries are the result of physical damage to the human body caused by acute exposure to intolerable levels of energy (radiation, thermal, mechanical, electrical, or chemical) or by the sudden absence of heat or oxygen.[68] The severity and impact of injuries are essentially determined by the amount of energy that is released. Injuries are classified under two categories: unintentional and intentional. Unintentional injuries result from involuntary actions, while intentional injuries result from actions with the intent to inflict injury upon oneself or another person. Unintentional injuries include but are not limited to: motor vehicle accidents, poisoning, burns, suffocation, falls and drowning. Intentional injuries on the other hand include: homicides, suicides, assault, violence and abuse. These injuries can result in fatal and non fatal consequences leading to premature death and disability.

The World Health Organization (WHO) provides the following definition regarding injury[69]: "An injury is the physical damage that results when a human body is suddenly or briefly subjected to intolerable levels of energy. It can be a bodily lesion resulting from acute exposure to energy in amounts that exceed the threshold of physiological tolerance, or it can be an impairment of function resulting from a lack of one or more vital elements. The time between exposure to the energy and appearance of the injury is short." In the

International Classification of Diseases (ICD) the external causes of injury are classified by intent. The categories of injuries include:

- Unintentional (i.e. accidental)
- Intentional (i.e. deliberate)
    - Interpersonal (e.g. assault and homicide)
    - Self-harm (e.g. abuse of drugs and alcohol, self-mutilation, suicide)
    - Legal intervention (e.g. by law enforcement)
    - War, civil insurrection and disturbances (e.g. demonstrations and riots)

All injuries can be characterized from the perspective of energy transfer that exceeds a threshold. The five forms of physical energy that can cause injury are mechanical, electric, radiation, thermal and chemical. If this result occurs unintentionally it is defined as unintentional injury. The majority of unintentional injuries occur as a result of motor vehicle accidents, falls, poisonings, drowning, fires, suffocation, burns and firearms. In 2001, more than 3.5 million deaths were reported worldwide for unintentional injuries.[68]

2.11.1 Motor vehicle accidents

Motor vehicle collisions are the leading cause of trauma deaths worldwide.[70] More people die from unintentional injuries associated with motor vehicle crashes than any type of injury. Motor vehicle injuries occur most commonly in male teenagers and young adults ranging from 15 to 24 years of age. This age group has the highest mortality rate and accounts for one third of all deaths from motor vehicle crashes.[71] In Canada, yearly motor vehicle related deaths were significantly reduced by 52% with a decrease from 5,933 in 1979 to 2,875 in 2004. Much of this decline has been attributed to technological advances and legislation enforcements. Despite the significant decrease, motor vehicle crashes remain the leading cause of death for young people today.[72]

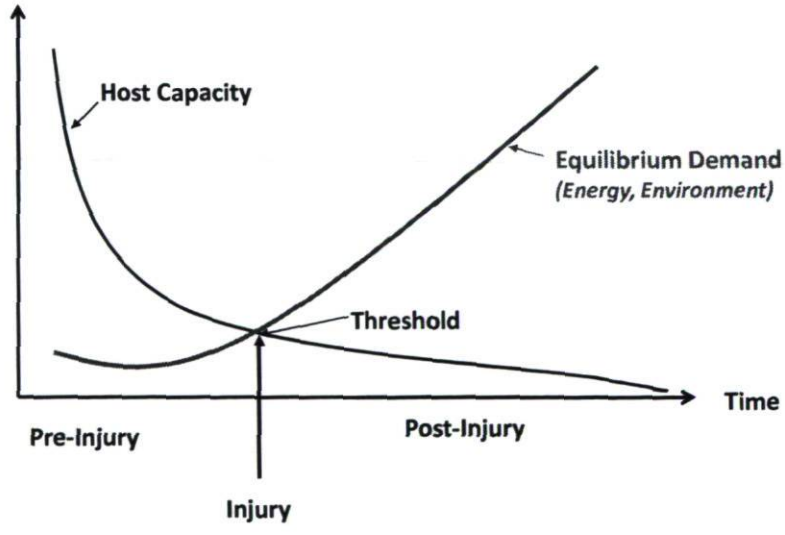
2.11.2 Falls

The second leading cause of unintentional fatal injuries is falls. Fall related injuries are the leading cause of hospitalization for all ages accounting for 34% of injury admissions in 2009.[73] The fall-related injury rate is nine times greater among seniors than among those less than 65 years of age.[74] Almost 62% of injury-related hospitalizations for seniors are the result of falls.[75] Almost half of seniors who fall experience a minor injury, and 5% to 25% sustain a serious injury such as a fracture or a sprain.[76,77] The magnitude of the problem of falls among older adults is reflected in the 300% increase in publications on the issue between 1985 and 2005.[78]

2.12 Causal model for injuries

Injuries result from the transfer of energy to the human host. Figure (1.1) provides a model for understanding the role of the environment in the causal pathway for injuries.

Figure 1.1: Model for Injury Causation



The transfer of energy to the host is the last step in the causal pathway for injuries. However, there are many factors that influence the nature of this exchange and its consequences. The transfer of energy to a human host could be achieved through vehicles such as a motor vehicle or vectors such as another human. In order for the injury to occur the outside agent capable of causing the injury meets the host that is vulnerable to the agent in an environment that allows the host and the agent to interact.

2.13 Medications and injuries

Prescription medications are substances which are considered as drugs under the Food and Drugs Act and which are sold for human use under a written form by a physician or other medical professional. Non prescribed drugs include over-the-counter medications which are therapeutic drugs not requiring a prescription and personal health supplies which include items used primarily to promote or maintain health. Drugs have a fundamental role in treating and preventing disorders and when used appropriately drugs may reduce mortality and morbidity and improve the quality of life in a population. However certain classes of drugs have demonstrated to pose a risk of injury by increasing the likelihood of falls, fall-related injuries, adverse drug events and motor vehicle accidents when used as monotherapy or concomitantly.

The use of medications such as antidepressants, antihypertensives, some analgesics, hypnosedatives and anxiolytics have been associated with an increased risk for injury occurrence.[12,15,79-82] The risk of injury increases even further when medications are used in combination.[7,8,16,83-85]

2.13.1 Medications and motor vehicle accidents

There are numerous studies which have demonstrated that driving under the influence of medications is related to an increased risk of having a motor vehicle accident.[9,10,12,15,17,22,86-91] Experimental studies have shown that psychoactive drugs have the ability to impair functions relevant to driving, including sensory functions and perception as well as cognitive skills and motor function skills.[92,93] A study conducted by Skegg confirmed that patients receiving benzodiazepines and other minor tranquilizers were nearly five times

more likely to experience a serious motor vehicle accident than subjects who had not used the drug.[92] Another study looked at subjects who were hospitalized due to injuries from a motor vehicle accident and found that they were more likely to have received a prescription for hypnotics during the three month period prior to the accident than subjects who were identified as passengers.[94] Carisoprodol, a drug used for acute lower back pain has also shown evidence of an increased risk of injury relating to a motor vehicle accident.[10] The results showed that having a prescription for carisoprodol increased the standardized incident ratio for being involved in an motor vehicle accident to 3.7 (95% CI: 2.9-4.8) the first week after the date of dispense. Other drugs such as diazepam showed similar results.[10]

2.13.2 Medications and falls

There are epidemiologic studies which have also identified several medications that contribute to an associated risk of falls in the elderly.[4-6,95-97] Seniors tend to take more drugs than the younger population and with age, they develop altered mechanisms for digesting and metabolizing drugs. The use of polypharmacy, defined as taking five or more prescribed medications, has been proven to be a significant factor in many falls.[6,84] The use of psychotropic drugs, such as benzodiazepines, antidepressants, neuroleptics and anticonvulsants has been identified to have a two-fold increased risk of falls and fractures, compared to individuals not taking these drugs. These studies have also shown that there is an association between falling and the number of drugs used.[8,97,98]

Chapter 3: Rationale

The association between the use of certain medications and increased risk for motor vehicle collisions and fall related injuries has been extensively demonstrated in several epidemiologic studies up to date. However, there still remains a lack of evidence and knowledge on which statistical approaches and methods are best suited to provide the most accurate and statistically efficient results to demonstrate these findings.

There are extensive epidemiologic studies that have applied various statistical approaches and designs to estimate the risk of an outcome such as injury or trauma due to exposures. The case-control design is the reference design for the analysis of rare risks where the investigators select the participants based on the outcome status.[99] Data on outcome and exposure are collected at one point in time. The measure of association for the case-control design is the odds ratio. Although the case-control design has the ability to analyze rare outcomes such as traumatic injuries, the design also has its limitations. Some of these include possible temporal biases (the inability to ensure that exposure preceded the outcome) and selection bias for controls in matching cases and controls based on subject characteristics to control for confounding.

In the last 10 years additional observational studies have emerged as alternative methods and provide risk estimates without the need to enroll controls and are well suited to answer questions in pharmacoepidemiology; these include the case crossover design and the case-time-control design. The case-crossover design developed by Maclure assesses the effects of brief exposures on a specified event where the cases serve as their own historical controls. This method is appropriate when exposures are transient in time and have acute short-term effects. More recently, the case-time-control design was developed as an extension of the case-crossover design that in addition to the case series, a series of controls are used to adjust for exposure time trends.

A limited amount of studies in a variety of study settings up to date have applied the case-crossover and the case-time-control designs to evaluate the effect of intermittent exposures

on the risk of acute events.[38,45-48,100] The results conducted by Zambon et al., Corrao et al., and Meyer et al., demonstrated that the case-crossover and case-time-control analyses showed consistent findings among the measures of the odds ratio. However, the studies conducted by Schneider et al. and Hernandez-Diaz et al. showed inconsistent findings in the measures of effect from the two methodologies and concluded the importance in evaluating temporal trends when using a case-crossover design. Although these studies have applied the case-crossover and the case-time-control designs, an in-depth comparison to evaluate the association between the risk of traumatic injuries and exposure to prescribed medications using population databases has not been conducted up to date. Therefore there is a need to better understand how the association between exposure to certain drugs and risk of injury could be correctly estimated from large databases. The results of the current thesis could have major implications in the ability to provide valid recommendations regarding the risk for injury associated with drug use.

Chapter 4: Study Objectives

The aim of the current thesis was to compare the case-crossover and case-time-control analyses for assessing the relationship between use of specific prescription drugs and the risk of a traumatic injury using population databases. In addition, the rate of agreement from the measures of effect between the two methodologies was also assessed.

Chapter 5: Methods

5.1 Study Design

This was an observational database study that utilized a source population of residents from the province of Quebec, an area situated in east-central Canada. The main inclusion criterion in the case series analysis was to include subjects that were injured between January 1, 2000 and December 31, 2000. The control series analysis comprised of non-injured individuals that were treated surgically and were matched for age, gender, level of trauma care center, and date of discharge from the hospital. Trauma subjects were identified from the Quebec Trauma Registry (QTR), non-injured control subjects were identified from the hospitalization database (MED-ECHO) from the Ministère de la Santé et des Services Sociaux (Quebec Ministry of Health and Social Services), and information regarding the exposure of subjects to prescribed medications was retrieved from the Régie de l'assurance maladie du Quebec (RAMQ) database. Males and females were included in the study. The confidentiality of all patient records was ensured since no recognition key was present.

5.2 Data Acquisition and Data Linkage

Information regarding the incidence of traumatic injuries was retrieved from the QTR database between January 1, 2000 and December 31, 2000. The QTR was established in 1992 and includes information on patient demographics (age, gender); mechanism of injury, on-site care, emergency room care, in-hospital procedures including diagnostic and therapeutic intervention and surgical treatment, duration of hospital and intensive care unit stay, incidence of complication and injury severity measures

All patients who experienced a traumatic injury were matched with a control subject based on the following characteristics: age ±1 year, gender, level of trauma care center, and date of discharge from the hospital ± 1 year. All data information pertaining to the control subjects were retrieved from the hospitalization database MED-ECHO.

Information regarding the exposure of subjects to prescribed medications was retrieved from the RAMQ database from January 1, 1999 and December 31, 2000 for 12 months prior to the event of the injury. The RAMQ contains all the prescriptions filled in any community-based pharmacy in Quebec. The drug classification codes available from this file were recorded with the Drug Identification Numbers (DIN). A third classification, the Anatomical Therapeutic Classification (ATC), was derived from the DIN using a cross-reference file obtained from Health Canada (2009). The ATC classification system was used in the categorization of drugs for the current study. Time of exposure to a prescribed medication was estimated based on the service date of treatment as recorded in the RAMQ database. All records were deleted and excluded from the study analysis if the prescribed medications were dispensed on or after the subject's date of injury.

Records from the QTR, MED-ECHO and the RAMQ databases were linked using a unique subject identifier number which allowed the linkage in all databases. Subjects who could not be matched based on the unique identifier were excluded from the analysis. For subjects with more than one accident reported during the year 2000, only the first recorded accident was retained in the database to minimize the risk of reporting the same accident more than once.

5.3 Data Analysis

Two statistical approaches were used to determine the risk of injury in patients taking prescribed medications in order to address the study objective. The first approach was based on the case-crossover design and the second approach was based on the case-time control design. All analyses were performed using the SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL).

5.3.1 Case-Crossover Design:

In the case-crossover analysis each subject who reported an accident was used as his own historical control. The case period was defined as the 14-day period prior to the occurrence of the accident. Each subject with an accident contributed a case period. There were 25 potential 14-day control periods for each accident that covered the 50 weeks in the year prior to the accident. Therefore the total period of the study was the entire year prior to the accident. Each control period selected was required to be accident-free.

Exposure to each medication was determined from the start date of treatment. If, according to the data from the RAMQ database, the patient was prescribed the medication for any day during the case period or the control periods, the subject was considered as having been exposed to the medication during that period. If the subject was not taking the medication during the individual period as shown by the RAMQ data, the subject was considered as not having been exposed to the medication. Exposure to the case period did not include the date of the accident.

The statistical hypothesis tested is that the rate of exposure to the tested medication is higher for the case periods when compared to the control periods. The analysis involves the calculation of period at risk and periods at no risk for each patient. A period at risk is one where the subject was exposed to the medication in question. A period at no-risk is one during which the subject was not taking the medication in question. The null hypothesis is that the rate of case (traumatic injury) periods at risk is equal to the rate of control (no traumatic injury) periods at risk. The incidence rate ratio (IRR) is the ratio of the at risk rate for the case periods to the at risk rate for the control periods. For the IRR the variance was estimated using the Mantel-Haenzel approach (1.3) based on the consideration that each occurrence at-risk case period is an independent Poisson Variate. Ninety five percent confidence intervals were calculated with the test-based approach (1.4). Statistical testing for significance was not conducted since the confidence intervals were used to assess significance.

The IRR_{MH} introduced by Rothman[101] is the ratio of the,

$$\frac{\text{rate of occurrence of cases in prescription} - \text{exposed subjects}}{\text{rate of occurrence of cases in non} - \text{prescription exposed subjects}}$$

The IRR_{MH} was employed using the following formula (1.3) and using the data layout shown in Table (1.2),

$$IRR_{MH} = \frac{\sum i\, a_{1i}\, N_{0i}/T_i}{\sum i\, a_{0i}\, N_{1i}/T_i} \tag{1.3}$$

Table 1.2 Data layout

	Exposed	**Non-exposed**	**Total**
Cases	α_{1i}	α_{0i}	M_i
Person-time	N_{1i}	N_{0i}	T_i

To compute the confidence interval of the IRR_{MH}, the variance estimator for the logarithm was employed using the following formula (1.4) proposed by Greenland and Robins[34]:

$$\text{Var}\,[\ln(IRR_{MH})] = \frac{\sum i\, M_i\, N_{1i}\, N_{0i}/T_i^2}{(\sum i\, a_{1i}\, N_{0i}/T_i)(\sum i\, a_{0i}\, N_{1i}/T_i)} \tag{1.4}$$

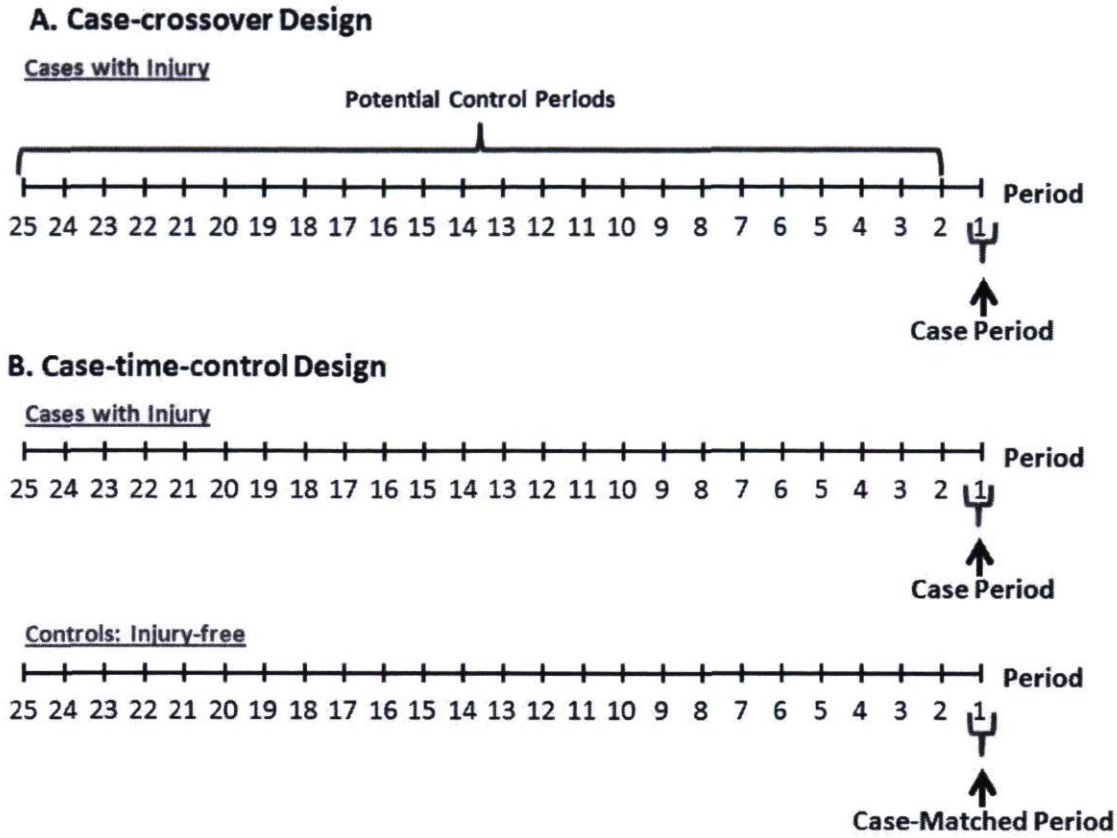
5.3.2 Case-Time-Control Design:

In the case-time-control analysis, an injury-free matched control was assigned to each case subject who reported a traumatic injury. For each case a control was matched with respect to age, gender, level of trauma care center, and date of discharge from the hospital. The controls that were discharged from the hospital were due to hospitalization for minor surgery.

The first step in this approach was to apply the case-crossover analysis to the control cohort. For each injury-free control, case and control periods were defined according to the accident date of the corresponding accident case. Under the null hypothesis there would be no significant associations for IRR in this analysis. If significant IRR are identified this would suggest a spurious association.

The second step in the case-time-control approach was the calculation of the odds ratio. The odds ratio describing the increased risk for being exposed to the medication in question is calculated as the ratio of the IRR for the cases over the controls. The variance is the pooled variance for the IRR estimates of the cases and the controls and ninety five percent confidence intervals were calculated using the test-based method. The case-crossover design and the case-time-control design are depicted in Figure (1.2) to provide a visual understanding of the two study methodologies.

Figure 1.2: Case-Crossover and Case-Time-Control Designs



Chapter 6: Results

6.1 Subject Identification

A total of 11,310 subjects that experienced at least one traumatic injury in the year 2000 were identified from the QTR. Of these, there were 204 subjects who reported more than one accident; however the most recent accident was retained for data analysis in these subjects to minimize the risk of reporting the same accident more than once. Of the 11,310 subjects, 2,417 were retained and included in the case-crossover analysis after data cleaning, available treatment exposure from the RAMQ database, and removing the treatment exposures for periods that were not in the 52 week time window prior to the accident. All 2,417 subjects who experienced an injury in the year 2000 were matched to 2,417 controls based on age, gender, level of trauma care center, and the date of discharge from the hospital.

6.2 Patient Characteristics

The mean (SD) age was 68.4 (15.3) years for the cases and 67.6 (14.9) years for the controls. With respect to gender, 54.2 % were female for the cases and the controls. With regards to the cases, the majority of traumatic injuries were due to a fall (n=1803, 74.6%) and motor vehicle accidents (n=394, 16.3%).

6.3 Analyses:

6.3.1 Case-Crossover Analysis:

The objective of the case-crossover analysis was to calculate the association between risk of traumatic injury and exposure to prescribed medications in the case subjects. The expectation would be that certain prescribed medications demonstrate significant associations in this analysis.

6.3.2 Case-Time-Control Analysis:

The objective of the case-time-control analysis was to remove potential confounding by indication and temporal trends in the case-crossover design. This is because the case-crossover design is aimed at identifying transient acute effects and those arising from long-term uses of medications.

The first step of the case-time-control analysis was to repeat the case-crossover analysis in the matched control cohort. The expectation would be that there would be no significant associations in this analysis. If a positive association was identified for both the cases and the controls, this would suggest that the association observed in the cases was spurious and due to confounding.

The second step of this analysis was to present the results as odds ratios (OR) that estimate the relative risk for having a traumatic injury associated with exposure to the prescribed medications in question after adjusting for confounding by indication and temporal trends.

With respect to both study designs, negative associations include risk estimates with a value <1 and positive associations include risk estimates with a value >1.

6.4 Case-Crossover and Case-Time-Control Results

There were 38/101 (37.6%) medications as described by the ATC Level III class which showed inconsistent results due to the opposite direction of the measure of effect in the risk estimates from the case-crossover and the case-time-control designs. These results are described in the sections below by ATC Level I class.

6.4.1 Alimentary Tract and Metabolism Medications:

In the case-crossover analysis, the IRR showed a negative association in the risk of traumatic injuries, whereas the OR showed a positive association in the case-time-control analysis for the following prescribed medications: digestives including enzymes (IRR= 0.697 vs. OR=1.000), insulin and analogues (IRR=0.859 vs. OR=2.483), oral blood glucose

lowering drugs (IRR=0.929 vs. OR=1.145), and vitamin B1 plain and in combination with vitamin B6 and vitamin B12 (IRR=0.947 vs. OR=2.107). The measure of effect showed opposite associations for the case-crossover and case-time-control analyses for calcium (IRR=4.042 vs. OR=0.675) (Table 1, Figures 1-2).

6.4.2 Antiinfectives for Systemic Use:

In the case-crossover analysis, the IRR showed a negative association in the risk of traumatic injuries while the OR showed a positive association in the case-time-control analysis for the following prescribed medications: other antibacterials (IRR= 0.996 vs. OR=1.187) and quinolone antibacterials (IRR=0.988 vs. OR=1.081). The measure of effect in case-crossover versus case-time-control analysis showed a reverse association in antimycotics for systemic use (IRR=2.878 vs. OR=0.489) (Table 2, Figures 3).

6.4.3 Antineoplastic and Immunomodulating Agents:

In the case-crossover design, the IRR showed a negative association in the risk of traumatic injuries, whereas the OR showed a positive association in the case-time-control analysis for the following prescribed medications: alkylating agents (IRR= 0.901 vs. OR=1.012) and hormone anatagonists and related agents (IRR=0.890 vs. OR=1.042) (Table 3, Figure 4).

6.4.4 Antiparasitic Products, Insecticides and Repellents:

No contrasting associations for the measures of effect in the case-crossover and the case-time-control analyses were observed for this class of medications (Table 4, Figure 5).

6.4.5 Blood and Blood Forming Organ Medications:

In the case-crossover analysis, the IRR showed a positive association in the risk of traumatic injuries, while the OR showed a negative association in the case-time-control analysis for the following prescribed medications: vitamin B12 and folic acid (IRR= 1.253 vs. OR=0.668) and antithrombotic agents (IRR=1.410 vs. OR=0.985) (Table 5, Figure 6).

6.4.6 Cardiovascular System Medications:

Plain ACE inhibitors (IRR=1.038 vs. OR=0.928), centrally acting antiadrenergic agents (IRR=1.230 vs. OR=0.777), and cardiac stimulants excluding cardiac glycosides (IRR=1.708 vs. OR=0.512) were associated with a higher risk for injury in the case-crossover analysis, whereas a negative association was observed in the case-time-control analysis. Contrasting associations were observed for the measure of effect in peripherally acting antiadrenergic agents (IRR=0.962 vs. OR=1.009), cardiac glycosides (IRR=0.812 vs. OR=1.072), and diuretics and potassium-sparing agents (IRR=0.890 vs. OR=1.064) (Table 6, Figures 7-9).

6.4.7 Dermatological Preparations:

In the case-crossover analysis, the IRR showed a negative association in the risk of injury, whereas the OR showed a positive association in the case-time-control analysis for the following prescribed medications: antipsoriatics for topical use (IRR= 0.466 vs. OR=2.113). The measure of effect in case-crossover versus case-time-control analysis showed a reverse association for emollients and protectives (IRR=2.077 vs. OR=0.438) (Table 7, Figure 10).

6.4.8 Genito-urinary System and Sex Hormones:

In the case-crossover analysis, the IRR showed a negative association in the risk of traumatic injuries, whereas the OR showed a positive association in the case-time-control analysis for hormonal contraceptives for systemic use (IRR= 0.625 vs. OR=1.869). The IRR showed a positive measure of effect in the case-crossover analysis and a negative measure of effect in the case-time-control analysis for other sex hormones and modulators of the genital system (IRR=3.072 vs. OR=0.752) and other urologicals including antispasmodics (IRR=1.045 vs. OR=0.742) (Table 8, Figure 11).

6.4.9 Musculo-skeletal System Medications:

In the case-crossover analysis, the IRR showed a negative association in the risk of injury, while the OR showed a positive association in the case-time-control analysis for muscle relaxants centrally acting agents (IRR= 0.927 vs. OR=1.040) (Table 9, Figure 12).

6.4.10 Nervous System Medications:

In the case-crossover analysis, the IRR showed a negative association in the risk of traumatic injuries, whereas the OR showed a positive association in the case-time-control analysis for antiepileptics (IRR=0.955 vs. OR=1.074) and anxiolytics (IRR=0.993 vs. OR=1.069). The IRR showed a positive measure of effect in the case-crossover analysis and a negative measure of effect in the case-time-control analysis for antimigraine preparations (IRR=1.045 vs. OR=0.324) and antivertigo preparations (IRR=2.250 vs. OR=0.260) (Table 10, Figures 13-14).

6.4.11 Respiratory System Medications:

Adrenergic for systemic use (IRR=0.866 vs. OR=1.068), adrenergic inhalants (IRR=0.960 vs. OR=1.623), other anti-asthmatics for systemic use (IRR=0.882 vs. OR=1.859) and other anti-asthmatic inhalants (IRR=0.974 vs. OR=1.414) were negatively associated with a risk for injury in the case-crossover analysis, while a positive association was observed in the case-time-control analysis. The measure of effect in case-crossover versus case-time-control analysis showed a reverse association in decongestants and other nasal preparations for topical use (IRR=1.055 vs. OR=0.694) (Table 11, Figures 15).

6.4.12 Sensory Organ Medications:

In the case-crossover analysis, the IRR showed a negative association in the risk of injury, while the OR showed a positive association in the case-time-control analysis for the use of antiinfectives (IRR= 0.839 vs. OR=1.092). The measure of effect in case-crossover versus case-time-control analysis showed a reverse association for antiglaucoma preparations and miotics (IRR=1.146 vs. OR=0.894) (Table 12, Figure 16).

6.4.13 Systemic Hormonal Preparations (excluding sex hormones and insulins):

In the case-crossover analysis, the IRR showed a negative association in the risk of injury, while the OR showed a positive association in the case-time-control analysis for the use of plain corticosteroids for systemic use (IRR= 0.786 vs. OR=1.158), and thyroid preparations (IRR=0.949 vs. OR=1.262). The measure of effect in case-crossover versus case-time-control analysis showed a reverse association for anti-parathyroid hormones (IRR=1.610 vs. OR=0.136) (Table 13, Figure 17).

6.4.14 Various Medications:

No contrasting associations for the measures of effect in the case-crossover and the case-time-control analyses were observed for this class of medications (Table 14, Figure 18).

6.5 Agreement of Results for Case-Crossover and Case-Time-Control Analyses

The positive and negative associations observed in both the case-crossover and case-time-control designs were summed together and divided by the total number of observations for each ATC Level I medication class in the event that the associations were in the same direction for both study designs. This was evaluated to determine the rate of agreement for the measures of effect between the two study methodologies. These results are described in Tables 15-27.

In addition, the Cohen's Kappa was produced to assess the agreement between the sum of concordant and discordant observations for the measures of effect in the case-crossover and case-time-control analyses. The concordant observations represented the agreement in the direction of the measures of effect assessed with the case-crossover and the case-time-control analyses. The discordant observations represented the disagreement in the direction of the measures of effect assessed with the case-crossover and the case-time-control analyses. Kappa values less than 0.70 indicate poor agreement despite whether statistical significance is observed.

6.5.1 Agreement Rate in Alimentary Tract and Metabolism Medications:

The rate of agreement in this class of prescribed medications was 61.5% (Kappa=0.198). The results demonstrated that the case-crossover analysis is four times more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury (Table 15).

6.5.2 Agreement Rate in Antiinfectives for Systemic Use:

The rate of agreement in this class of prescribed medications was 66.7% (Kappa=0.341). The results demonstrated that the case-crossover analysis is two times more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury (Table 16).

6.5.3 Agreement Rate in Antineoplastic and Immunomodulating Agents:

The rate of agreement in this class of prescribed medications was 50.0% (Kappa was not calculable). The results demonstrated that the case-crossover analysis is four times more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury (Table 17).

6.5.4 Agreement Rate in Blood and Blood Forming Organ Medications:

The rate of agreement in this class of prescribed medications was 50.0% (Kappa was not calculable). The results demonstrated that the case-crossover analysis is four times more likely to produce a positive association compared to the case-time-control analysis in estimating the risk of injury (Table 18).

6.5.5 Agreement Rate in Cardiovascular System Medications:

The rate of agreement in this class of prescribed medications was 72.7% (Kappa=0.411) (Table 19).

6.5.6 Agreement Rate in Dermatological Preparations:

The rate of agreement in this class of prescribed medications was 75.0% (Kappa=0.467) (Table 20).

6.5.7 Agreement Rate in Genito-urinary System and Sex Hormones:

The rate of agreement in this class of prescribed medications was 57.1% (Kappa=0.087). The results demonstrated that the case-crossover analysis is two times more likely to produce a positive association compared to the case-time-control analysis in estimating the risk of injury (Table 21).

6.5.8 Agreement Rate in Musculo-skeletal System Medications:

The rate of agreement in this class of prescribed medications was 75.0% (Kappa was not calculable) (Table 22).

6.5.9 Agreement Rate in Nervous System Medications:

The rate of agreement in this class of prescribed medications was 66.7% (Kappa=0.250) (Table 23).

6.5.10 Agreement Rate in Respiratory System Medications:

The rate of agreement in this class of prescribed medications was 28.6% (Kappa= -0.207). The results demonstrated that the case-crossover analysis is four times more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury (Table 24).

6.5.11 Agreement Rate in Sensory Organ Medications:

The rate of agreement in this class of prescribed medications was 60.0% (Kappa=0.167) (Table 25).

6.5.12 Agreement Rate in Systemic Hormonal Preparations (excluding sex hormones and insulins):

The rate of agreement in this class of prescribed medications was 25.0% (Kappa= -0.500). The results demonstrated that the case-crossover analysis is two times more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury (Table 26).

6.5.13 Agreement Rate in All Medications:

There were a total of 101 prescribed medications that were evaluated for the purpose of the current analysis. The case-crossover analysis identified 23 medications negatively associated for the risk of injury, while for the same medications in question; the case-time-control analysis identified them as being positively associated for risk of injury. Consequently, there were 15 medications positively associated in the case-crossover analysis while the same medications were negatively associated in the case-time-control design. There were 63 total ATC level III classes of prescribed medications which were consistent in the measures of effect between the two study methods. The rate of agreement in all medications was 63/101 (62.4%) (Kappa=0.219). Overall, the results demonstrated that the case-crossover analysis is 1.5 times more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury (Table 27).

Chapter 7: Discussion

In the current observational population database study, two analytical approaches, the case-crossover and the case-time-control design, were used to estimate the risk of traumatic injuries associated with exposure to prescribed medications. The same data was applied to both designs to compare the associations estimated with the case-crossover design and the case-time-control design. The rate of agreement in the risk estimate direction was also evaluated. The following discussion begins with a description of the important findings that were derived from the current thesis analysis. Possible explanations of the study results are discussed followed by the study's limitations and strengths.

The results showed that the case-crossover design is 1.5 times more likely to produce a negative association compared to the case-time-control design when taking into account all 101 prescribed medications evaluated in the current analysis. Consequently, the results demonstrated that the case-crossover analysis is overestimating a negative association in the risk for potential traumatic injury, while the case-time-control analysis is overestimating a positive association for certain prescribed medications. In addition, there was a low level of agreement (62.4%) in the risk estimate direction between the two statistical methodologies. The comparison of the two methods shows the need to account for time trends in exposures when using a case-crossover design. Other studies in the literature that have applied the case-crossover and the case-time-control designs, under different study settings however, have also demonstrated similar findings.[45,48] The study conducted by Hernandez-Diaz et al. which evaluated the association between use of folic acid antagonists during the second and third pregnancy months and the risk of cardiovascular defects demonstrated that the case-crossover yielded an odds ratio of 1.0 (95% CI: 0.5-2.0) while the case-time-control yielded an odds ratio of 2.9 (95% CI: 1.2-7.2).[45] The conclusion of this study showed that although the case-crossover design controlled for between person confounding and avoided issues of control selection, it may have been biased by time trends of exposure prevalence during pregnancy.

Up to date, the conventional approach to evaluate the risk of injury in association with drug exposure has been to apply the conventional case-control design or to calculate the standardized incidence ratio (SIR) using population based registries. Although the case-control design has the ability to analyze rare outcomes such as traumatic injuries, its downfall is that the design is unable to control for confounding by indication, it can also lead to misclassification, especially in underreporting of drugs. In addition it cannot yield incidence rates because subjects are selected based on outcome. Selection bias may also occur if the control group doesn't come from the same population as the cases.[102] The SIR is also a commonly used method to provide risk estimates in traumatic injury associated with the use of medications.[9,89-91] The SIR provides an estimate of the occurrence of a given outcome (e.g. traumatic injury) in a population relative to the expected number of cases in that given population. However the SIR must be interpreted cautiously based on its size and stability. This is because a SIR can have the same size but not the same stability. For example, a SIR of 1.5 based on 4 expected cases and 6 observed cases indicates 50% more likelihood of injury, but the excess is based only on two extra cases. On the other hand, a SIR of 1.5 based on 400 expected cases and 600 observed cases represents the same excess in injury, however because the SIR is based on a larger number of cases, the estimate is more stable. The major advantage of applying the case-crossover and the case-time-control designs is that they have the ability to evaluate transient effects of an intermittent exposure on the onset of acute outcomes.[24,36,103]

In the current study the case-crossover risk estimate for drug use was more likely to underestimate an association for risk of injury compared to the case-time-control design, more specifically for the following class of ATC level I medications: alimentary tract and metabolism, anti-infectives for systemic use, antineoplastic and immunomodulating agents, musculo-skeletal system, respiratory system, and systemic hormonal preparations. The difference in results between the two designs for certain prescribed medications that led to different risk estimates may be due to the changes in time trends and adjusting for confounding by indications. Although the case-crossover design avoids the difficulty of selecting a group of control subjects, the case period and control periods still need to be

defined, which is a crucial step in case-crossover studies, and is a difficult challenge that is not so evident and easy to figure out. One difficulty is related to the problem regarding the induction periods and carryover effects. A carryover effect occurs when the effect of the exposure during a control period lasts long enough to have an impact on the occurrence of the outcome. However, the carryover effect can be removed by spacing the control period from the case period. Another problem is related to the characteristics of the exposure series with respect to time trends in the exposure. If the exposure series demonstrates a time trend, selecting the control periods before the case period can lead to a systematic selection bias of the control periods. The exposure odds ratio can in turn be biased and the direction of the bias can depend on the type of time trend. This is relevant in the current study because the outcome (injury) may be affected by the exposures (prescribed medications) depending on the time of day and the season that the injury occurred. The case-time-control design accounts for exposure time trends which is provided by the odds ratio among the controls and was used to adjust the exposure odds ratio among cases.

In the literature review we observed that injury causation is multifactorial and depends on the host, the vector and the environment in order for the injury to occur. A possible explanation for the underestimation of the case-crossover analysis may be explained by the fact that injury causation wasn't adjusted for these three important factors in the current study. Epidemiologic studies which have assessed the risk of motor vehicle accidents and falls associated with the use of medications emphasize on the host and make the assumption that the vector and the environment are constant factors which is not a valid assumption.[4,6,10,22,89-91] For example if a subject was taking a prescribed medication and driving a vehicle (vector) in the winter season under snowy conditions (environment) compared to a subject that was driving a vehicle (vector) in summer weather under clear road conditions (environment), the calculation of the risk estimates after adjusting for these parameters could very well show different results. Therefore it may be that both methods are biased and consequently present the need for developing multi-variate methods that adjust for these factors that contribute to injury causation.

In addition, time of exposure to a prescribed medication was estimated based on the service date of treatment as recorded in the RAMQ database; however duration of treatment exposure wasn't considered for both methods and may have also influenced the results. The case and control windows were defined as 14-day exposure windows, however if a patient was prescribed a certain medication for 30 days, the patient was only included as being exposed for the relevant period and consequently the effect of the exposure was not cumulative to the following period. This point again raises the question regarding selecting the appropriate and correct exposure assessment window length which could be very challenging when applying the case-crossover and case-time-control methods because misspecification of the case and control periods can lead to potential non-differential misclassification of the exposure and can yield a risk estimate toward the null hypothesis.[104] Another limitation in the two study methodologies is that there was no way to identify subject compliance with prescribed medications from the population databases and to assess when the drug was actually taken versus when it was dispensed.[37]

Furthermore, there is the concern regarding the biological plausibility of the associations for certain prescribed medications and the risk of injury. For some medications, for example analgesics and other nervous system drugs, a direct pharmacological effect could be assumed. However for others, such as anti-infectives, laxatives and calcium use, it may be due to the underlying condition rather than exposure to the medication itself which caused an association. Without adjusting for the indication pertaining to the prescription it may not be possible to conclude a direct pharmacological effect. The exposure to oestrogen medications and anti-thyroid preparations were also associated with an increased risk for an injury in both the case-crossover and case-time-control analysis. These observations may be caused by confounding or may be due to statistical artefacts. There is also the issue that both statistical methodologies assume independence of each drug effect. This is also not a valid assumption since some patients were more likely taking more than one drug at the same time. In turn, this may cause spurious associations to appear with some drugs because drug interactions as well as the number of drugs taken at the same time were not taken into consideration and adjusted in the current analysis.

In addition, it is important to note that all risk estimates were considered in the calculation of agreement for the measure of effect in all ATC level I medication classes regardless of statistical significance. Although there were 28 drugs significantly associated with the risk of injury in the current population database, there were not enough medications per ATC level I class that would allow the calculation of agreement and therefore all risk estimates were considered in the analysis. However it is important to note that the primary objective was to compare the two study methods for assessing the relationship between the use of certain prescribed medications and the risk of a traumatic injury and not to evaluate which prescribed medications were significantly associated with the risk of injury.

The primary strength of this study is the high data quality ascertained by using population-based databases which were linked using an encrypted unique subject identification number and which allowed the use of data on exposure that were collected before the onset of outcome. Also because these data are collected prospectively, they were not affected by recall or reporting bias. Another advantage of the case-crossover design if used by itself, is that is it less complicated and much less costly because no control subjects are required to conduct the study.[103] In addition, using more than one control period per case window increases the precision of the risk estimates. The case-time-control design however requires the need to include control subjects as would a conventional case-control study; therefore the cost and complexity are not advantages in this design. The case-crossover design is also useful to evaluate the effects of drug use in subjects with diseases that worsen over time or that vary in severity from subject to subject or the effects of intermittent drug use. [37] The appeal of this design is that within-subject comparisons avoid confounding by subject specific characteristics that are constant over time and bypasses the need for a control group, and also decreases the time required for data collection.[24] The case-time-control on the other hand can deal with time trends of exposure which the case-crossover design cannot control for.[41] In addition, because the greatest efficiency in the results of the risk estimates is achieved by using the whole year prior to the event of the accident as stated by Mittleman,[25] the precision of the effect size in the current analysis was improved

because the number of time periods selected were 25 potential 14-day control periods that covered the whole year prior to the injury.

By comparing the results obtained from the case-crossover and the case-time-control analyses both methods are a promising alternative to the traditional approaches. However because the results showed that the case-crossover tends to underestimate the association between the use of certain prescribed medications and the risk of injury it may be that this method is highly affected by non-differential misclassification and is diluting the true strength of the risk estimates as observed with the case-time-control analysis. I believe that in order to make a more valid conclusion on these findings and to detect which methodology is better suited to assess the association between the risk of injury and exposure to certain prescribed medications using large population databases, new multivariate methods must be developed to properly capture and control for environmental and vector parameters to adjust for the multifactorial nature of the association between exposure and injuries including, patient characteristics, disease comorbidity, and poly-pharmacy.

Chapter 8: Conclusion

The results of this study demonstrated that the case-crossover methodology is more likely to produce a negative association compared to the case-time-control analysis in estimating the risk of injury associated with the use of certain prescribed medications. The present findings also showed a poor level of agreement between the two study methods in the direction of the risk estimates. In addition, the current epidemiological methods may be prone to bias because they do not adjust for environmental and vector interactions which are pivotal factors that contribute to injury causation. New multivariate methods must be developed taking these factors into consideration and are required to help confirm these conclusions.

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Table 1: Summary Analysis CCO vs. CTC: Alimentary tract and metabolism

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANABOLIC AGENTS FOR SYSTEMIC USE	ANABOLIC STEROIDS						
	OTHER ANABOLIC AGENTS						
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ ANTIINFECTIVE AGENTS	ANTIDIARRHEAL MICROORGANISMS						
	ANTIPROPULSIVES	1.342	0.668-2.694	0.968	0.407-2.302	1.386	0.631-3.042
	ELECTROLYTES WITH CARBOHYDRATES						
	INTESTINAL ADSORBENTS						
	INTESTINAL ANTIINFECTIVES	0.989	0.348-2.815	2.609	1.086-6.270	0.379	0.144-0.995
	INTESTINAL ANTIINFLAMMATORY AGENTS	1.671	0.579-4.821	0.897	0.387-2.078	1.863	0.716-4.845
	OTHER ANTIDIARRHEALS						
ANTIEMETICS AND ANTINAUSEANTS	ANTIEMETICS AND ANTINAUSEANTS	1.057	0.177-6.316				
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS						
BILE AND LIVER THERAPY	BILE THERAPY						
	DRUGS FOR BILE THERAPY AND LIPOTROPICS IN COMBINATION						
	LIVER THERAPY, LIPOTROPICS						
DIGESTIVES, INCL. ENZYMES	DIGESTIVES, INCL. ENZYMES	0.697	0.146-3.332	0.697	0.102-4.744	1.000	0.174-5.758

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 1: Summary Analysis CCO vs. CTC: Alimentary tract and metabolism (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
DRUGS FOR ACID RELATED DISORDERS	ANTACIDS						
	ANTIFLATULENTS						
	ANTIREGURGITANTS						
	DRUGS FOR TREATMENT OF PEPTIC ULCER	1.397	1.178-1.657	0.951	0.789-1.146	1.469	1.228-1.757
	OTHER ANTACIDS, DRUGS FOR TREATMENT OF PEPTIC ULCER AND FLAT						
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	ANTISPASMODICS AND ANTICHOLINERGICS IN COMBINATION WITH OTHER DRUGS						
	ANTISPASMODICS IN COMBINATION WITH ANALGESICS						
	ANTISPASMODICS IN COMBINATION WITH PSYCHOLEPTICS						
	BELLADONNA AND DERIVATIVES, PLAIN						
	PROPULSIVES	1.060	0.711-1.579	0.889	0.566-1.397	1.191	0.778-1.825
	SYNTHETIC ANTISPASMODIC AND ANTICHOLINERGIC AGENTS						
DRUGS USED IN DIABETES	INSULINS AND ANALOGUES	0.859	0.476-1.550	0.346	0.114-1.048	2.483	1.022-6.031
	ORAL BLOOD GLUCOSE LOWERING DRUGS	0.929	0.714-1.209	0.812	0.616-1.070	1.145	0.874-1.500
	OTHER DRUGS USED IN DIABETES						
LAXATIVES	LAXATIVES	0.705	0.201-2.474	2.949	0.767-11.335	0.239	0.065-0.879
MINERAL SUPPLEMENTS	CALCIUM	4.042	2.801-5.832	5.989	3.847-9.323	0.675	0.450-1.013
	OTHER MINERAL SUPPLEMENTS	0.452	0.027-7.530				
	POTASSIUM	1.249	0.908-1.718	0.960	0.646-1.428	1.300	0.907-1.864

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 1: Summary Analysis CCO vs. CTC: Alimentary tract and metabolism (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO--Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
OTHER ALIMENTARY TRACT	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS						
STOMATOLOGICAL PREPARATIONS	STOMATOLOGICAL PREPARATIONS	6.872	2.324-20.324				
TONICS	TONICS						
VITAMINS	ASCORBIC ACID (VIT C), INCL. COMBINATIONS						
	MULTIVITAMINS, COMBINATIONS Standard dose						
	MULTIVITAMINS, PLAIN						
	OTHER PLAIN VITAMIN PREPARATIONS			0.917	0.132-6.387		
	OTHER VITAMIN PRODUCTS, COMBINATIONS						
	VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	1.597	0.801-3.183	1.014	0.404-2.547	1.574	0.698-3.551
	VITAMIN B-COMPLEX, INCL. COMBINATIONS						
	VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN B6 AND B12	0.947	0.372-2.412	0.450	0.041-4.918	2.107	0.343-12.955

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 2: Summary Analysis CCO vs. CTC: Anti-infectives for systemic use

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTIBACTERIALS FOR SYSTEMIC USE	AMINOGLYCOSIDE ANTIBACTERIALS						
	AMPHENICOLS						
	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	0.399	0.196-0.812	0.851	0.524-1.383	0.469	0.255-0.861
	COMBINATIONS OF ANTIBACTERIALS						
	MACROLIDES AND LINCOSAMIDES	0.575	0.319-1.038	1.088	0.692-1.711	0.529	0.312-0.895
	OTHER ANTIBACTERIALS	0.996	0.298-3.328	0.840	0.457-1.541	1.187	0.457-3.083
	OTHER BETA-LACTAM ANTIBACTERIALS	1.282	0.812-2.024	0.779	0.423-1.433	1.647	0.961-2.822
	QUINOLONE ANTIBACTERIALS	0.988	0.651-1.499	0.914	0.651-1.284	1.081	0.739-1.581
	SULFONAMIDES AND TRIMETHOPRIM	1.524	0.926-2.509	1.006	0.494-2.050	1.515	0.820-2.801
	TETRACYCLINES	0.227	0.021-2.456	0.502	0.072-3.517	0.452	0.051-3.975
ANTIMYCOBACTERIALS	DRUGS FOR TREATMENT OF LEPRA	1.350	0.130-14.029				
	DRUGS FOR TREATMENT OF TUBERCULOSIS	12.480	1.112-140.029				
ANTIMYCOTICS FOR SYSTEMIC USE	ANTIMYCOTICS FOR SYSTEMIC USE	2.878	0.980-8.452	5.888	2.238-15.491	0.489	0.176-1.361
ANTIVIRALS FOR SYSTEMIC USE	DIRECT ACTING ANTIVIRALS	2.545	0.723-8.957	1.010	0.221-4.611	2.519	0.625-10.158
IMMUNE SERA AND IMMUNOGLOBULINS	IMMUNE SERA						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 3: Summary Analysis CCO vs. CTC: Antineoplastic and immunomodulating agents

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTINEOPLASTIC AGENTS	ALKYLATING AGENTS	0.901	0.229-3.548	0.890	0.055-14.350	1.012	0.113-9.061
	ANTIMETABOLITES	0.531	0.191-1.476	2.605	0.972-6.986	0.204	0.075-0.556
	CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES						
	OTHER ANTINEOPLASTIC AGENTS						
	PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS						
ENDOCRINE THERAPY	HORMONE ANTAGONISTS AND RELATED AGENTS	0.890	0.460-1.723	0.854	0.370-1.971	1.042	0.490-2.213
	HORMONES AND RELATED AGENTS	0.710	0.283-1.783	2.961	0.908-9.654	0.240	0.083-0.692
IMMUNOSTIMULANTS	CYTOKINES AND IMMUNOMODULATORS	1.820	0.259-12.765				
IMMUNOSUPPRESSIVE AGENTS	IMMUNOSUPPRESSIVE AGENTS	1.887	0.436-8.179				

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 4: Summary Analysis CCO vs. CTC: Antiparasitic products, insecticides and repellents

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTHELMINTICS	ANTICESTODALS						
	ANTINEMATODAL AGENTS						
	ANTITREMATODALS						
ANTIPROTOZOALS	AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES			1.260	0.681-2.331		
	AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS						
	ANTIMALARIALS	1.413	0.907-2.203	0.372	0.153-0.905	3.799	1.881-7.671
ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS	ECTOPARASITICIDES, INCL. SCABICIDES						
	INSECTICIDES AND REPELLENTS						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 5: Summary Analysis CCO vs. CTC: Blood and blood forming organs

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTIANEMIC PREPARATIONS	IRON PREPARATIONS	1.308	0.868-1.970	0.288	0.126-0.657	4.540	2.369-8.700
	OTHER ANTIANEMIC PREPARATIONS	1.877	0.805-4.373	1.571	0.358-6.905	1.194	0.358-3.987
	VITAMIN B12 AND FOLIC ACID	1.253	0.805-1.951	1.875	1.063-3.306	0.668	0.402-1.112
ANTIHEMORRHAGICS	ANTIFIBRINOLYTICS						
	VITAMIN K AND OTHER HEMOSTATICS						
ANTITHROMBOTIC AGENTS	ANTITHROMBOTIC AGENTS	1.410	1.071-1.856	1.431	1.073-1.908	0.985	0.743-1.306
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	BLOOD AND RELATED PRODUCTS						
	HEMODIALYTICS AND HEMOFILTRATES						
	I.V. SOLUTION ADDITIVES						
	I.V. SOLUTIONS						
	IRRIGATING SOLUTIONS	22.115	0.445-1098.239				
	PERITONEAL DIALYTICS						
OTHER HEMATOLOGICAL AGENTS	OTHER HEMATOLOGICAL AGENTS						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 6: Summary Analysis CCO vs. CTC: Cardiovascular system

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ACE INHIBITORS, COMBINATIONS	1.239	0.492-3.117	1.037	0.418-2.573	1.195	0.478-2.987
	ACE INHIBITORS, PLAIN	1.038	0.858-1.256	1.119	0.918-1.364	0.928	0.764-1.127
	ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	3.381	0.955-11.962	1.025	0.460-2.282	3.298	1.145-9.498
	ANGIOTENSIN II ANTAGONISTS, PLAIN	1.262	0.865-1.843	1.186	0.846-1.663	1.064	0.743-1.523
	OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM						
ANTIHYPERTENSIVES	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	1.230	0.545-2.774	1.582	0.692-3.618	0.777	0.342-1.765
	ANTIADRENERGIC AGENTS, GANGLION-BLOCKING						
	ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	0.962	0.443-2.091	0.953	0.451-2.013	1.009	0.471-2.163
	ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION						
	ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON			1.551	0.253-9.519		
	COMBINATIONS OF ANTIHYPERTENSIVES IN ATC-GR. C02						
	OTHER ANTIHYPERTENSIVES						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 6: Summary Analysis CCO vs. CTC: Cardiovascular system (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
BETA BLOCKING AGENTS	BETA BLOCKING AGENTS	0.956	0.781-1.169	0.975	0.810-1.174	0.980	0.808-1.190
	BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES						
	BETA BLOCKING AGENTS AND OTHER DIURETICS	7.000	0.058-851.424	0.361	0.033-3.896	19.405	0.439-857.887
	BETA BLOCKING AGENTS AND THIAZIDES						
	BETA BLOCKING AGENTS AND VASODILATORS						
	BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS						
CALCIUM CHANNEL BLOCKERS	CALCIUM CHANNEL BLOCKERS AND DIURETICS						
	NON-SELECTIVE CALCIUM CHANNEL BLOCKERS						
	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECT	1.145	0.873-1.501	0.639	0.480-0.850	1.792	1.356-2.367
	SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECT	0.898	0.705-1.144	1.122	0.891-1.412	0.801	0.632-1.014
CARDIAC THERAPY	ANTIARRHYTHMICS, CLASS I AND III	0.978	0.582-1.643	1.866	1.035-3.364	0.524	0.301-0.913
	CARDIAC GLYCOSIDES	0.812	0.575-1.147	0.758	0.543-1.058	1.072	0.764-1.505
	CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES	1.708	0.348-8.382	3.333	0.208-53.294	0.512	0.053-4.910

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 6: Summary Analysis CCO vs. CTC: Cardiovascular system (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
CARDIAC THERAPY CONT.	OTHER CARDIAC PREPARATIONS						
	VASODILATORS USED IN CARDIAC DISEASES	1.062	0.826-1.366	1.022	0.791-1.321	1.040	0.806-1.340
DIURETICS	DIURETICS AND POTASSIUM-SPARING	0.890	0.596-1.329	0.837	0.590-1.188	1.064	0.730-1.550
	HIGH-CEILING DIURETICS	1.182	0.928-1.504	0.871	0.664-1.142	1.356	1.049-1.753
	LOW-CEILING DIURETICS, EXCL. THIAZIDES	0.685	0.419-1.119	0.724	0.474-1.108	0.945	0.597-1.496
	LOW-CEILING DIURETICS, THIAZIDES	1.445	1.018-2.051	1.010	0.709-1.438	1.431	1.007-2.034
	POTASSIUM-SPARING AGENTS	1.916	1.052-3.490	0.965	0.430-2.165	1.986	0.975-4.047
PERIPHERAL VASODILATORS	PERIPHERAL VASODILATORS	1.390	1.143-1.689	3.091	0.051-187.818	1.218	1.007-1.472
SERUM LIPID REDUCING AGENTS	CHOLESTEROL AND TRIGLYCERIDE REDUCERS	7.426	0.192-286.500	1.141	0.949-1.372	2.402	0.049-117.100
VASOPROTECTIVES	ANTIHEMORRHOIDALS FOR TOPICAL USE	0.644	0.257-1.616	1.394	0.599-3.249	0.462	0.191-1.117
	ANTIVARICOSE THERAPY	3.200	0.090-113.341				
	CAPILLARY STABILIZING AGENTS						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 7: Summary Analysis CCO vs. CTC: Dermatologicals

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTI-ACNE PREPARATIONS	ANTI-ACNE PREPARATIONS FOR SYSTEMIC USE						
	ANTI-ACNE PREPARATIONS FOR TOPICAL USE						
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL	ANTIBIOTICS AND CHEMOTHERAPEUTICS, COMBINATIONS						
	ANTIBIOTICS FOR TOPICAL USE	0.509	0.218-1.188	0.963	0.431-2.151	0.528	0.231-1.207
	CHEMOTHERAPEUTICS FOR TOPICAL USE	0.423	0.060-2.974	1.081	0.223-5.233	0.392	0.066-2.306
ANTIFUNGALS FOR DERMATOLOGICAL USE	ANTIFUNGALS FOR SYSTEMIC USE	0.541	0.072-4.080	0.679	0.100-4.598	0.797	0.111-5.703
	ANTIFUNGALS FOR TOPICAL USE	1.133	0.673-1.909	0.581	0.238-1.415	1.952	0.941-4.050
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.						
ANTIPSORIATICS	ANTIPSORIATICS FOR SYSTEMIC USE						
	ANTIPSORIATICS FOR TOPICAL USE	0.466	0.026-8.518	0.221	0.007-7.145	2.113	0.086-52.028

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 7: Summary Analysis CCO vs. CTC: Dermatologicals (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTISEPTICS AND DISINFECTANTS	ANTISEPTICS AND DISINFECTANTS						
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS						
	CORTICOSTEROIDS, COMBINATIONS WITH ANTISEPTICS						
	CORTICOSTEROIDS, OTHER COMBINATIONS	1.250	0.467-3.345	0.221	0.031-1.601	5.651	1.183-26.983
	CORTICOSTEROIDS, PLAIN	0.844	0.593-1.201	0.934	0.663-1.316	0.904	0.638-1.280
EMOLLIENTS AND PROTECTIVES	EMOLLIENTS AND PROTECTIVES	2.077	0.560-7.701	4.736	0.884-25.384	0.438	0.097-1.977
	PROTECTIVES AGAINST UV-RADIATION						
MEDICATED DRESSINGS	MEDICATED DRESSINGS						
OTHER DERMATOLOGICAL PREPARATIONS	OTHER DERMATOLOGICAL PREPARATIONS						
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	CICATRIZANTS						
	ENZYMES						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 8: Summary Analysis CCO vs. CTC: Genito-urinary system and sex hormones

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMB. WITH CORTICOSTER **-Females**	0.892	0.212-3.758	1.237	0.295-5.178	0.721	0.172-3.029
	ANTIINFECTIVES/ANTISEPTICS IN COMBINATION WITH CORTICOSTEROIDS **-Females**						
	CONTRACEPTIVES FOR TOPICAL USE-**Females**						
OTHER GYNECOLOGICALS	OTHER GYNECOLOGICALS-**Females**	1.280	0.106-15.418				
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	OXYTOCICS-**Females**						
	ANDROGENS **-Male**						
	ANDROGENS AND FEMALE SEX HORMONES IN COMBINATION						
	ANTIANDROGENS	0.608	0.165-2.236				
	ESTROGENS	1.146	0.864-1.520	0.920	0.719-1.176	1.246	0.956-1.623
	GONADOTROPINS AND OTHER OVULATION STIMULANTS-**Females**						
	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE-**Females**	0.625	0.280-1.393	0.334	0.143-0.782	1.869	0.818-4.268
	OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	3.072	0.867-10.879	4.086	1.511-11.051	0.752	0.241-2.346
	PROGESTOGENS-**Females**	1.093	0.681-1.753	1.002	0.639-1.570	1.091	0.688-1.730

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 8: Summary Analysis CCO vs. CTC: Genito-urinary system and sex hormones (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM cont.	PROGESTOGENS AND ESTROGENS IN COMBINATION-**Females**						
	DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY -**Males**	1.352	0.841-2.173	0.990	0.644-1.521	1.366	0.869-2.148
UROLOGICALS	OTHER UROLOGICALS, INCL. ANTISPASMODICS	1.045	0.632-1.729	1.408	0.645-3.071	0.742	0.385-1.431
	URINARY ANTISEPTICS AND ANTIINFECTIVES						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 9: Summary Analysis CCO vs. CTC: Musculo-skeletal system

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTIGOUT PREPARATIONS	ANTIGOUT PREPARATIONS	1.196	0.723-1.980	0.854	0.496-1.471	1.400	0.829-2.364
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	1.380	1.151-1.654	1.328	1.090-1.618	1.039	0.860-1.256
	ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION						
	SPECIFIC ANTIRHEUMATIC AGENTS						
DRUGS FOR TREATMENT OF BONE DISEASES	DRUGS AFFECTING MINERALIZATION	1.037	0.733-1.467	0.992	0.626-1.573	1.045	0.695-1.572
MUSCLE RELAXANTS	MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	0.927	0.451-1.907	0.892	0.394-0.394	1.040	0.481-2.247
	MUSCLE RELAXANTS, DIRECTLY ACTING AGENTS						
	MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS						
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM						
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 10: Summary Analysis CCO vs. CTC: Nervous system

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANALGESICS	ANTIMIGRAINE PREPARATIONS	1.045	0.239-4.574	3.219	0.770-13.464	0.324	0.076-1.389
	OPIOIDS	1.135	0.849-1.516	0.875	0.651-1.175	1.298	0.968-1.739
	OTHER ANALGESICS AND ANTIPYRETICS	1.131	0.979-1.305	1.104	0.941-1.297	1.024	0.879-1.192
ANESTHETICS	ANESTHETICS, GENERAL						
	ANESTHETICS, LOCAL						
ANTI-PARKINSON DRUGS	ANTICHOLINERGIC AGENTS	0.699	0.370-1.322	0.832	0.380-1.823	0.840	0.411-1.716
	DOPAMINERGIC AGENTS	0.793	0.477-1.317	0.983	0.469-2.061	0.807	0.428-1.522
ANTIEPILEPTICS	ANTIEPILEPTICS	0.955	0.726-1.255	0.889	0.620-1.277	1.074	0.779-1.479
OTHER NERVOUS SYSTEM DRUGS	ANTISMOKING AGENTS	10.759	2.745-42.167	7.987	1.354-47.114	1.347	0.276-6.564
	ANTIVERTIGO PREPARATIONS	2.250	0.121-41.793	8.654	0.100-747.514	0.260	0.006-11.272
	OTHER NERVOUS SYSTEM DRUGS						
PSYCHOANALEPTICS	PARASYMPATHOMIMETICS			0.968	0.162-5.775		
	ANTI-DEMENTIA DRUGS	1.473	0.202-10.724				
	ANTIDEPRESSANTS	1.226	1.019-1.474	1.205	0.923-1.574	1.018	0.809-1.280
	PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION						
	PSYCHOSTIMULANTS AND NOOTROPICS						
PSYCHOLEPTICS	ANTIPSYCHOTICS	1.225	0.914-1.643	0.942	0.587-1.513	1.300	0.877-1.929
	ANXIOLYTICS	0.993	0.850-1.160	0.929	0.779-1.109	1.069	0.905-1.262
	HYPNOTICS AND SEDATIVES	1.268	0.944-1.703	0.853	0.574-1.267	1.486	1.048-2.108

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 11: Summary Analysis CCO vs. CTC: Respiratory system

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ANTIHISTAMINES FOR SYSTEMIC USE	ANTIHISTAMINES FOR SYSTEMIC USE	1.371	0.222-8.454	0.613	0.082-4.576	2.238	0.329-15.221
COUGH AND COLD PREPARATIONS	COUGH SUPPRESSANTS AND EXPECTORANTS, COMBINATIONS COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRESSANTS OTHER COLD COMBINATION PREPARATIONS	0.998	0.423-2.353	1.080	0.422-2.765	0.923	0.376-2.271
	ADRENERGICS FOR SYSTEMIC USE	0.866	0.538-1.394	0.811	0.431-1.527	1.068	0.610-1.870
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASE	ADRENERGICS, INHALANTS	0.960	0.738-1.250	0.592	0.418-0.837	1.623	1.193-2.209
	OTHER ANTI-ASTHMATICS FOR SYSTEMIC USE	0.882	0.545-1.428	0.475	0.219-1.029	1.859	0.976-3.540
	OTHER ANTI-ASTHMATICS, INHALANTS	0.974	0.742-1.277	0.689	0.482-0.983	1.414	1.031-1.940
NASAL PREPARATIONS	DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE NASAL DECONGESTANTS FOR SYSTEMIC USE	1.055	0.629-1.768	1.520	0.960-2.405	0.694	0.426-1.131
OTHER RESPIRATORY SYSTEM PRODUCTS	OTHER RESPIRATORY SYSTEM PRODUCTS						
THROAT PREPARATIONS	THROAT PREPARATIONS						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 12: Summary Analysis CCO vs. CTC: Sensory organs

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS	ANTIINFECTIVES						
	CORTICOSTEROIDS	4.510	0.438-46.404				
	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION						
	OTHER OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS						
	ANTIGLAUCOMA PREPARATIONS AND MIOTICS	1.146	0.778-1.690	1.283	0.897-1.833	0.894	0.616-1.298
	ANTIINFECTIVES	0.839	0.463-1.520	0.769	0.381-1.550	1.092	0.570-2.092
	ANTIINFLAMMATORY AGENTS	1.288	0.709-2.339	0.428	0.157-1.171	3.008	1.315-6.879
	ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMBINATION						
	DECONGESTANTS AND ANTIALLERGICS						
OPHTHALMOLOGICALS	DIAGNOSTIC AGENTS						
	LOCAL ANESTHETICS						
	MYDRIATICS AND CYCLOPLEGICS	1.083	0.130-8.987	0.553	0.075-4.099	1.958	0.249-15.377
	OCULAR VASCULAR DISORDER						
	OTHER OPHTHALMOLOGICALS	0.311	0.020-4.775	1.583	0.364-6.880	0.196	0.022-1.761
	SURGICAL AIDS						
	ANTIINFECTIVES	1.098	0.109-11.100				
	CORTICOSTEROIDS						
OTOLOGICALS	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION						
	OTHER OTOLOGICALS						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 13: Summary Analysis CCO vs. CTC: Systemic hormonal preparations, excluding sex hormones and insulins

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
CALCIUM HOMEOSTASIS	ANTI-PARATHYROID HORMONES	1.610	0.404-6.420	11.863	3.143-44.776	0.136	0.035-0.527
	PARATHYROID HORMONES						
CORTICOSTEROIDS FOR SYSTEMIC USE	ANTIADRENAL PREPARATIONS						
	CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS						
	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	0.786	0.542-1.140	0.679	0.424-1.088	1.158	0.757-1.770
PANCREATIC HORMONES	GLYCOGENOLYTIC HORMONES						
PITUITARY, HYPOTHALAMIC HORMONES AND ANALOGUES	ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES						
	HYPOTHALAMIC HORMONES						
	POSTERIOR PITUITARY LOBE HORMONES						
THYROID THERAPY	ANTITHYROID PREPARATIONS	4.000	0.300-53.398	0.457	0.036-5.871	8.749	0.668-114.554
	IODINE THERAPY						
	THYROID PREPARATIONS	0.949	0.753-1.197	0.752	0.598-0.946	1.262	1.002-1.590

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 14: Summary Analysis CCO vs. CTC: Various

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
ALL OTHER NON-THERAPEUTIC PRODUCTS	ALL OTHER NON-THERAPEUTIC PRODUCTS						
ALL OTHER THERAPEUTIC PRODUCTS	ALL OTHER THERAPEUTIC PRODUCTS	1.636	0.110-24.284	1.470	0.068-31.601	1.114	0.062-20.011
ALLERGENS	ALLERGENS						
CONTRAST MEDIA	MAGNETIC RESONANCE IMAGING CONTRAST MEDIA						
	ULTRASOUND CONTRAST MEDIA						
	X-RAY CONTRAST MEDIA, IODINATED						
	X-RAY CONTRAST MEDIA, NON-IODINATED						
DIAGNOSTIC AGENTS	OTHER DIAGNOSTIC AGENTS						
	URINE TESTS						
DIAGNOSTIC RADIOPHARMACEUTICALS	CARDIOVASCULAR SYSTEM						
	CENTRAL NERVOUS SYSTEM						
	HEPATIC AND RETICULO ENDOTHELIAL SYSTEM						
	INFLAMMATION AND INFECTION DETECTION						
	OTHER DIAGNOSTIC RADIOPHARMACEUTICALS						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 14: Summary Analysis CCO vs. CTC: Various (Continued)

ATC Level II	ATC Level III	CCO-Cases		CCO-Controls		CTC	
		IRR	95% C.I.	IRR	95% C.I.	OR	95% C.I.
DIAGNOSTIC RADIOPHARMACEUTICALS	RENAL SYSTEM						
	RESPIRATORY SYSTEM						
	SKELETON						
	THYROID						
	TUMOUR DETECTION						
GENERAL NUTRIENTS	DIET FORMULATIONS FOR TREATMENT OF OBESITY						
	INFANT FORMULAS						
	OTHER NUTRIENTS	1.289	0.249-6.670				
	PROTEIN SUPPLEMENTS						
THERAPEUTIC RADIOPHARMACEUTICALS	ANTIINFLAMMATORY AGENTS						
	OTHER THERAPEUTIC RADIOPHARMACEUTICALS						
	PAIN PALLIATION (BONE SEEKING AGENTS)						

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; C.I.=confidence intervals

Table 15: Agreement for Measure of Effect in Alimentary Tract and Metabolism Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIPROPULSIVES	1.342	1.386	Same (pos)
INTESTINAL ANTIINFECTIVES	0.989	0.379	Same (neg)
INTESTINAL ANTIINFLAMMATORY AGENTS	1.671	1.863	Same (pos)
DIGESTIVES, INCL. ENZYMES	0.697	1.000	Neg/pos
DRUGS FOR TREATMENT OF PEPTIC ULCER	1.397	1.469	Same (pos)
PROPULSIVES	1.060	1.191	Same (pos)
INSULINS AND ANALOGUES	0.859	2.483	Neg/pos
ORAL BLOOD GLUCOSE LOWERING DRUGS	0.929	1.145	Neg/pos
LAXATIVES	0.705	0.239	Same (neg)
CALCIUM	4.042	0.675	Pos/neg
POTASSIUM	1.249	1.300	Same (pos)
VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	1.597	1.574	Same (pos)
VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN B6 AND B12	0.947	2.107	Neg/pos

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	6	4	0.198	0.416
	Negative	1	2		

Agreement: 8/13=61.5%; CCO is 4.0 times more likely to produce negative association

Table 16: Agreement for Measure of Effect in Antiinfectives for Systemic use Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
BETA-LACTAM ANTIBACTERIALS, PENICILLINS	0.399	0.469	Same (neg)
MACROLIDES AND LINCOSAMIDES	0.575	0.529	Same (neg)
OTHER ANTIBACTERIALS	0.996	1.187	Neg/pos
OTHER BETA-LACTAM ANTIBACTERIALS	1.282	1.647	Same (pos)
QUINOLONE ANTIBACTERIALS	0.988	1.081	Neg/pos
SULFONAMIDES AND TRIMETHOPRIM	1.524	1.515	Same (pos)
TETRACYCLINES	0.227	0.452	Same (neg)
ANTIMYCOTICS FOR SYSTEMIC USE	2.878	0.489	Pos/neg
DIRECT ACTING ANTIVIRALS	2.545	2.519	Same (pos)

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	3	2	0.341	0.294
	Negative	1	3		

Agreement: 6/9=66.7%
CCO is 2.0 times more likely to produce negative association

Table 17: Agreement for Measure of Effect in Antineoplastic and Immunomodulating Agents Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ALKYLATING AGENTS	0.901	1.012	Neg/pos
ANTIMETABOLITES	0.531	0.204	Same (neg)
HORMONE ANTAGONISTS AND RELATED AGENTS	0.890	1.042	Neg/pos
HORMONES AND RELATED AGENTS	0.710	0.240	Same (neg)

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	0	2	NC	NC
	Negative	0	2		

Agreement: 2/4=50.0%
NC=Non computable

Table 18: Agreement for Measure of Effect in Blood and Blood Forming Organs Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
IRON PREPARATIONS	1.308	4.540	Same (pos)
OTHER ANTIANEMIC PREPARATIONS	1.877	1.194	Same (pos)
VITAMIN B12 AND FOLIC ACID	1.253	0.668	Pos/neg
ANTITHROMBOTIC AGENTS	1.410	0.985	Pos/neg

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	2	0	NC	NC
	Negative	2	0		

Agreement: 2/4=50.0%
NC=Non computable

Table 19: Agreement for Measure of Effect in Cardiovascular System Class

ATC Level II	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ACE INHIBITORS, COMBINATIONS	1.239	1.195	Same (pos)
ACE INHIBITORS, PLAIN	1.038	0.928	Pos/neg
ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	3.381	3.298	Same (pos)
ANGIOTENSIN II ANTAGONISTS, PLAIN	1.262	1.064	Same (pos)
ANTIADRENERGIC AGENTS, CENTRALLY ACTING	1.230	0.777	Pos/neg
ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	0.962	1.009	Neg/pos
BETA BLOCKING AGENTS	0.956	0.980	Same (neg)
BETA BLOCKING AGENTS AND OTHER DIURETICS	7.000	19.405	Same (pos)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECT	1.145	1.792	Same (pos)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECT	0.898	0.801	Same (neg)
ANTIARRHYTHMICS, CLASS I AND III	0.978	0.524	Same (neg)
CARDIAC GLYCOSIDES	0.812	1.072	Neg/pos
CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES	1.708	0.512	Pos/neg
VASODILATORS USED IN CARDIAC DISEASES	1.062	1.040	Same (pos)
DIURETICS AND POTASSIUM-SPARING	0.890	1.064	Neg/pos
HIGH-CEILING DIURETICS	1.182	1.356	Same (pos)
LOW-CEILING DIURETICS, EXCL. THIAZIDES	0.685	0.945	Same (neg)
LOW-CEILING DIURETICS, THIAZIDES	1.445	1.431	Same (pos)
POTASSIUM-SPARING AGENTS	1.916	1.986	Same (pos)
PERIPHERAL VASODILATORS	1.390	1.218	Same (pos)
CHOLESTEROL AND TRIGLYCERIDE REDUCERS	7.426	2.402	Same (pos)
ANTIHEMORRHOIDALS FOR TOPICAL USE	0.644	0.462	Same (neg)

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

Table 19: Agreement for Measure of Effect in Cardiovascular System Class (Continued)

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	11	3	0.411	0.054
	Negative	3	5		

Agreement: 16/22=72.7%

Table 20: Agreement for Measure of Effect in Dermatologicals Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIBIOTICS FOR TOPICAL USE	0.509	0.528	Same (neg)
CHEMOTHERAPEUTICS FOR TOPICAL USE	0.423	0.392	Same (neg)
ANTIFUNGALS FOR SYSTEMIC USE	0.541	0.797	Same (neg)
ANTIFUNGALS FOR TOPICAL USE	1.133	1.952	Same (pos)
ANTIPSORIATICS FOR TOPICAL USE	0.466	2.113	Neg/pos
CORTICOSTEROIDS, OTHER COMBINATIONS	1.250	5.651	Same (pos)
CORTICOSTEROIDS, PLAIN	0.844	0.904	Same (neg)
EMOLLIENTS AND PROTECTIVES	2.077	0.438	Pos/neg

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	2	1	0.467	0.187
	Negative	1	4		

Agreement: 6/8=75.0%

Table 21: Agreement for Measure of Effect in Genito-urinary System and Sex Hormones Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIINFECTIVES AND ANTISEPTICS, EXCL. COMB. WITH CORTICOSTER -**Females**	0.892	0.721	Same (neg)
ESTROGENS	1.146	1.246	Same (pos)
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE-**Females**	0.625	1.869	Neg/pos
OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	3.072	0.752	Pos/neg
PROGESTOGENS-**Females**	1.093	1.091	Same (pos)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY -**Males**	1.352	1.366	Same (pos)
OTHER UROLOGICALS, INCL. ANTISPASMODICS	1.045	0.742	Pos/neg

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	3	1	0.087	0.809
	Negative	2	1		

Agreement: 4/7=57.1%
CCO: 2.0 times more likely to produce positive association

Table 22: Agreement for Measure of Effect in Musculo-skeletal System Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIGOUT PREPARATIONS	1.196	1.400	Same (pos)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	1.380	1.039	Same (pos)
DRUGS AFFECTING MINERALIZATION	1.037	1.045	Same (pos)
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	0.927	1.040	Neg/Pos

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	3	1	NC	NC
	Negative	0	0		

Agreement: 3/4=75.0%
NC=Non computable

Table 23: Agreement for Measure of Effect in Nervous System Class

ATC Level II	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIMIGRAINE PREPARATIONS	1.045	0.324	Pos/neg
OPIOIDS	1.135	1.298	Same (pos)
OTHER ANALGESICS AND ANTIPYRETICS	1.131	1.024	Same (pos)
ANTICHOLINERGIC AGENTS	0.699	0.840	Same (neg)
DOPAMINERGIC AGENTS	0.793	0.807	Same (neg)
ANTIEPILEPTICS	0.955	1.074	Neg/pos
ANTISMOKING AGENTS	10.759	1.347	Same (pos)
ANTIVERTIGO PREPARATIONS	2.250	0.260	Pos/neg
ANTIDEPRESSANTS	1.226	1.018	Same (pos)
ANTIPSYCHOTICS	1.225	1.300	Same (pos)
ANXIOLYTICS	0.993	1.069	Neg/pos
HYPNOTICS AND SEDATIVES	1.268	1.486	Same (pos)

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	6	2	0.250	0.386
	Negative	2	2		

Agreement: 8/12=66.7%

Table 24: Agreement for Measure of Effect in Respiratory System Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIHISTAMINES FOR SYSTEMIC USE	1.371	2.238	Same (pos)
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS	0.998	0.923	Same (neg)
ADRENERGICS FOR SYSTEMIC USE	0.866	1.068	Neg/pos
ADRENERGICS, INHALANTS	0.960	1.623	Neg/pos
OTHER ANTI-ASTHMATICS FOR SYSTEMIC USE	0.882	1.859	Neg/pos
OTHER ANTI-ASTHMATICS, INHALANTS	0.974	1.414	Neg/pos
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE	1.055	0.694	Pos/neg

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	1	4	-0.207	0.427
	Negative	1	1		

Agreement: 2/7=28.6%
CCO is 4.0 times more likely to produce negative association

Table 25: Agreement for Measure of Effect in Sensory Organs Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTIGLAUCOMA PREPARATIONS AND MIOTICS	1.146	0.894	Pos/neg
ANTIINFECTIVES	0.839	1.092	Neg/pos
ANTIINFLAMMATORY AGENTS	1.288	3.008	Same (pos)
MYDRIATICS AND CYCLOPLEGICS	1.083	1.958	Same (pos)
OTHER OPHTHALMOLOGICALS	0.311	0.196	Same (neg)

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	2	1	0.167	0.709
	Negative	1	1		

Agreement: 3/5=60.0%

Table 26: Agreement for Measure of Effect in Systemic Hormonal Preparations, excl. sex hormones and insulins Class

ATC Level III	Measure of Effect		Direction
	CCO (IRR)	CTC (OR)	
ANTI-PARATHYROID HORMONES	1.610	0.136	Pos/neg
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	0.786	1.158	Neg/pos
ANTITHYROID PREPARATIONS	4.000	8.749	Same (pos)
THYROID PREPARATIONS	0.949	1.262	Neg/pos

CCO=case-crossover; CTC=case-time-control; IRR=incidence rate ratio; OR=odds ratio; Pos=positive association; Neg=negative association

		CCO		Kappa Statistic	P-value
		Positive	Negative		
CTC	Positive	1	2	-0.500	0.248
	Negative	1	0		

Agreement: 1/4=25.0%
CCO is 2.0 times more likely to produce negative association

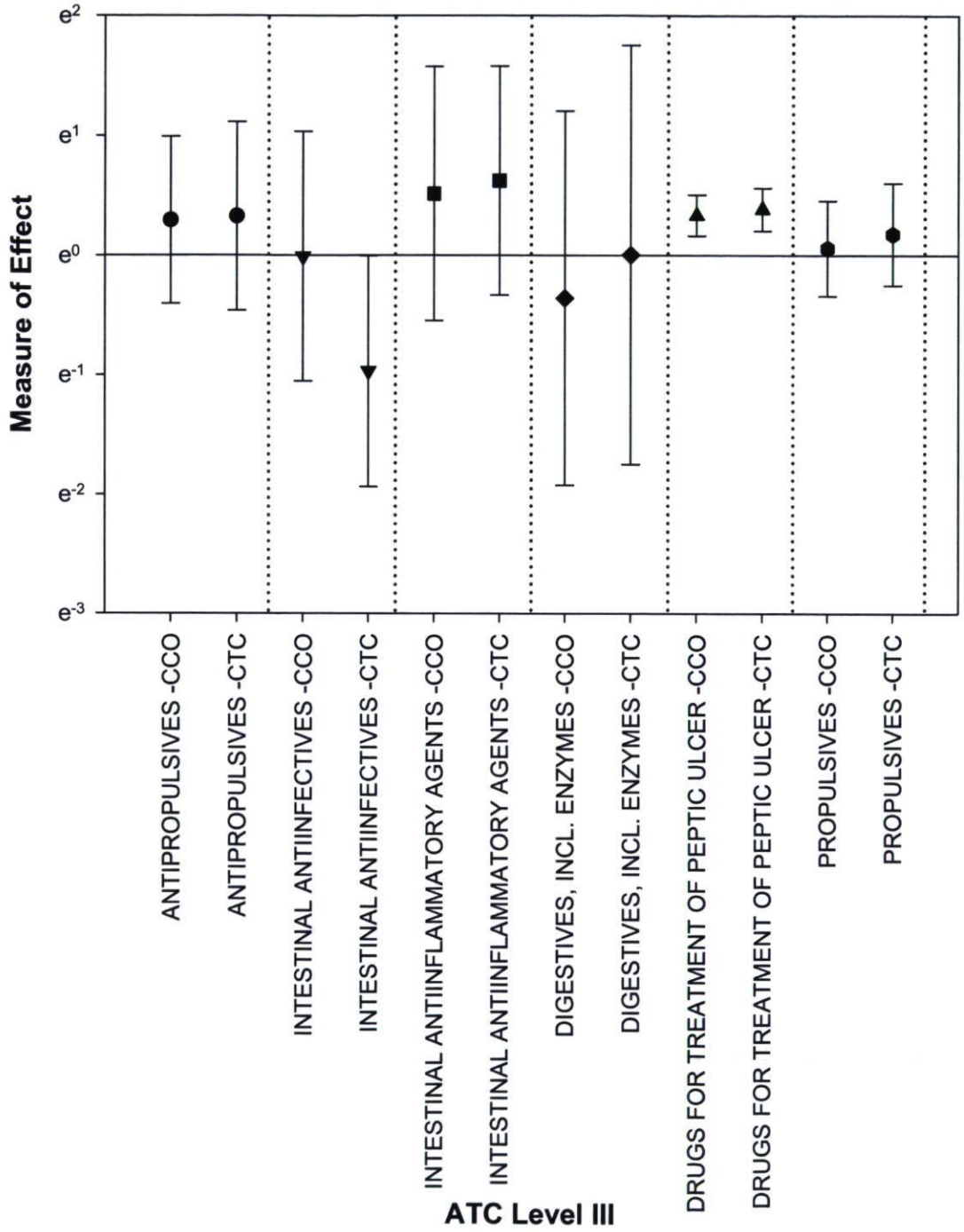
Table 27: Agreement for Measure of Effect in all ATC Level III medications [1]

		CCO		Kappa Statistic	P-value
		Positive	**Negative**		
CTC	**Positive**	42	23	0.219	0.026[2]
	Negative	15	21		

Agreement: 63/101=62.4%
CCO is 1.5 times more likely to produce negative association

[1] The ATC Level I class for Antiparasitic products, insecticides and repellents and Various have also been included in the agreement calculation above
[2] Statistically significant associations are marked with a *

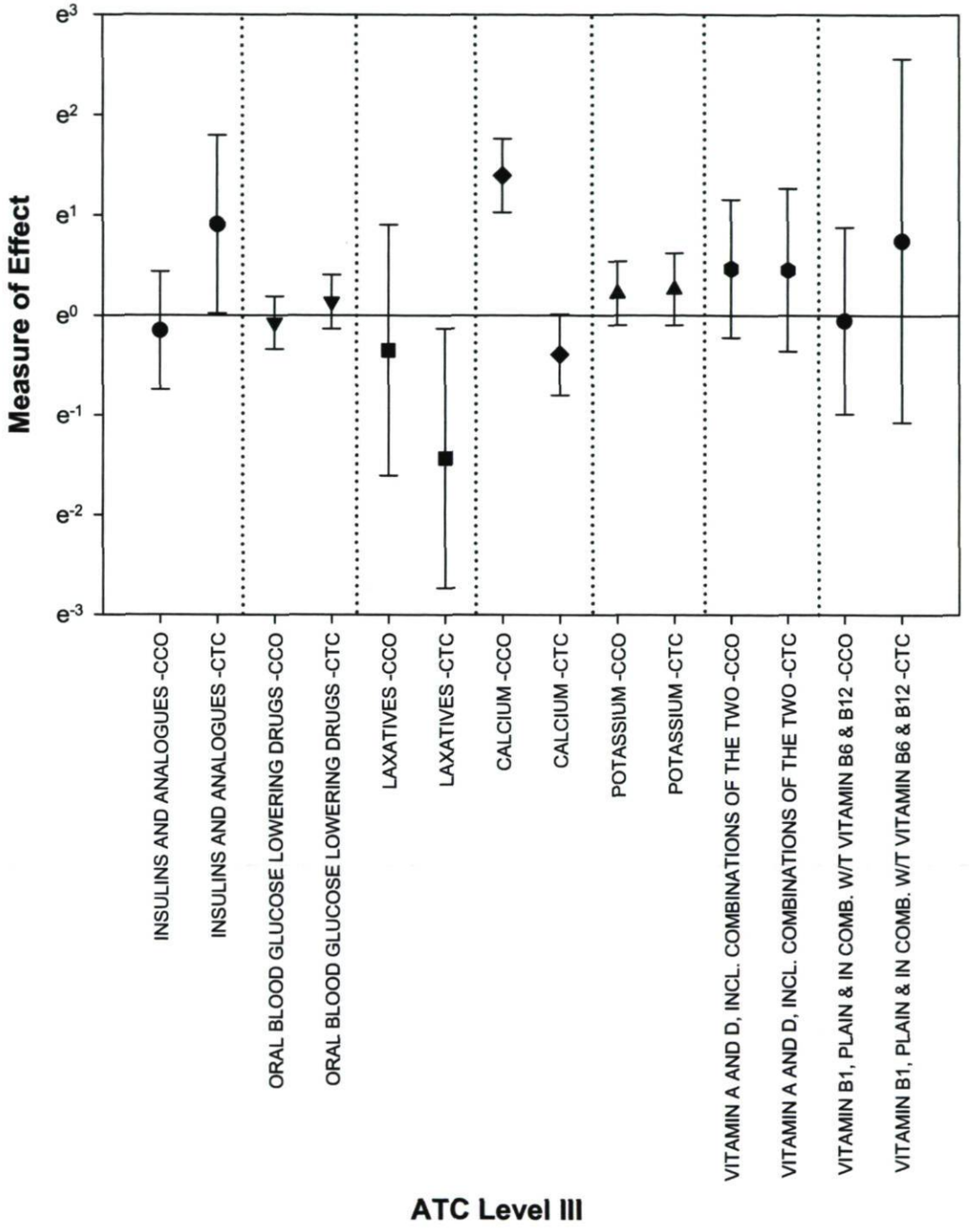
Figure 1: CCO vs. CTC Measure of Effect in Alimentary Tract and Metabolism Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

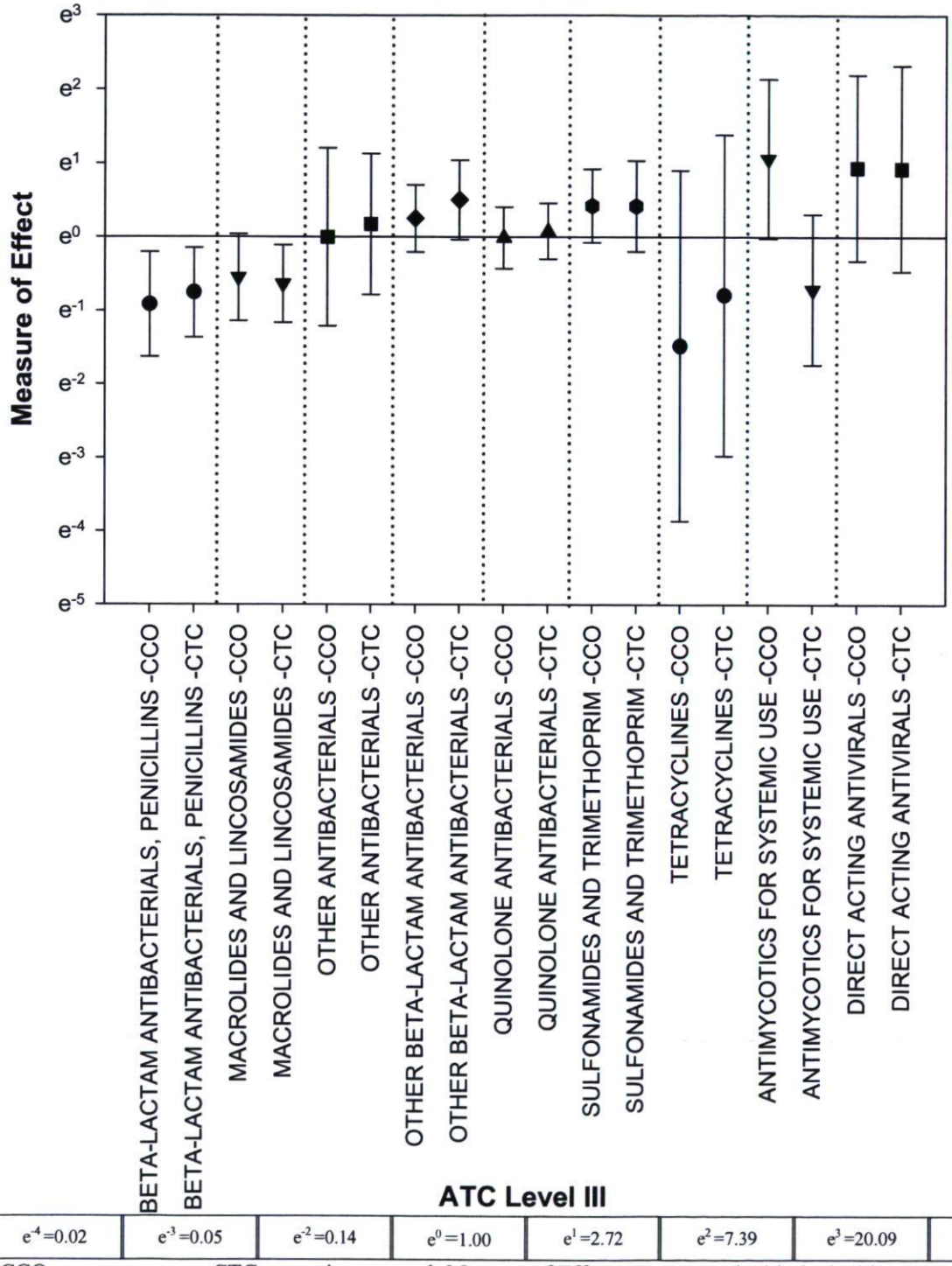
Figure 2: CCO vs. CTC Measure of Effect in Alimentary Tract and Metabolism Class (Continued)



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC.

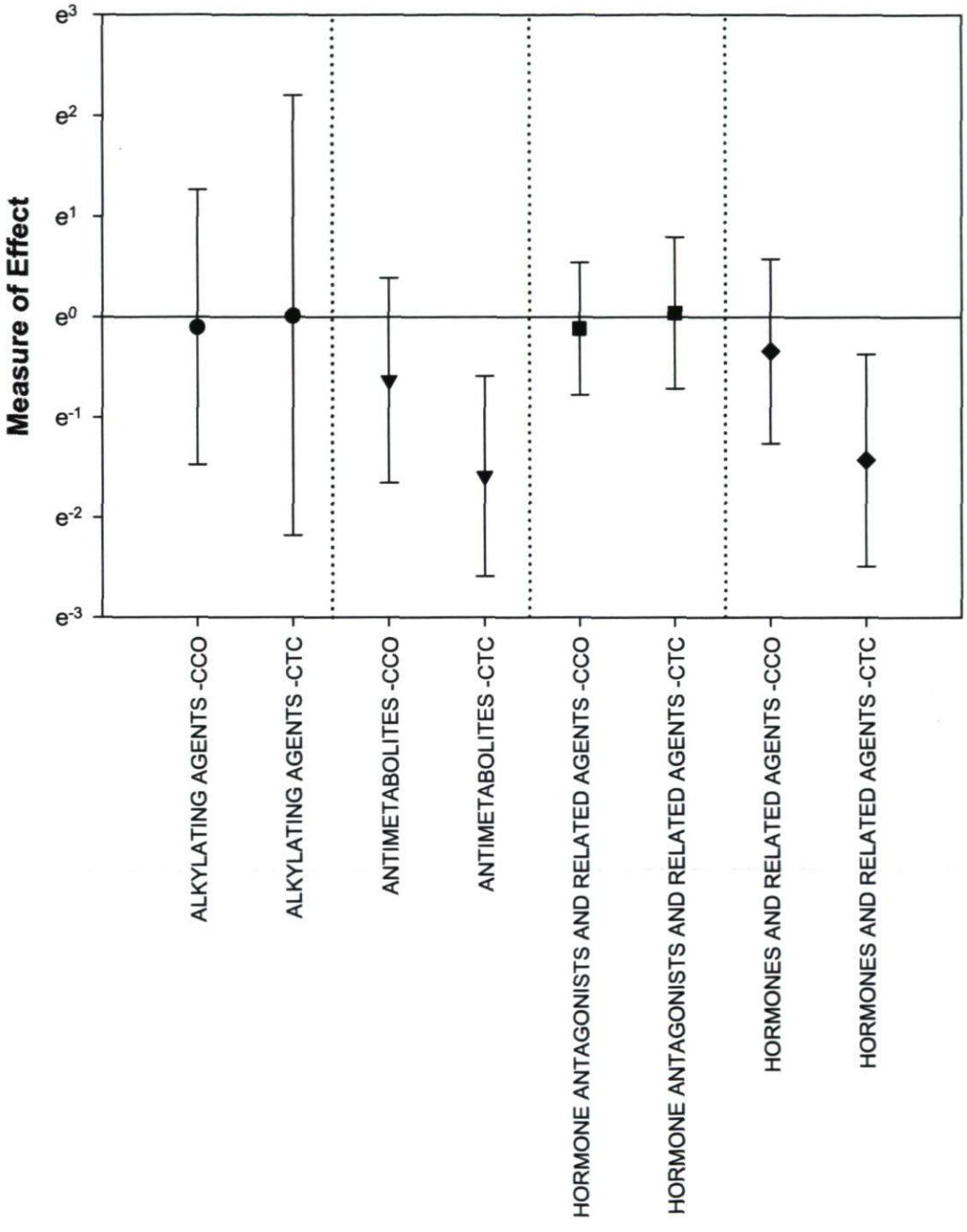
Figure 3: CCO vs. CTC Measure of Effect in Anti-infectives for Systemic Use Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC.

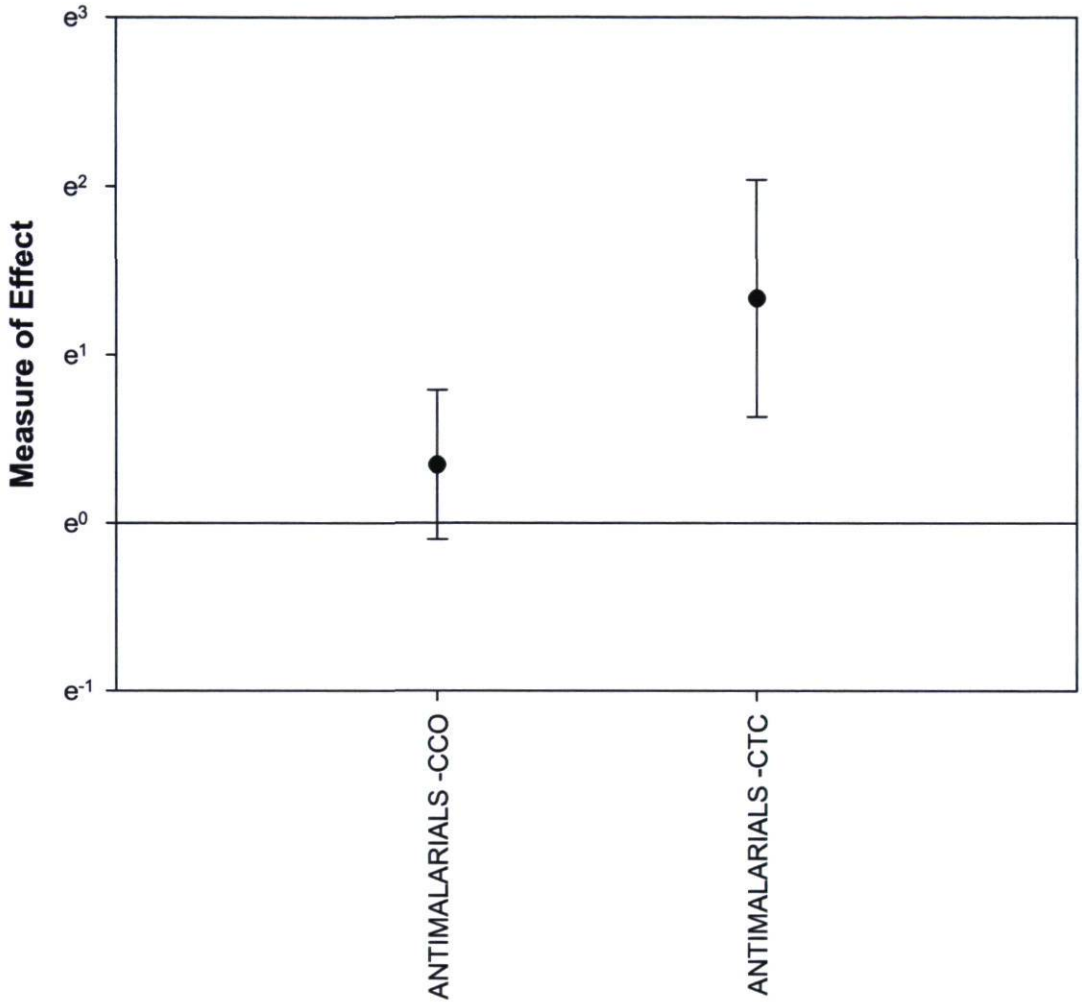
Figure 4: CCO vs. CTC Measure of Effect in Antineoplastic and Immunomodulating Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

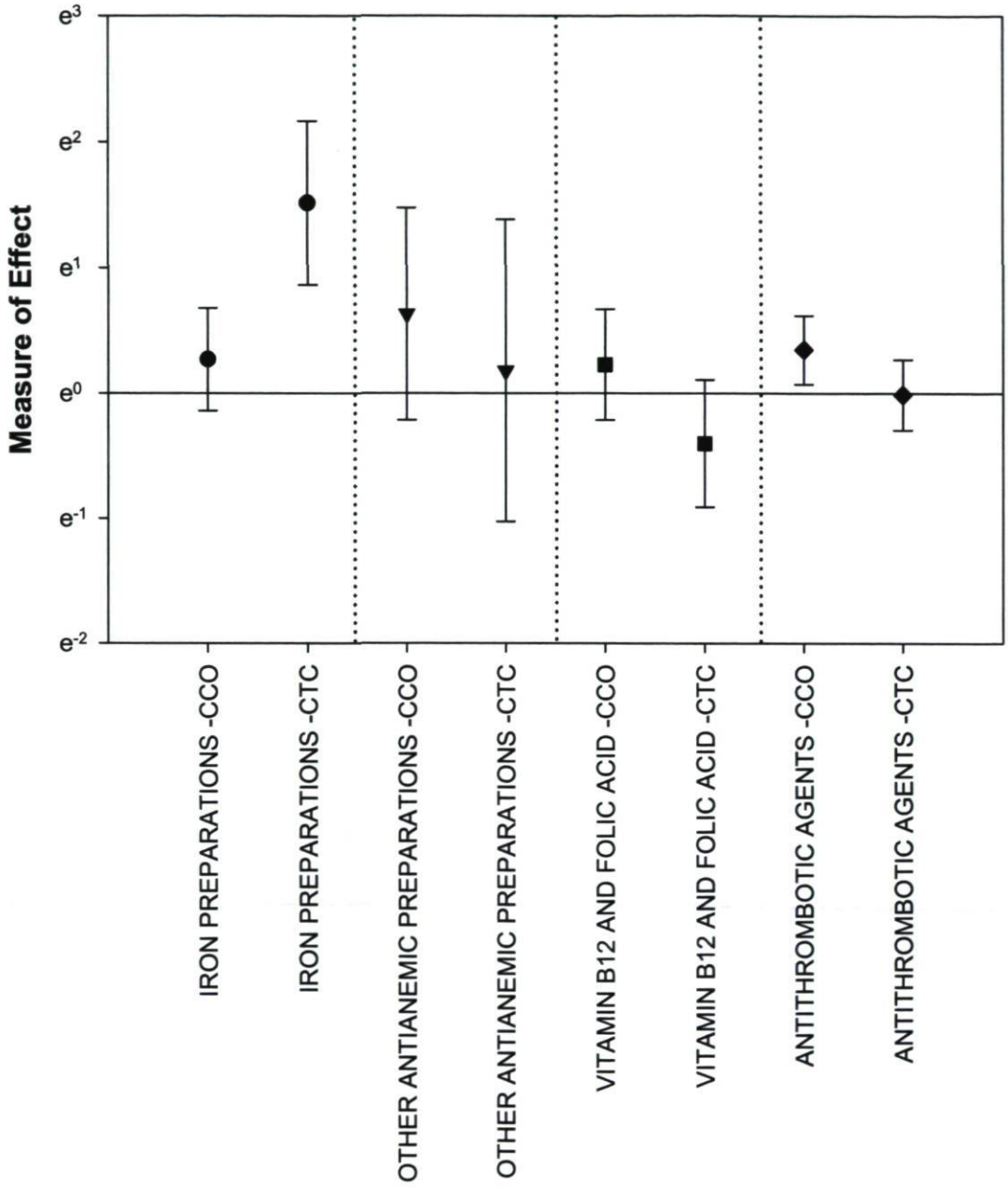
Figure 5: CCO vs. CTC Measure of Effect in Antiparasitic products, insecticides and repellents Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

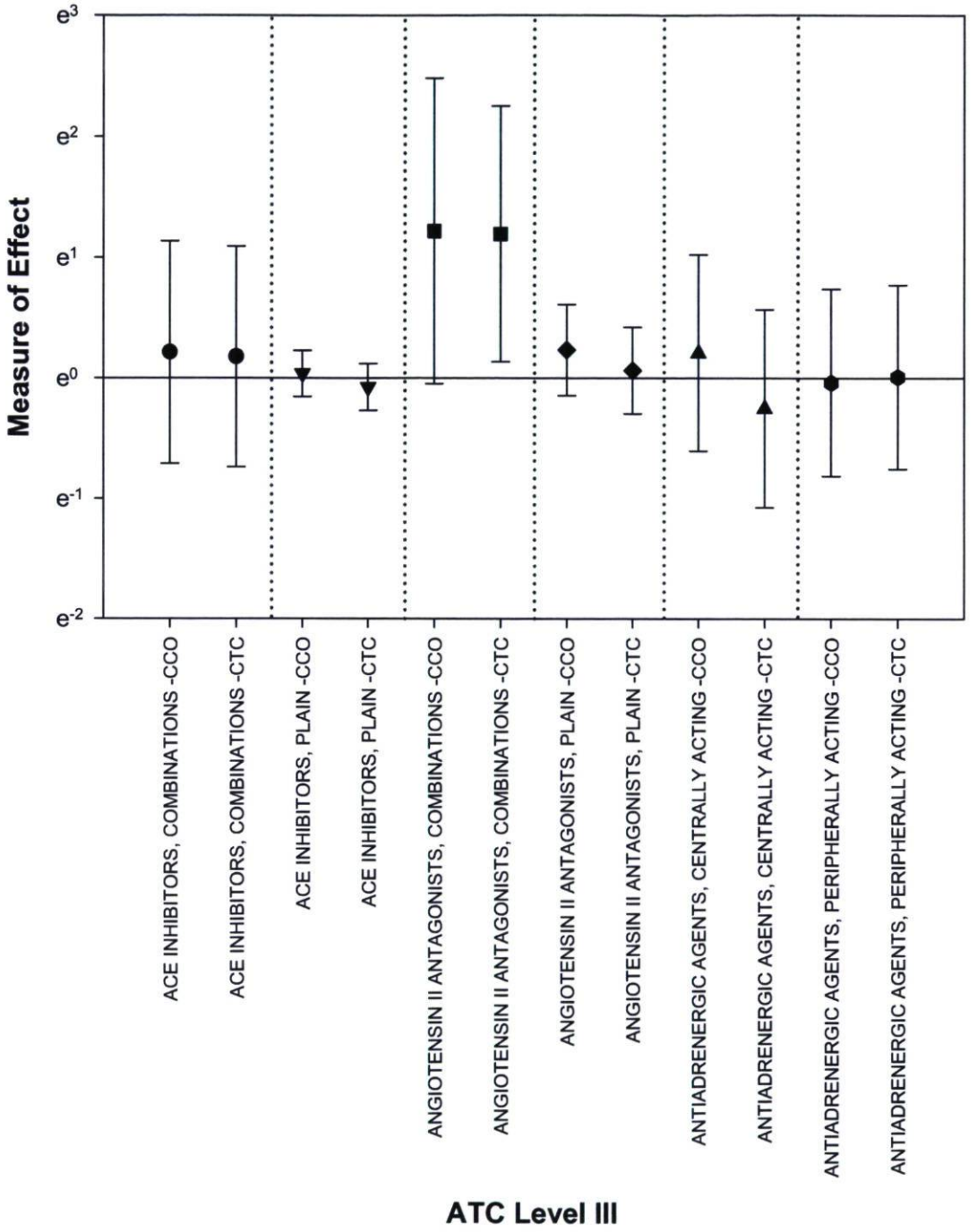
Figure 6: CCO vs. CTC Measure of Effect in Blood and blood forming organs Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

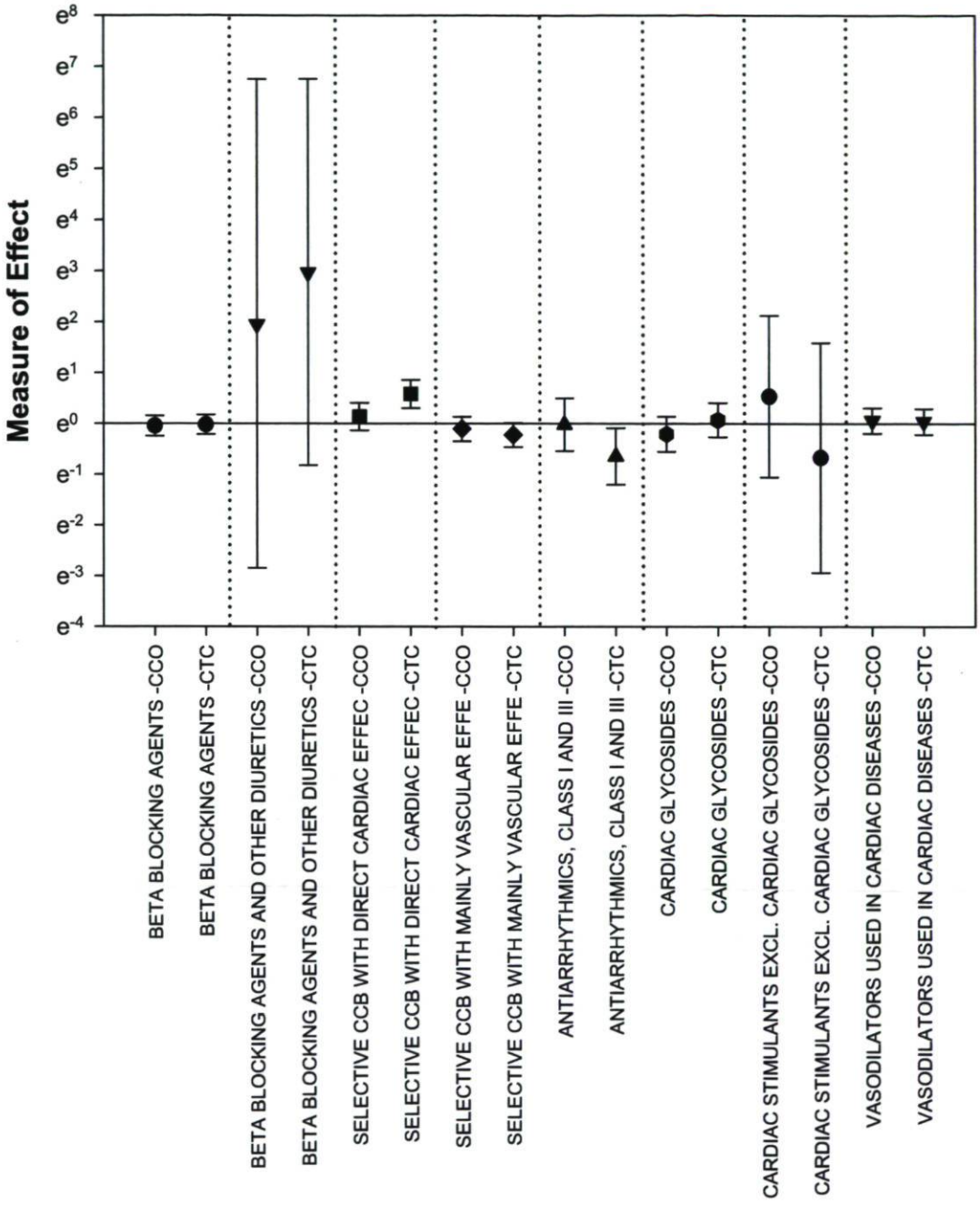
Figure 7: CCO vs. CTC Measure of Effect in Cardiovascular system Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

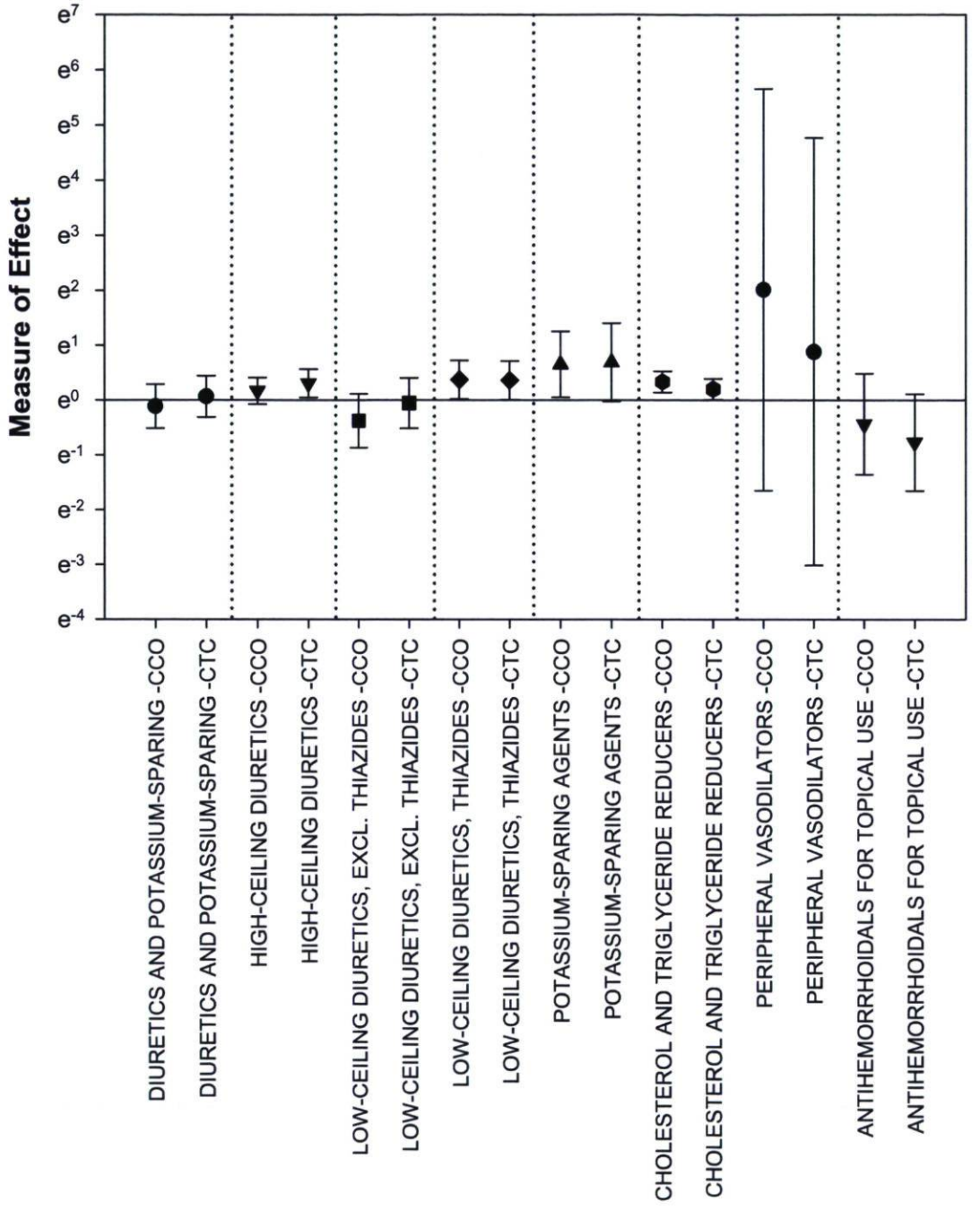
Figure 8: CCO vs. CTC Measure of Effect in Cardiovascular system Class (Continued)



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

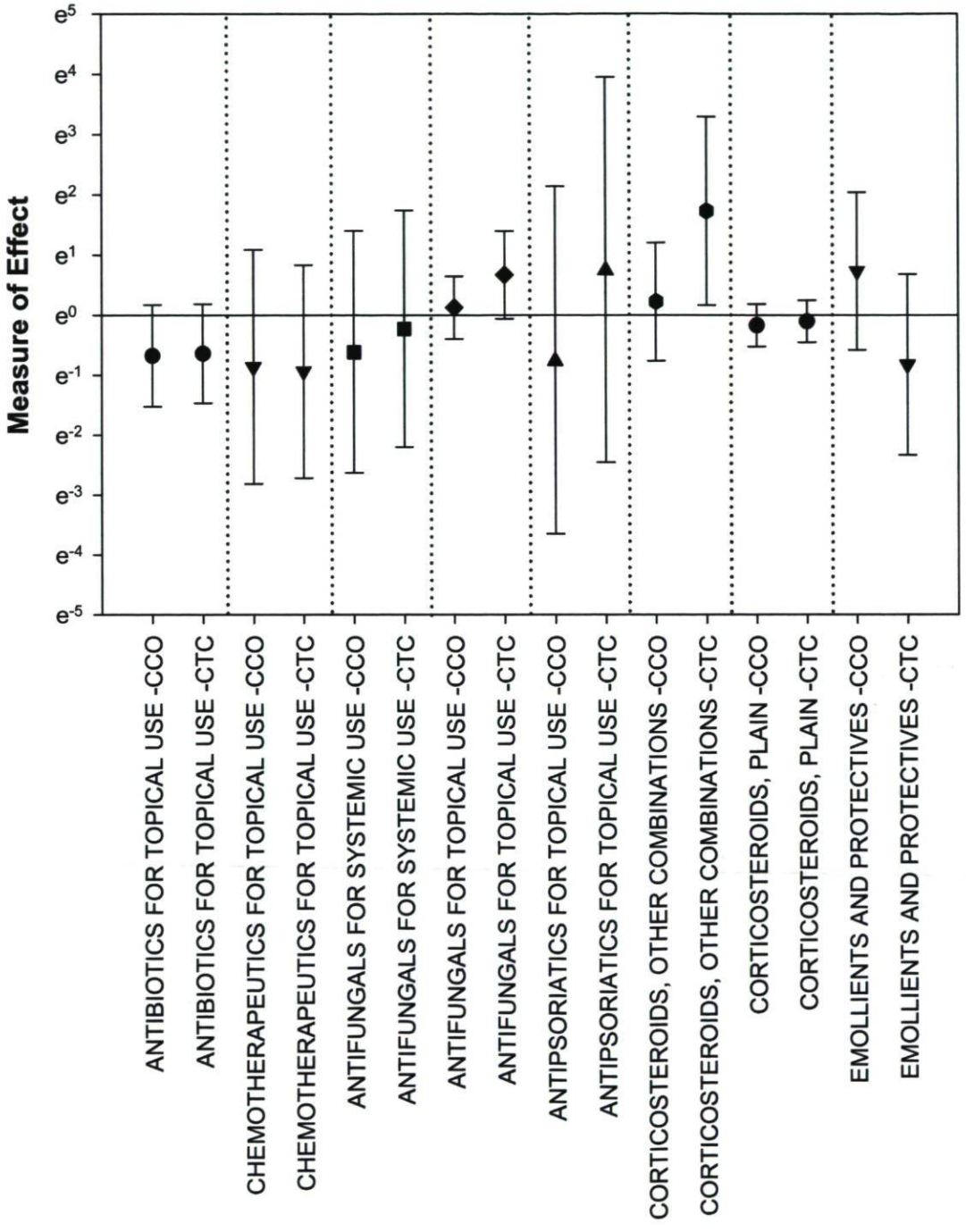
Figure 9: CCO vs. CTC Measure of Effect in Cardiovascular system Class (Continued)



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

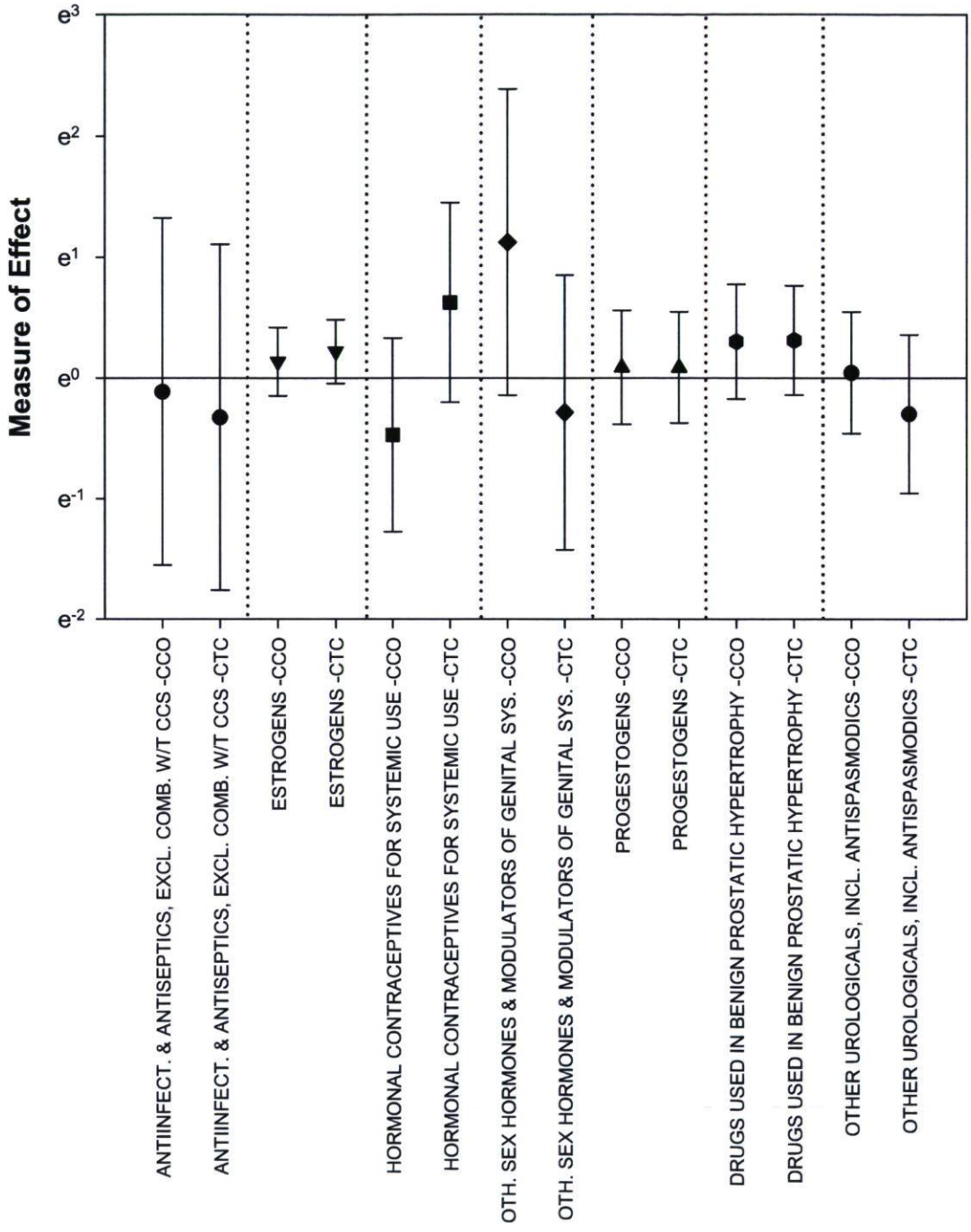
Figure 10: CCO vs. CTC Measure of Effect in Dermatological preparations Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

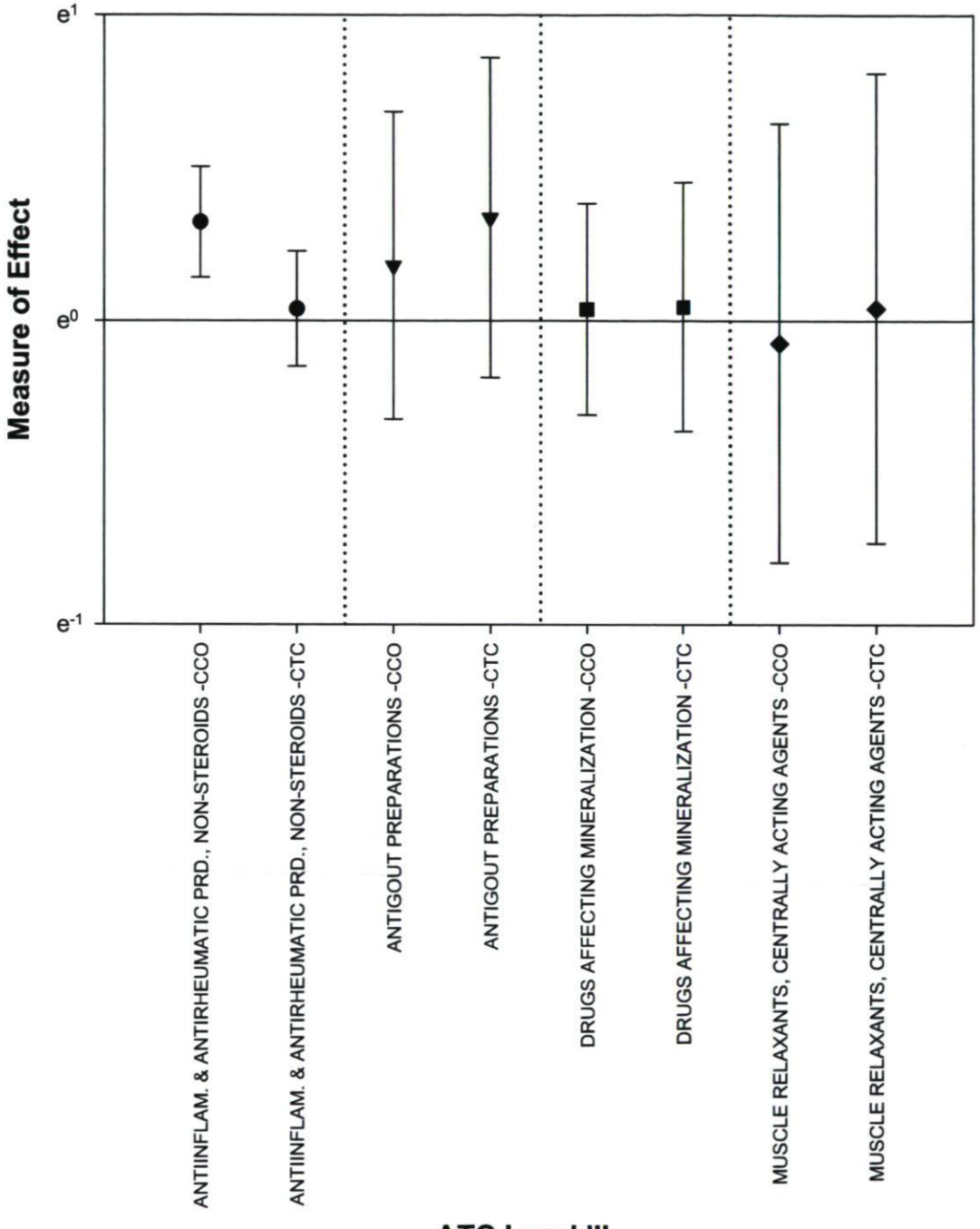
Figure 11: CCO vs. CTC Measure of Effect in Genito-urinary system and sex hormones Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

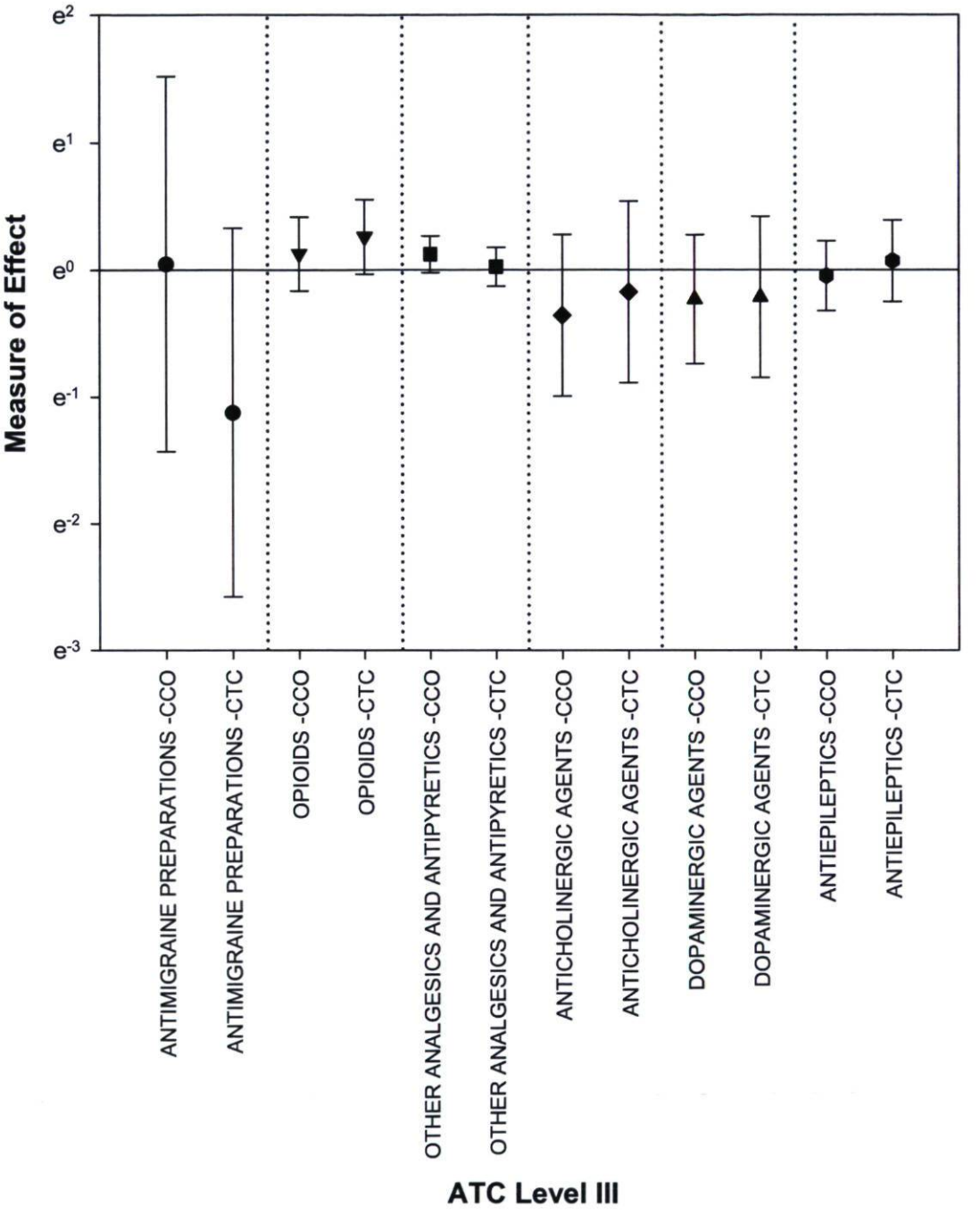
Figure 12: CCO vs. CTC Measure of Effect in Musculo-skeletal system Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

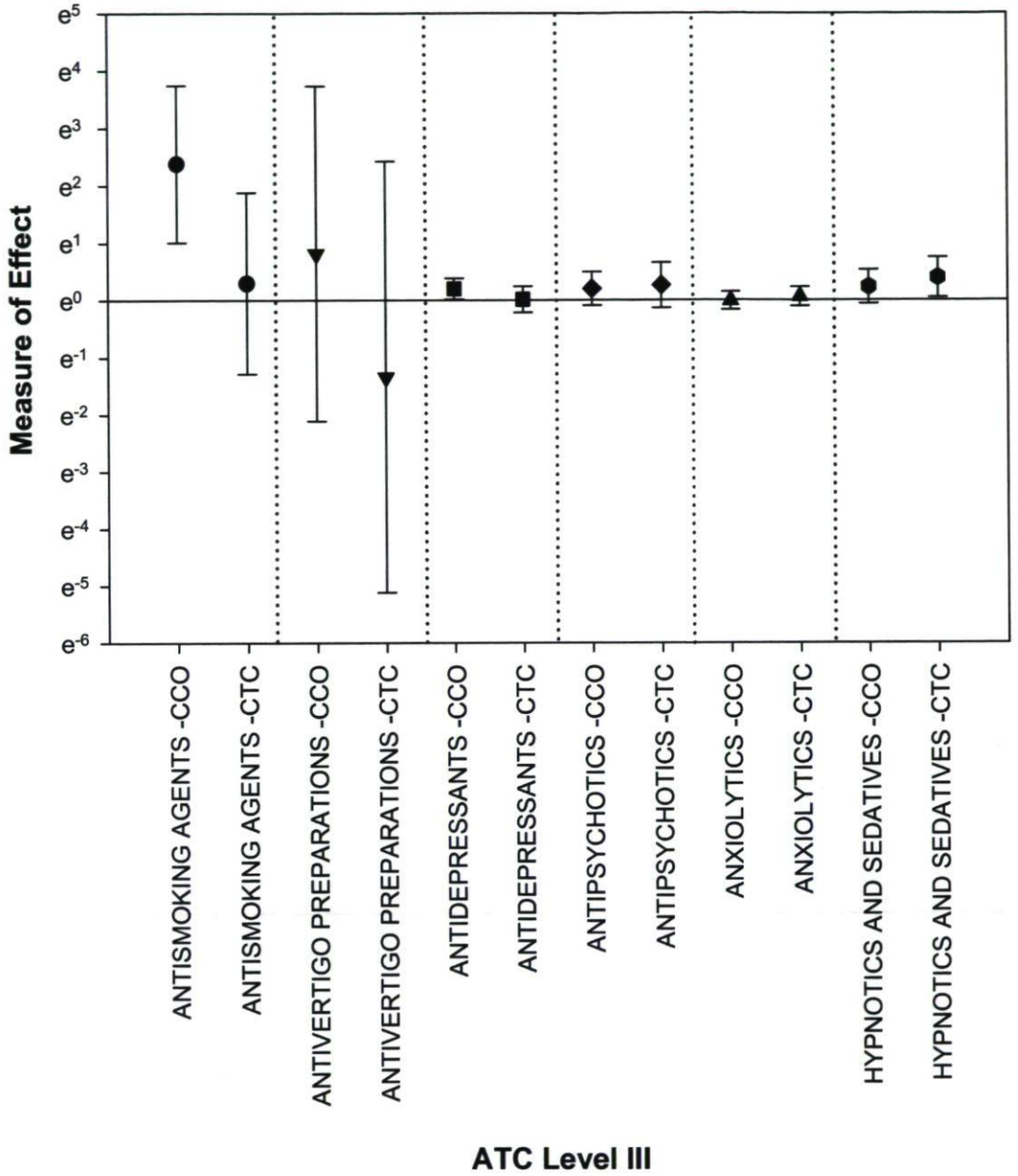
Figure 13: CCO vs. CTC Measure of Effect in Nervous system Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

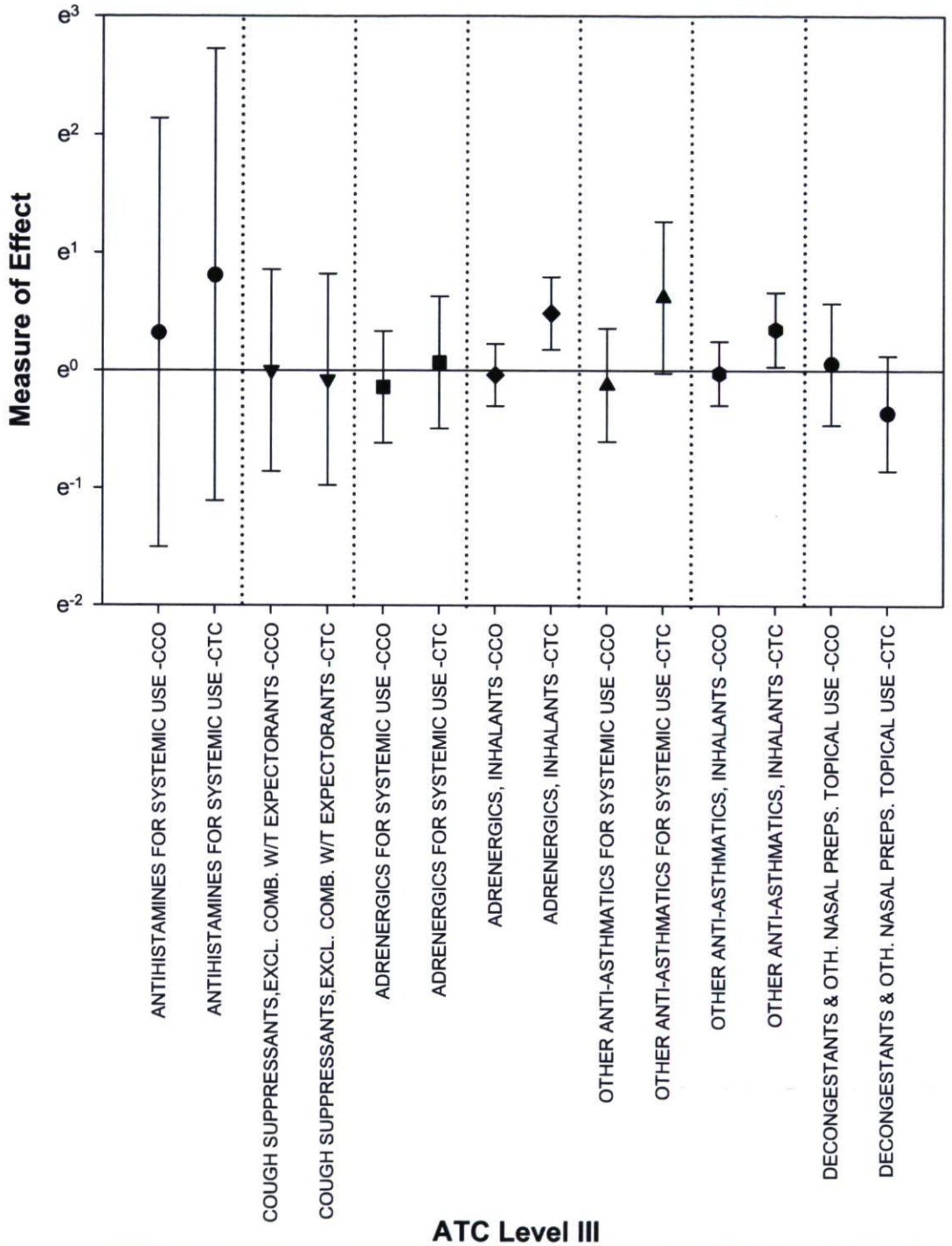
Figure 14: CCO vs. CTC Measure of Effect in Nervous system Class (Continued)



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

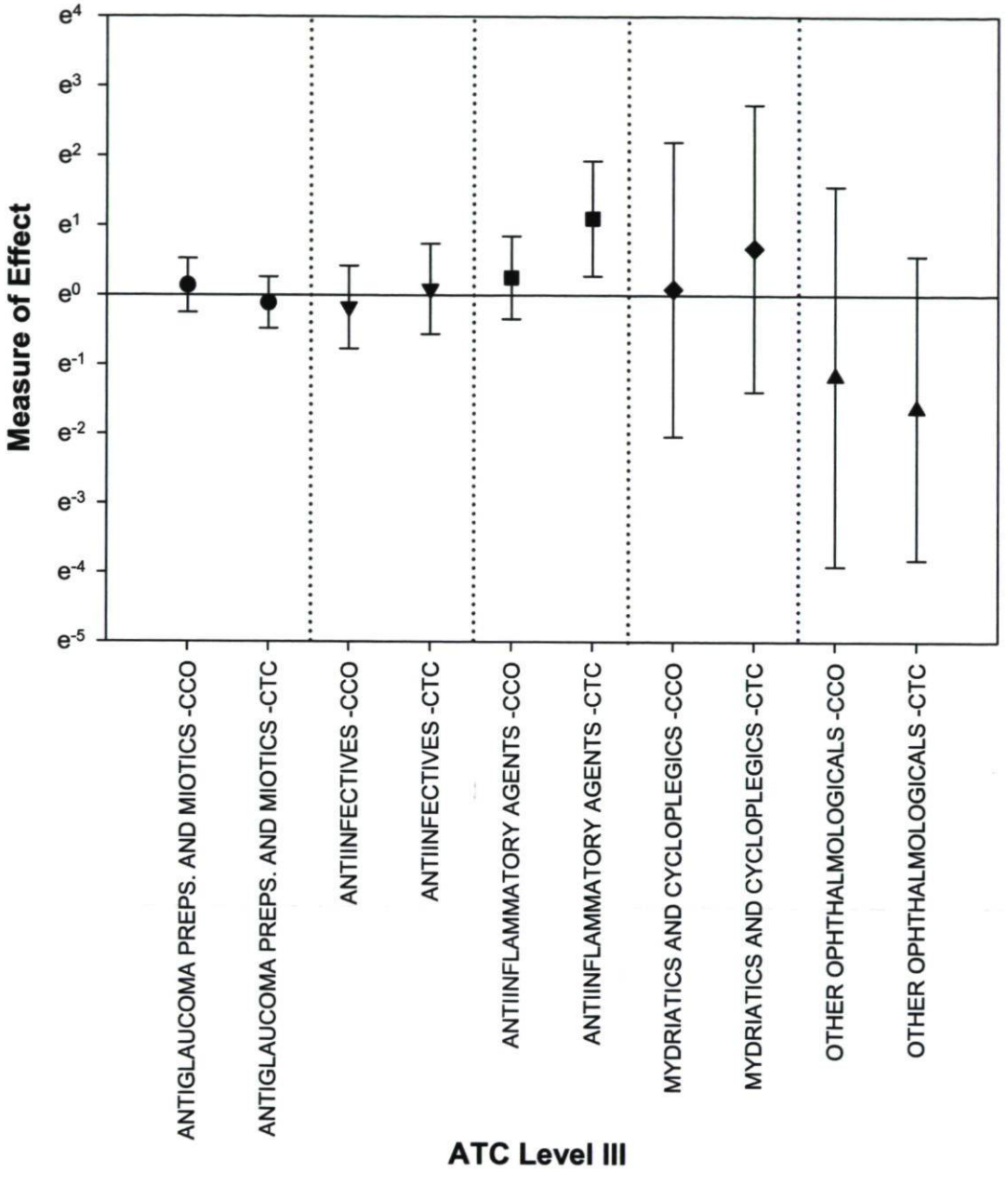
Figure 15: CCO vs. CTC Measure of Effect in Respiratory system Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

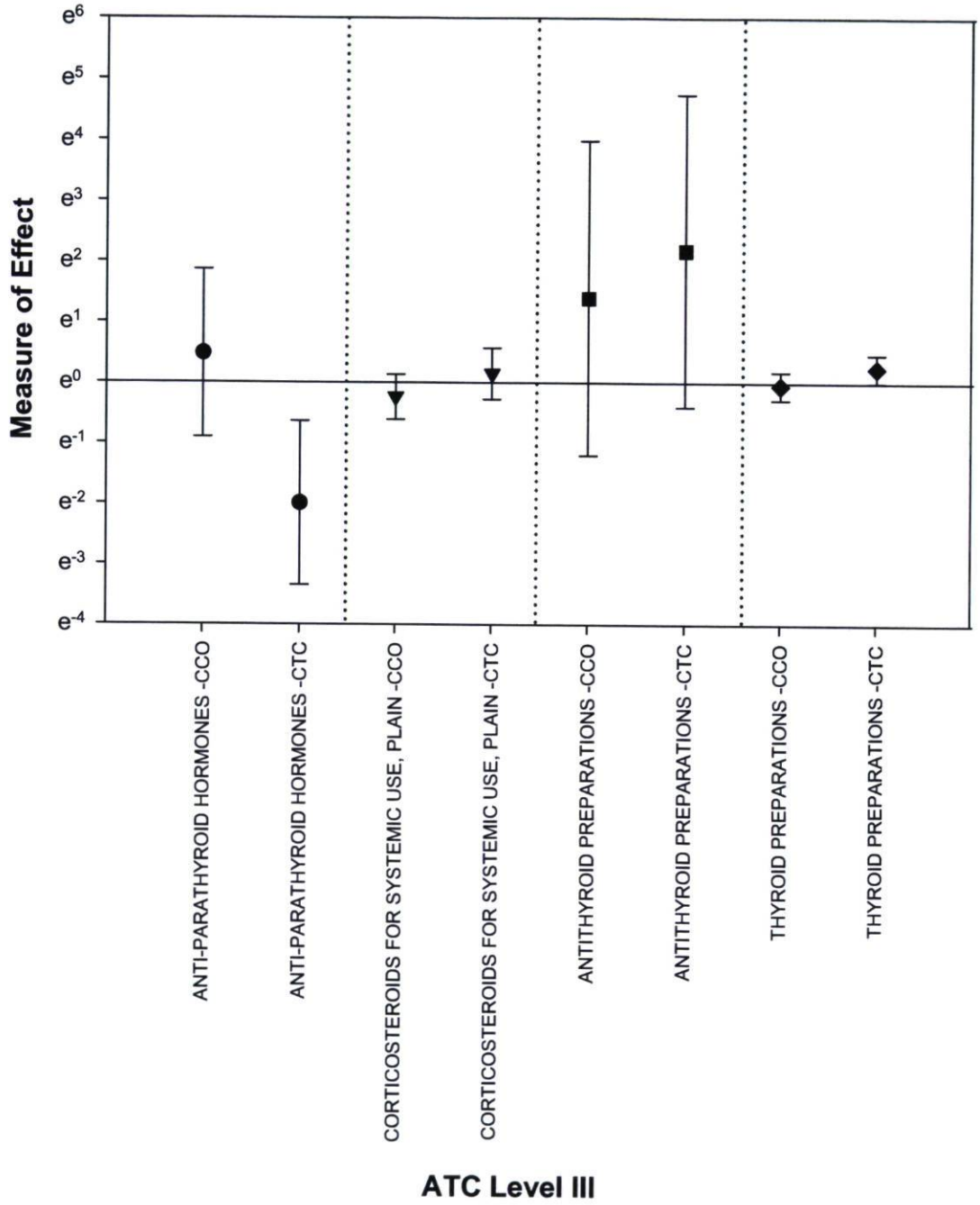
Figure 16: CCO vs. CTC Measure of Effect in Sensory system Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

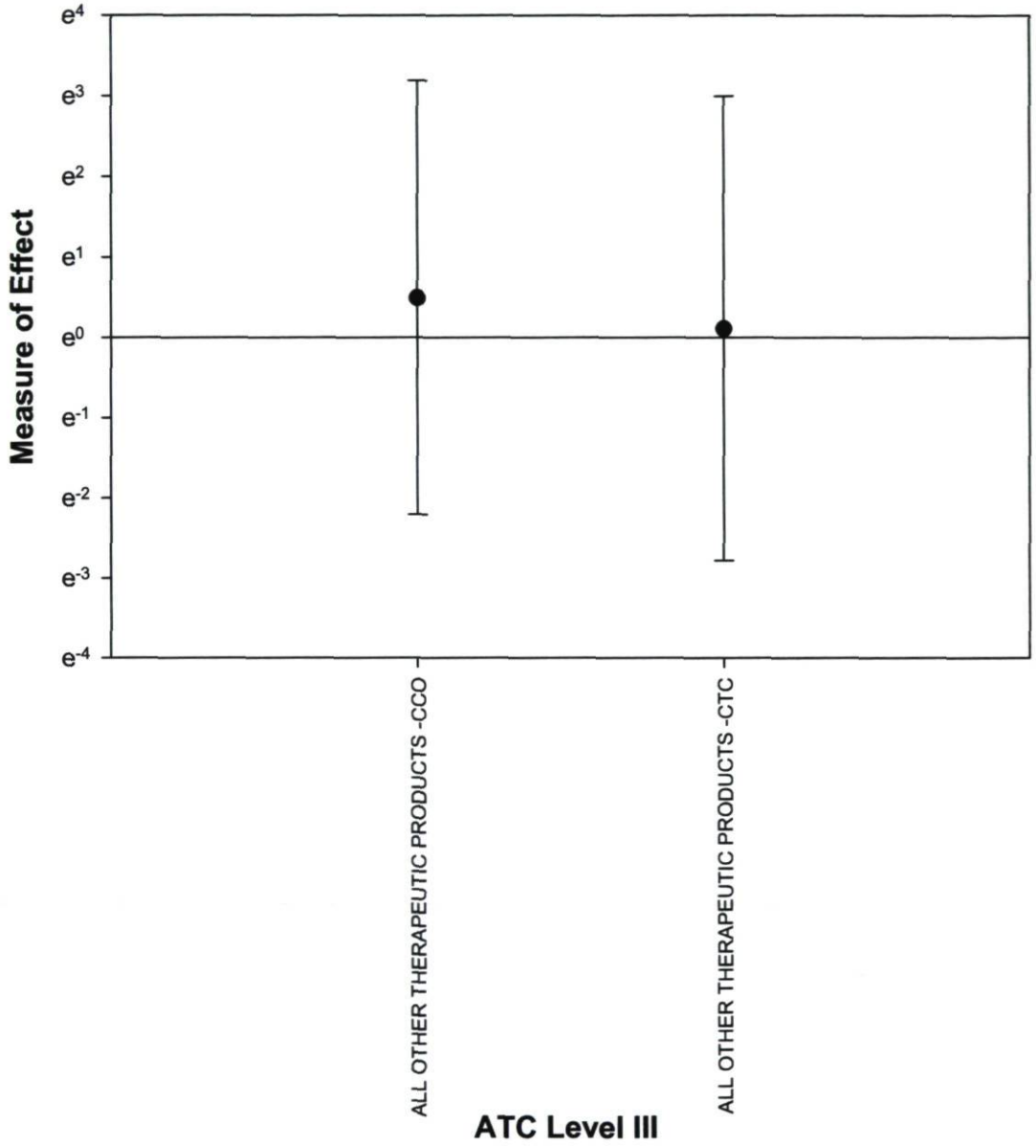
Figure 17: CCO vs. CTC Measure of Effect in Systemic hormonal preparations, excluding sex hormones Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC

Figure 18: CCO vs. CTC Measure of Effect in Various Class



e^{-4}=0.02	e^{-3}=0.05	e^{-2}=0.14	e^{0}=1.00	e^{1}=2.72	e^{2}=7.39	e^{3}=20.09	e^{4}=54.60

CCO=case-crossover; CTC=case-time-control; Measure of Effect was assessed with the incidence rate ratio for CCO and with the Odds Ratio for CTC