Seguimiento longitudinal de cohortes para valoración de resultados tras lesiones

Longitudinal population follow-up for outcome assessment after injuries.

Trabajo presentado por D. Juan Pons de Villanueva
para optar al título de Doctor en Cirugía y Medicina.

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CERTIFICA

que Don Juan Pons de Villanueva, Licenciado en Medicina, ha realizado bajo mi dirección el trabajo de investigación que lleva por título *"Seguimiento longitudinal de cohortes para valoración de resultados tras lesiones".*

Examinado y revisado dicho trabajo doy mi conformidad para que su presentación y para que sea defendido y juzgado como tesis para obtener el grado de Doctor en Medicina.

Y para que así conste y surta los efectos oportunos, firmo el presente certificado en Pamplona, a 26 de abril de 2010.

Dra. M. Seguí Gómez

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A mis padres.

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Soy consciente de que muchos leerán estas líneas con especial interés. Se preguntará el lector, *¿quién hay detrás de este trabajo?* Ciertamente una tesis no es el trabajo de uno solo y pretenderlo sería presunción. Responder a esta cuestión minuciosamente me parece imposible y agradecer satisfactoriamente a esas personas, más todavía. La siguiente sucesión de nombres podría hacer pensar en un agradecimiento mecánico, protocalario, cuando lo que pretendo es todo lo contrario.

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FOREWORD

This thesis' aim is the study of injuries. This aim is approached through two cohorts: the National Study on Costs and Outcomes of Trauma (NSCOT) cohort and the Seguimiento Universidad de Navarra (SUN) cohort, as described in the *Matherials and Methods* section. Two types of injuries are studied: those secondary to motor vehicle crashes and those due to physical activity. The global aim is subdivided in five specific aims, as detailed in the *Objectives* section.

Cohort	*Aim*	
NSCOT	Motor vehicle crashes in people ≥ 65 y.o., comparison with general population	#3
	Motor vehicle crashes in people ≥ 65 y.o., prognostic factors for outcomes	#4
SUN	Motor vehicle crashes, validation of questionnaire	#1
	Motor vehicle crashes, change in health	#2
	Injuries due to physical activity	#5

INTRODUCTION

Injury

Worldwide, injury is a leading cause of death and disability for all age groups except persons 60 years of age or older (Peden 2000). Nevertheless, because of the ageing of the population, injuries in the elderly are to become a more relevant issue.

The older population is growing at a considerably faster rate than that of the world's total population. In absolute terms, the number of older persons has more than tripled since 1950 and will almost triple again by 2050. In relative terms, the percentage of older persons is projected to double worldwide by the middle of this century (United Nations).

Within the European Union, external causes of injury were the 4th leading cause of death for all ages in years 2002-2004. It was the leading cause of death in people 1 to 24 year old (European Comission). In the United States of America (US), unintentional injury, homicide and suicide were in 2003 between the ten main causes of death, being in the younger the first cause (Wisqars).

The most frequent mechanisms of injury leading to death are motor vehicle crashes (MVCs), suicide, violence, falls, drowning, poisoning and fires (Peden 2004). Within these, MVCs are between the leading causes of injury. In people 15 to 24 years of age, MVCs produced 50% of the deaths due to injury (European Comission). MVC-related injuries specifically have been prognosed to become the fifth leading cause of death in year 2030 (World Health Organisation 2008). Furthermore, West et al., found that MVC has a higher mortality risk than other injury mechanisms (West 2000).

Table 1. Ranking of causes of death in US, Europe and Spain.

Cause of death US[1]	%	Cause of death[2]	EU-27	Spain
Diseases of heart	26,6	Cancer	175.6	158.3
Malignant neoplasms	22.8	Heart disease	96.2	51.9
Cerebrovascular diseases	5.9	**Accidents**	**25.8**	**21.7**
Chronic lower respiratory diseases	5.3	Nervous system	17.1	20.6
Accidents (unintentional injuries)	**4.8**	Pneumonia	15.7	9.9
Diabetes mellitus	3.1	Chronic liver disease	13.8	9.0
Alzheimer's disease	2.9	Diabetes mellitus	13.6	12.7
Influenza and pneumonia	2.6	Suicide	10.4	6.2
Renal	1.8	Alcohol abuse	2.7	0.6
Septicemia	1.4	Homicide, assault	1.0	0.8
		AIDS	1.1	2.7
		Drug dependence	0.6	0.2

1. Reference: Heron 2009 (data for year 2005).
2. Source: EUROSTAT. Standardized death rates. Data for year 2008. http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Causes_of_death_and_infant_mortality

Outcome measures

Measuring the health impact of injuries is necessary to realise about the size of the problem (Seguí-Gómez 2003). Outcomes can be divided in three categories depending on what they measure: mortality, health related quality of life measures (HRQL) and costs.

MORTALITY

Within injuries, this is the most studied outcome, the easiest to detect and measure. Death incidence, is one way of measuring deaths. In Spain, in year 2008, there were 3,100 mortal victims of MVC (death counted within 30 days after MVC) (Dirección General de Tráfico). But most interesting is to know years of potential live lost (YPLL). In the United States, in people less than 85 years of age, unintentional injury caused 11.2% of YPLL and suicide 3.6%, being respectively the third and fourth causes in rank after malignant neoplasms and heart disease in year 2003 (Wisqars).

HEALTH RELATED QUALITY OF LIFE (HRQL) MEASURES

Most importantly, injury mortality is only the “tip of the iceberg”. In year 2002, MVCs were the 9th leading cause of Disability Adjusted Life Years lost (Peden 2004) and it is expected to become the 3rd (Murray 1996). In year 2003, in the US, there were 29,237,747 Emergency department encounters, 1,544,854 hospitalizations and 146,941 deaths caused by injuries (Wisqars). In the European Union, in the period 2002-2004, there were 1.872.613 non-fatal MVCs and 46.795 fatal MVCs (European Comission). In Spain, in 2008, besides 3,100 mortal victims, there were 134,047 people implicated in MVCs (Dirección General de Tráfico).

These figures show that mortality reflects only a small portion of people affected by MVCs. The study of disabilities due to MVCs must be addressed to have a real panorama of MVCs epidemiology.

In order to describe how injuries affect people who were not killed by them, several outcomes measures have been issued (Kane 2000, Seguí-Gómez 2003, Drummond 2001).

MOS Short Form 36 questions (SF-36).

The SF-36 is a multi-purpose general health survey which contains 36 questions. It is summarized in eight scales: Physical functioning (PF), Role physical (RP), Bodily pain (BP), General health (GH), Vitality (VT), Social functioning (SF), Role emotional (RL) and Mental health (MH).

It can also be presented as two summary scores: Physical component score (PCS) and Mental component score (MCS). Confidence intervals around individual scores are much smaller for the two summary scores than for the eight scales (Ware 1998). They capture more that 80% of the reliable variance in the eight subscales (Ware 2001).

Within physical scales, both PF and RP with BP and PCS have been shown to be the most valid SF-36 dimensions for measuring physical health (Ware 1993, 1998). MH is the most valid measure of mental health.

SF-36 does not include some health concepts such as sleep adequacy, cognitive (relavant in brain injury) and sexual functioning, health distress, family functioning, self-esteem, recreation, communication, spirituality and symptoms related to any specific condition. Anyway, SF-36 has been shown to explain about two-thirds of the reliable variance of health status (Ware 1998).
The interpretation of results has been made much easier with the standardization of raw scores. Raw values can be standardized to transform scores to a mean of 50 and standard deviation of 10. This transformation achieves the same mean and standard deviation for all eight scales and for the physical and mental summary measures.

Six dimensional preference-based SF-36 derived index (SF-6D).

The six dimensional health classification (SF-6D) is a measure developed by Brazier et al. which attempts to reconcile a profile health status measure, the SF-36, with the quality-adjusted life-year (QALY) approach by deriving a single index measure based on people's preferences. The QALY approach bases the scoring of health status questionnaires on people's preferences. A simplified health state classification was constructed based on a selection of items from the SF-36 for defining health states which is amenable to reliable valuation by respondents. Each dimension of the SF-6D has between two and six ranked statements or levels. A health state is composed of six statements, one from each dimension. A total of 9,000 possible health states were defined in this way. The values of all 9,000 possible health states defined by the SF-6D were estimated by statistical inference from the sample of 59 health states valued by respondents (Brazier 1998, 2002).

Functional Capacity Index (FCI).

This instrument was creaed to complement the inespecificity of other general health measures, aiming to describe health status in the injured population. It assesses both functional and cognitive dimensions. The FCI is a preference based, multi-attribute functional outcome measure that provides a specific score which summarizes function across 10 dimensions (MacKenzie 1996). It was designed to measure the reduced capacity of an individual to perform certain tasks considered important for everyday living. Dimensions included are excretory function, eating, sexual function, ambulation, hand and arm movements, bending and lifting, speech, auditory function, visual function and cognitive function. It does not assess psychosocial well-being. It was validated in a population of blunt trauma patients (MacKenzie, 2002). FCI profiles are converted into overall FCI scores by applying FCI level values and dimension weights and substracting from one to obtain scores that range from 0 (maximum impact on everyday living) to 1 (no impact on everyday living).

As the FCI measures tasks for everyday living regardless their social role, it is less sensitive to enviromental influences and more sensitive to medical interventions. Besides, it incorporates upper extremity function as a separate domain with high weight and should therefore be more sensitive to changes in this dimension.

EuroQol (EQ-5D).

The EuroQol is a generic measure of health status that defines health in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A single index value can be derived (Rabin01). The index has a scale ranging from 1 to -0.59 (1 and 0 indicate full health and death, respectively). Negative values for health states can be interpreted as health states valued worse than dead (Brooks 1996).

Health Utilities Index (HUI).

The Health Utility Index (HUI) is a preference based system for measuring health status. It consists of two systems independent and complementary, HUI2 and HUI3. HUI2 attributes are sensation, mobility, emotion, cognition, self-care, pain and fertility. HUI3 attributes are vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Current questionnaires determine 32 variables from which different summaries can be obtained: attribute levels, single-attribute utility scores, overall health state-vectors and overall HRQL utility scores defined such that score for dead is 0 and the score for perfect health is 1, allowing for negative values (-0.03 for HUI2 and -0.36 for HUI3). Differences of 0.03 or greater in mean HUI overall HRQL scores are important, smaller differences may be significant in some contexts (Furlong 2001, Grootendorst 2000, Horsman 2003).

Post-traumatic Stress Disorder (PTSD).

The Post Traumatic Stress Disorder Checklist, PCL (Blanchard 1996) assesses 17 symptoms which are rated by the participant on a scale indicating the degree to which the respondent has been bothered by a particular symptom from 1 (not at all) to 5 (extremely). Total PCL score can range form 0 to 100.

Activities of daily living (ADL).

This measure surveys the capacity of some of the most basic functions: bathing, dressing, going to toilet, transferring, continence and feeding. The degree to which these are affected can be measured as being independent, needing help or devices (Katz 1963).

Instrumental activities of daily living (IADL).

Impairment in these functions shows a less severe degree of disability than in ADL. They describe activities necessary for independent living in the community. Although there is no universal operational definition, some of the items recorded in different scales are use of telephone, shopping, meal preparation, housekeeping, laundry, transportation, self-medication and money management (Kane 2000, page 34).

Social functioning.

Several measures of social functioning have been developed. Two of the most reliable measures are (1) *infrequent in-person social contact*, defined as no face-to face contact, in a typical week, with friends, neighbours or relatives living outside of the household and (2) *being home-bound*, defined as not leaving the home or leaving the home less than once a week, weather permitting (Simonsick 1998).

Center for Epidemiologic Studies Depression Scale (CES-D).

It is a 20-item self-report instrument that quantifies depressive symptoms. From these, 16 items describe negative symptoms, whereas 4 are worded positively to minimize response bias. For each one of the symptoms patients use a four choice range (rarely/none of the time, some of the time, much of the time, most/all of the time). Total score ranges from 0 to 20 (Cole 2000). For this study we used a revised version which uses five options instead of four for the assessment of symptoms' frequency. To meet DSM-IV diagnostic criteria for a *major depressive episode* requires a response in the most intense category in 5 of the 9 DSM symptom groups, and either dysphoria or anhedonia.

Glasgow Outcome Scale (GOS).

The GOS was developed for brain injured patients. It classifies patients in five categories: death, persistent vegetative state, severe disability (conscious but disabled), moderate disability (disabled but independent) and good recovery (Jennett 1975).

Musculoskeletal function assessment (MFA).

This is a patient assessed health status instrument designed to detect small differences among patients with musculoskeletal disorders of the extremities. It asks patients to assess their functioning on 100 items divided in 10 categories: self care, sleep and rest, hand and fine motor, mobility, housework, employment and work, leisure and recreation, family relationships, cognition and thinking, emotional adjustment – coping - adaptation. All categories and total scores have been standardized on a scale of 0 to 100, with zero representing minimum disfunction and 100 representing maximum disfunction (Martin 1996). Its criterion and construct validity has been assessed (Engelberg 1996). Posteriorly a short form has been developed (Swiontkowski 1999).

Other outcomes used in referenced papers

- Bull disability scale (Braithwaite 1998)
- Functional independence measure (Richmond 2002)
- Impact of Events Scale (Richmond 1998)
- Mississipi PSSD Score (Michaels 2001)
- Qualify of Well Being Scale (Holbroock 1999)
- Sickness impact profile (Bergner 1981, Jurkovich 1995, Richmond 1998)
- Quality of Well Being Scale (QWS) (Neumann 2000, Seguí-Gómez 2003)

Table 2. Summary for health dimensions assessed in some of the HRQL scoring systems.

	SF-36	SF-6D	FCI	EQ-5D	HUI2	HUI3	MFA
General health	+						
Physical functioning	+[1]	+					
Eating			+				
Sleep							+
Vision			+		+	+	
Hearing			+		+	+	
Speech			+		+	+	
Excretory			+				
Ambulation	+		+	+	+	+	+
Usual activities				+			
Self-care	+			+	+		+
Upper limb			+			+	+
Bending-lifting	+		+				
Sexual			+				
Housework							+
Employement and work							+
Leisure and recreation							+
Pain	+	+		+	+	+	
Fertility					+		
Emotion	+				+	+	
Cognitive			+		+	+	
Family relationships							+
Social	+	+					
Coping – adaptation							+
Depression/ anxiety	+[2]	+		+			

1. PF, RP
2. VT, RE, MH

Injury severity scoring

Injury severity is one of the main determinants of outcome after injury. A great scientific effort has been done to reproducibly and validly quantifiy injury severity. Each classification system has tryed to cluster all relevant factors in order to better predict outcome. We briefly review here scoring systems used in this study and the reviewed literature.

ANATOMIC SCORING

Anatomic scores study the impact of the injury depending on the structure affected and its severity.

Abbreviated Injury Scale (AIS).

The AIS is an anatomically based, consensus derived, global severity scoring system that classifies each injury in every body region according to its relative importance on a 6 point ordinal scale. This scale, first published in 1971 (Comitee 1971, 1972), contains more than 2,000 different injuries. Besides a unique code each injury is given a severity level ranging from 1 to 6 depending on its threat to survival (1 minor, 2 moderate, 3 severe, not life-threatening, 4 severe, life threatening, survival probable, 5 critical, survival uncertain, 6 unsurvivable). It distributes injury location within six regions: head & neck, face, chest, abdominal, extremities & pelvic girdle, external. Revisions were published in 1980, 1985 and 1990 (updated in 1998). The last release was in year 2005, which was updated in year 2008 (Genarelli 2006).

Organ injury severity scales (OIS).

The Organ Injury Scale (OIS) committee of the American Association for the Surgery of Trauma (AAST) was organized with the purpose of devising injury severity scales for individual organs (AAST).

Injury Severity Score (ISS).

The ISS was created as a measure of the severity of injury in persons with multiple injuries which, when considered separately, do not invariably result in death. It was developed in the context of MVCs, thus for blunt injuries, but further development spread it use to other mechanisms of injury. It uses AIS severity levels and combines them into a single value that correlates with mortality. Each injury is assigned an AIS score and allocated to one of six body regions (head and neck, face, chest, abdomen, extremity -including pelvis-, external). Only the three highest AIS scores from *different* body regions are used, having their score squared and added. In the case of a level 6 injury, the score is automatically set to 75 (this avoids that someone having a single unsurvivable injury may have an ISS lower to any other survivor with several injuries). Range of values is 1 to 75 (Baker 1974, 1976). The main contribution of Baker was to quantify the fact that death rates increase in the presence of injuries in a second or third body area even when the additional injuries would not normally be themselves life-threatening. Even within deaths on arrival, less time of survival was associated with a higher ISS. One of its drawbacks is that the mortality rates are significantly different between pairs of triplets that generate the same ISS total (Russell 2004).

It has been shown that ISS is not a good predictor for disability (MacKenzie 1986, Bull 1985).

New Injury Severity Score (NISS).

It is a development of the ISS which takes into account the three maximum AIS, *irrespective* of body region. It allows for multiple injuries assessment to a *single* body region. The aims of the change were to overcome the fact that ISS leaves some injuries out of scoring if they are all in the same body region and that in fact it may ignore more severe injuries in one body region in favour of less severe injuries in other regions. It also ranges from 1 to 75. It has a better discrimination between survivors and non-survivors (Osler 1997) and for multiple organ failure (Balogh 2000).

Anatomic Profile (AP).

The injuries are grouped into four different components.
- A = serious injuries (AIS ≥3) to the head, brain or spinal cord.
- B = serious injuries (AIS ≥3) to the thorax or anterior neck
- C = serious injuries to other body regions
- D = face injuries, all minor and moderate injuries (AIS ≤ 2).

Each component is calculated as the square root of the sum of squares of the AIS scores of all injuries within each region. All injuries associated with a component contribute to the AP value. This score has the advantage to account for all injuries (Sacco 1988, Copes 1990).

A one-valued summary score is provided by the logistic regression relating AP component values to survival probability. For this, D component was found to have no prognostic relevance (Copes 2000).

Modified Anatomic Profile Score (APS).

Also AIS based, it is a four number characterisation. The four numbers are the maximum AIS scores (across all body regions) and the modified A-B-C component score of the original Anatomic Profile. As before, the modified AP component score values (A, B, C) are equal to the square root or the sum of the squares of the AIS values for all serious injuries (AIS ≥3) in specified body region groups. The APS is a single number defined as the weighted sum of the four modified AP number.

Specifically, $APS = 0.3199(A) + 0.4381(B) + 0.1406(C) + 0.7961(maxAIS)$ (Sacco1999).

Both NISS and APS have been proved to be more powerful predictors of mortality than ISS, but have not supplanted it, as a world-wide reference for injury quantification (Senkowski 1999, Lefering 2002, Chawda 2004).

Physiologic scoring

Physiologic scores study the impact of the injury on the physiologic status of the patient.

Glasgow Coma Score (GCS).

GCS is the sum of three coded values that describe a patient's motor, verbal and eye level of response to speech or pain (Table 3). It is accepted as a description of consciousness and predictor of outcome, created for head injury (Teasdale 1974). Healey et al. found that different motor-verbal-eye responses combinations resulting in a single GCS score had different mortalities. They proposed to simply assess the *motor subscore*, removing the eye subscore because it added nothing to the predictive power, and removing the verbal subscore because its contribution is not great and is occasionally impossible to assess, thus, leaving the motor score as the only measure (Healey 2003).

Table 3. Glasgow Coma Score coding (Teasdale 1974).

Eye opening		Best verbal response		Best motor response	
Spontaneous	4	Oriented	5	Obeying	6
To speech	3	Confused	4	Localising	5
To pain	2	Innappropriate	3	Withdraws	4
None	1	Incomprehensible	2	Flexing	3
		None	1	Extending	2
				None	1

Trauma score (TS).

The TS accouts for respiratory rate, respiratory effort, systolic blood pressure, capillary refill and GCS to predict survival after trauma (Champion 1981).

Revised Trauma Score (RTS).

The RTS was a development of the TS which corrected some of its defficiencies. Two versions have been developed. Both score form the first set of data obtained on the patient. Specifically it takes into account three data: GCS, systolic blood pressure and respiratory rate. RTS is a weighted sum of coded variable values: RTS= -3.5718 + 0,9368 GCS_c + 0,7326 SBP_c + 0,2908 RR_c. Values range from 0 (worst) to 7,84 (best) (Champion1989). Its utility in triage and predicting functional outcome have been questioned (Gabbe 2003). T-RTS is a version for use in triage, it is a simple sum of raw values which range from 0 to 12.

Table 4. Revised Trauma Score variable breakpoints

GCS	Sistolic blood pressure	Respiratory Rate	Coded value
13-15	>89	10-29	4
9-12	76-89	>29	3
6-8	50-75	6-9	2
4-5	1-49	1-5	1
3	0	0	0

Simplified Acute Physiology score (SAPS).

One of the first targeted to predict probability of survival. It relies only on physiologic data rather than chronic history and diagnosis information, which may be subjective and inaccurate to classify patients in probability of death irrespective of diagnosis. It includes 14 variables including age, GCS and other physiologic and biochemical data (heart rate, SBP, temperature, respiratory rate, ventilation, urinary output, urea, hematocrit, WBCC, glucose, potassium, sodium, bicarbonate) (LeGall 1984).

In general, different methods for predicting survival have been developed for the specific setting of Intensive Care Units, a thorough review of these overcomes the objectives of this thesis. They account for different physiological of biochemical parameters to predict probability of survival (Ohno-Machado 2006, Shrope 2009).

- Acute Physiology and Chronic Health Evaluation (APACHE) (Knaus 1985)
- APACHE II, APACHE III, APACHE IV
- Simplified Acute Physiology Score (SAPS) (LeGall 1984)
- SAPS II, SAPS III
- Mortality Prediction Model (MPM), MPM II
- Sequential Organ Failure Assessment (SOFA)
- Logistic Organ Dysfunction Score (LODS)
- Multiple Organ Dysfunction Score (MODS)
- Palliative Performance Index (PPI)

COMBINED SCORING SYSTEMS ESTIMATING SURVIVAL OUTCOME AFTER TRAUMA

A number of predictive regression models for mortality have been developed. These models take into account other factors, such as physiological variables, influencing on mortality.

A Severity Characterization of Trauma (ASCOT).

It uses the A-B-C *Anatomic Profile* components to describe anatomic injury and the three coded values of RTS (GCS, systolic blood pressure, respiratory rate) to describe physiology. Age is also included considered in a five-step system. Blunt and penetrating injury patients are separated for analysis (Champion 1990).

ICD-9 Injury Severity Score (ICISS).

Based on ICD-9 (not on AIS). Uses empirically derived survival risk ratios (SRR) avaliable for each ICD-9 code. It is calculated as the product of the individual survival probabilities of all ICD diagnoses (Rutledge 1993). This is specially usefull in hospitals, as a ICD coges can be translated into a survival probabilities.
The SRR were first from the North Carolina Hospital Discharge Database (Osler 1996) and more recently from the National Trauma Data Bank (Meredith 2003). It has also been shown to better discriminate between survivors and non-survivors than the ISS (Hannan 2005).

Trauma and Injury Severity Score (TRISS).

The TRISS is a score based in the TS or the RTS, ISS and age. Each component is weighted to provide an estimate of the probability of survival (Boyd 1987, Champion 1990).

Harborview Assessment for Risk of Mortality (HARM).

West et al. created a prediction model of in-patient mortality, including a list of factors clustered in the following categories: age related variables (5), mechanism of injury (15), injury categories (51), commorbidities (6) and interaction terms (3). It excludes physiologic data and uses AIS converted from ICD-9-CM diagnoses. The inclusion of commorbidities, mechanisms of injury and interactions are the main contributions of this system. It showed better survival predictibility than TRISS and ICISS (AUC 0.958, 0.947 and 0.940 respectively) (West 2000).

Comorbidities

Many victim's factors have been shown to correlate with outcome –mainly survival- after trauma. Age and sex are -as in most of events-, independent factors for survival (Wardle 1999). Baker et al. described in their paper, how age-associated increase in mortality was specially pronounced for less severe injuries (Baker 1974).

MEASUREMENT OF CO-MORBIDITY

At first sight it seems plausible that patient comorbidity is an independent factor on the injured patient's survival. Some particular comorbidities have been identified to affect vital prognosis. One problem in studying this factor is which diseases are taken into account, how they are defined, how they are weighted. Many methods are available to measure comorbidity: Burden of disease index, Charlson index, Cumulative Illness rating scale, Cornoni-Huntley index, Disease count, DUSOI index, Hallstrom index, Hurwitz index, Index of Coexisting Disease, Incalzi index, Kaplan index, Liu index, Shwartz, Functional Comorbidity Index and others (Groot 2003). For this study we used the Charlson comorbidity index.

Charlson Comorbidity Index (CCI).

The CCI was developed in 1987 (Charlson 1987). It includes 19 diseases which are weighted on the strength of their association with mortality. The diseases included are: myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia, lymphoma, moderate or severe liver disease, metastasic solid tumour and AIDS.

It assigns weights for these conditions from 1 to 6, resulting in a score which is the sum of assigned weights of the prevalent conditions and represents a measure of the burden of comorbid disease.

It has been shown to be valid in calculating comorbidity from databases (D'Hoore 1996, Schneeweis 2000). Some authors, though, have found it not to be capable of improving survival prediction when used to adjust for injury severity scores (Gabbe 2005). It does not take into account obesity (Neville 2004) and coagulopathy (Morris JAMA 1990, West 2000), which are also independent factors for mortality after trauma.

Functional Comorbidity Index.

Most comorbidity indexes have been developed to predict mortality. The Functional Comorbidity Index aimed to predict the SF-36 PF subscale. This index contains 18 conditions and allows to adjust for comorbidities when the outcome of interest is not survival but function (Groll 2005).
Conditions included are: arthritis osteoporosis, asthma, chronic obstructive pulmonary disease, acquired respiratory distress syndrome (ARDS) or emphysema, angina, congestive heart failure (or heart disease), myocardial infarct, neurological disease, stroke or transient ischemic attack, peripheral vascular disease, diabetes types I and II, upper gastrointestinal disease, depression, anxiety or panic disorders, visual impairment, hearing impairment, degenerative disc disease, obesity and/or BMI >30.

PRE-INJURY HEALTH STATUS

So far, we have spoken about comorbidities as a risk factor for mortality after injury, but, considered the other way around, comorbidities are also a risk factor for sustaining a MVC. Many specific medical conditions have been involved in a higher risk for a MVC, such as alcohol abuse, cardiovascular diseases, cognitive impairment, diabetes, neurologic and musculoskeletal disorders, psychiatric illnesses, respiratory, vestibular and vision disorders. Within these, alcohol abuse and dependence, dementia, epilepsy, multiple sclerosis, schizophrenia, sleep apnea and cataracts present a higher risk for MVC incidence (Charlton 2004, Vaa 2003).

Also, the implication of some medications in the development of a MVC has been studied, such as warfarin and bezodiazepines (Delaney 2006, Dubois 2008).

Outcome predictor variables

We have reviewed how to classify injury severity and comorbidity. The interesting issue now, is to know –within the injured population- which factors make a bigger impact on the victims. That is, the practical issue about outcomes is to look for factors which, apart from having an injury, have effect on an outcome in particular. This is the main objective of this study. Desirably these prognostic factors should be modifiable to be able to plan tasks to lessen injuries' impact. Here we provide a brief introduction to what will be reviewed in the following pages.

A large group of factors have been studied on its influence on outcomes. We summarise these factors in Table 5.

Table 5. Summary of prognostic factors for injury

General factor	Examples
Socio-demographic	Age, sex, race, health insurance, education, work
Pre-existing conditions	Conditions in particular Charlson comorbidity index or other Medication pre-injury
Mechanism of injury	Intentional – Unintentional Blunt – Penetrating
Vital constants	Systolic blood pressure, respiratory rate
Injury severity	Anatomic scoring: AIS, APS Physiologic scoring: GCS, shock presence, respiratory rate… Biochemical parameters Combined scores
Injury location	AIS regions, principal region injured.
Complications	Pneumonia, sepsis, adult respiratory distress syndrome, renal failure…
Treatment given	Time to definitive care Emergency Medicine Service, Centre Trauma Level, Disposition place
Functional status pre-injury	
Length of stay	In-hospital, Intensive case unit.

Most of these factors were studied on its effect on mortality. Of the listed factors none of them seems to be modifiable in the post-event: the injury is there as it comes. But knowing which are the clinically more relevant injuries helps in designing interventions to address them. Thus, the practical aim is to identify the factors for worse outcome, in order to taylor the patient's treatment to limit the effect of the prognostic factor on the outcome.

Studies' designs

Cohort studies are those in which outcomes are measured in a specific period of time in two or more groups of people experiencing different exposure levels in a variable of interest and study the association between different levels of exposure and events. In the case of MVCs, exposure is acute, thus, time of exposure is always instantaneous. Intensity of exposure may vary between participants, and this can be classified in different ways, such as injury severity, number of injuries, location of injuries and others.

There are two types of cohorts, regarding injuries, (1) those which measure exposure and events in general population and (2) longitudinal follow-up of injured people. The first help to measure injury incidence and are able to measure other important exposures previously to the event, avoiding bias from retrospective information.

Trauma regisitries are databases in which data from injured patients are systematically recorded. Data span from injury severity variables to any other factor relevant for injury research. Some trauma registries are based on a single institution or region. National databases can cluster voluntary participation from institutions nation-wide or compulsary (Quebec, Pennsylvania, Victoria, New York). Some examples of national trauma databases are the NTDB (US), TARN (UK), Canadian national trauma registry, German national trauma registry and Israel national trauma registry. The US Major Trauma Outcome Study –which ran from 1982 to 1989- is a reference for all of them (Moore 2008).

As for any injury mechanism, studies assessing the effect of MVCs do not agree in any methodological aspect. There is a wide variability in the source of patients, selection criteria (injury severity, age...), outcomes measured, time of follow-up, adjustment for confounding factors, retention rates, presence of a comparison group, and many other details, which make it very difficult to have a solid idea of the magnitude of the effect

Most of studies *comparing outcomes between people suffering a MVC and those who don't* are case-control studies. This is so because it is easier to select a set of people injured in a MVC and compare them to matched counterparts or general population data.

It should be emphasised that there are very few cohort studies assessing the incidence of MVCs in a cohort of people at risk at the initial time of observation. One example is the Dunedin Multidisciplinary Health and Development study, located in New Zealand (Begg 1999). In Europe, the Seguimiento Universidad de Navarra (SUN) cohort is one of the few with this design.

Injuries' effects on mortality & general health in comparison with general population

The first question regarding outcome after a MVC, is wether having a MVC gives a higer risk for dying. As said, *within elderly people*, there is not much information on cohorts assessing incident MVCs and comparing survival between injured people and not injured people. Most of studies compare mortality in a group of victims with other source of general population data of the same age stratum.

Battistella et al. retrospectively studied prognostic factors for death and self-assessed functional status in patients 75 year old or over attended in a Level I Trauma center. The mean follow-up was 5.4 years for 81% of the patients. Kaplan-Meyer analysis revealed that the trauma patients had a consistently poorer survival after discharge compared with the expected survival for a control population matched for age, gender and ethnicity (approximately 67% vs. 45% at 5 years) (Battistella 1998).

Gubler et al. also studied the effect of injury on survival in elderly patients. Relative risk adjusted for age, sex, and pre-existing conditions for mortality at 5 years for the injured group was 1.71 (95% CI 1.66 to 1.77) (Gubler 1997).

McGwin et al. in a retrospective cohort study of patients over 70 y.o., estimated the effect of injury on a 6-year survival rate comparing injured and non-injured patients from the Longitudinal Study of Aging, while adjusting for demographic (age and sex) and medical characteristics and the specific role of functional limitation. The hazard ratio for death, adjusting for demographic and health characteristics was 1.4 in the injured group. Once they included three measures of functional decline to the model (functional limitations, ADL and IADL) the association was not statistically significant (McGwin 2000).

Although these findings suggest poorer survival among injured elderly in comparison with general population of the same age, none are derived from a prospective cohort study with a comprehensive assessment of mortality and HRQL outcomes.

Risk factors influencing on mortality, short and long term outcomes

Research about the impact of injuries in the elderly people has been developed through the use of different study designs, times of follow-up and measures of outcome. Also here, there is a wide variability in the risk factors assessed (e.g. location, severity and mechanism of injury, comorbidities...). We have reviewed the literature available regarding outcomes after injury *specifically in elderly* people. The fact is that literature in this field is really scarce. As an example, the reader is invited to check out the references in one of the latest papers studying mortality in elderly trauma patients (Caterino 2010), in which –excluding ICU related papers- only 6 papers were published after year 2000, being the latest from year 2004.

AGE AS A FACTOR FOR WORSE SURVIVAL

Age has repeatedly been reported as a factor for worse outcome for injured people.

Mortality rates increase as a funtion of age, also when adjusting for injury severity, sex and pre-existing conditions (Morris J Trauma 1990).

Smith et al. compared survival after trauma of two populations < / > 65 y.o. The ISS at which the probability of death was 10%, was 17.3 in the elderly group versus 24.9 in the younger group (Smith 1990).

Perdue et al. compared survival between <65 and ≥ 65 y.o. trauma patients. OR for mortality after adjustment was 4.64 for the elder population (Perdue 1998).

Rixen et al. also observed that mortality increased after adjustment for other prognostic factors (Rixen 2001).

Taylor et al. showed that elderly patients have a higher mortality rate compared with the younger patients aged 18 to 64 years (6.7% vs 1.8%). Regression analysis confirmed that elderly patients died almost twice more risk than their younger trauma counterparts (OR 1.87; 95% CI 1.60, 2.18) (Taylor 2002).

Caterino et al. proposed to acknowledge an age of 70 as a cutoff for considering a patient to be elderly, as the 70 to 74 y.o. participants they studyed had greater mortality than all younger groups when stratified by ISS (Caterino 2010).

Aims' #3 and #4 objective is to study the outcome after injury *wihtin elderly patients* regarding the location and severity of the lesions. The ensuing literature review studies three issues, i) factors influencing on mortality in elderly people, ii) factors influencing on short-term outcomes excluding fatalities and iii) review of factors influencing on long term outcome excluding fatalities. Most of the publications mix different mechanisms of injury, making it difficult a specific study on MVCs.

REVIEW FOR FACTORS INFLUENCING ON MORTALITY WITHIN ELDER PEOPLE

Tornetta et al. studied 326 blunt trauma patients aged over 60 years. Overall mortality was 18.1%. Regression analysis showed that factors influencing on mortality were GCS score, ISS, transfusion requirement and fluid requirement. Within body systems, AIS score for thorax and head/neck were most predictive of mortality. Significant complications for mortality in adults were respiratory distress syndrome, sepsis and myocardial infarction (Tornetta 1999).

Grossman et al. studied a set of 31.207 trauma patients over 65 year old or over. In 64% of them the mechanism of injury was a fall. Multiple logistic regression model for preexisting conditions revealed that main factors for mortality were presence of liver disease (OR 5.11), renal disease (OR 3.12) and inmunocompromise (OR 2.05) (Grossman 2002).

Richmond et al. studied 3,702 patients ≥ 65 y.o. Higher effect prognostic factors for death were having a ISS ≥ 26 and development cardiovascular complications. Within body regions, injury in chest and head/neck regions were most likely to be lethal (Richmond 2002).

Taylor et al. studied a group of 7,117 trauma patients, and compared outcomes between age groups (65 to 74 years, 75 to 84 years and >85 years). There was an increase in death with age. After controlling for preexisting disease, gender, and ISS, patients aged 75 to 84 years were 1.4 times more likely to die (95% CI 1.1–1.8), and those >85 years were 2.7 times more likely to die (CI 2.1–3.5) compared with those aged 65 to 74 years (Taylor 2002).
Factors influencing on mortality (controlling for gender and age group) were SBP < 90 mm Hg (OR 3.3), GCS = 3 (OR = 8.3), respiratory rate < 10 (OR 8.9). Sepsis was also a risk factor for death (OR 3.5). ISS > 25 was associated with sepsis (OR 20.1). Patients who developed renal failure postinjury had an OR 10.8 for dying. Overall mortality rate was 6,7%.

Battistella et al. made a similar study but with only 93 participants at the end of follow-up (33% retention rate) (Batistella 1998).

Grossman et al. reviewed the Pensylvania State Registry and compared outcomes between < / > 80 year old participants within those aged ≥65. Higher mortality for the elderly elder was also present when adjusting for ISS (crude rate 10% vs 6.6%) (Grossman 2003).

West et al. described the ten most lethal injuries found in the develpvent of HARM: Loss of consciousness for >24 hours (irreversible), full-thickness cardiac laceration, unspecified cardiac injury, complete spinal cord injury C4 or above, superior vena cava or innominate vein, pulmonary laceration, cardiac contusion, traumatic amputation above the knee, major laceration of liver, thoracic aorta or great vessels. This is, mainly thoracic and abdominal injuries. This study was done in adult population and shows, in agreement with Tornetta et al. and Richmond et al., that the most lethal injuries are those located in the thorax, as in the elderly population.

Table 6. Summary of papers for mortality in elderly injured people.

Reference	N	Age	Follow-up time
Battistella 98	93	> 75	> 4 years
Tornetta 99	326	> 60	In-hospital
Grossman 02	31,207	> 65	In-hospital
Richmond 02	3,702	> 65	In-hospital
Taylor 02	7,117	> 65	In-hospital

Table 7. Summary of the magnitude of effects of risk factors for mortality in the elderly population.

	OR / RR	*Reference*
SOCIODEMOGRAPHIC CONDITIONS		
Age	1,06	Grossman 02
< / > 65	OR 1.87	Taylor 02
Race	Ns	Grossman 02
PHYSIOLOGIC STATUS		
SBP < 90	3,09	Grossman 02
	3.3 RR	
Pulse <60 / >120	1,68	Grossman 02
RR <10 / >24	1,68	Grossman 02
RR < 10	8.9	Taylor 02
INJURY SEVERITY		
ISS	1,09	Grossman 02
	1.04	Tornetta 99
RTS	1,04	Taylor 02
GCS	0,78	Grossman 02
	0.87	Tornetta 99
GCS = 3	8.3 RR	Taylor 02
	0,92	Taylor 02
MOI		
Blunt MOI	0,35	Richmond 02
INJURY LOCATION		
Abdominal / pelvic content higher AIS	0,55	Richmond 02
Extremity / pelvic girdle higher AIS	0,58	Richmond 02
Skin /external higher AIS	0,76	Richmond 02

	OR / RR	*Reference*
Chest / thorax higher AIS	1	Richmond 02
Head / neck higher AIS	Ref	Richmond 02
NUMBER BODY REGIONS INJURED	0,69	Richmond 02
Number of injuries	1,11	Richmond 02
COMPLICATIONS		
Cardiac complication	2,85	Richmond 02
Pulmonary complication	2,01	Richmond 02
Infectious complication	1,05	Richmond 02
Sepsis	3.43 OR	Taylor 02
Renal failure	10.8 OR	Taylor 02
PRE-EXISTING CONDITIONS		
Dementia - CNS degenerative disease	0,72	Grossman 02
Epilepsy	Ns	Grossman 02
Cardiac disease	Ns	Grossman 02
	1.77	Taylor 02
Hypertension	0,8	Morris 90
Ischemic heart disease	1,8	Morris 90
Congestive heart failure	1,74	Grossman 02
Diabetes mellitus (DM)	1,3	Morris 90
	1,25	Taylor 02
Insulin dependent DM	Ns	Grossman 02
Not insulin dependent DM	Ns	Grossman 02
Gastrointestinal	Ns	Grossman 02
Hematologic	Ns	Grossman 02
Congenital coagulopathy	3,2	Morris 90
Coumadin	Ns	Grossman 02
Psychiatric	Ns	Grossman 02
Inmunocompromise	Ns	Grossman 02
	2,16	Taylor 02
Steroids	1,59	Grossman 02
Liver disease	5,11	Grossman 02
	8.08	Perdue 98
Chirrosis	4,7	Morris 90
Cancer	1,84	Grossman 02
	2.34	Taylor 02
Arthritis	Ns	Grossman 02
Obesity	Ns	Grossman 02
	5.7 (1.9 – 19,6)	Neville 04
	0,9 (0,5 – 1,5)	Morris 90
Psycoses	0,7	
Alcohol or drug dependence	0,8 (0,6 – 1,1)	Morris 90
Drug abuse	Ns	Grossman 02
Alcohol abuse	Ns	Grossman 02
Pulmonary	Ns	Grossman 02
	1,39	Taylor 02
Chronic obstructive pulmonar disease	1,49	Grossman 02
	1,8	Morris 90
Renal	3,12	Grossman 02
Statin use	0.30 (0.1, 0.9)	Efron 08
TREATMENT		
Transfussion	1.11 OR	Tornetta 99
Fluid requirement	1.06	Tornetta 99
General surgical procedure	2.5	Tornetta 99
Surgery	0.59	Richmond 02

Ns: Not statistically significant.

COMPLICATIONS RELATED TO MORTALITY.

A very interesting question is to detect risk factors for complications. In the review for mortality several complications were identified as prognostic factors for mortality. The practical question is to identify these patients through risk factors for complications, and treat the complication before its development.

Risk factors for developing complications in general are higher ISS, pre-existing comorbid conditions and surgery (Richmond 2002). Grossman et al. did not find clinical relevant differences for complications comparing injured patiens over 80 y.o. to those < 80 y.o. (Grossman 2003). Pellicane et al. studied 374 trauma patients >65 y.o., finding that potentially preventable complications contributed to 62% of deaths from organ failure and 33% of sudden deaths.

Sepsis

Taylor et al. found that, age and preexisting conditions did not predict sepsis in the elderly population, but increasing ISS correlated with sepsis. ISS >25 was associated with a 20-fold increased risk for septic complications (OR 20.1; 95% CI 7.6, 52.7) (Taylor 2002).

Pneumonia

Pneumonia developed in 6.2% of elderly trauma patients. Significant risk factors for pneumonia were preexisting pulmonary disease (OR, 1.64; 95% CI, 1.1, 2.2) and increased injury severity measured as ISS >15 (OR, 5.8; 95% CI, 3.6, 9.2) (Taylor 2002).

Renal failure

A total of 419 elderly patients (5.9%) developed renal failure postinjury. These patients had a 10.8-fold increased risk for mortality (95% CI 5.9–19.6), had moderate to severe injury (ISS >15; OR, 5.7; 95% CI, 4.0–8.3) (Taylor 2002).

REVIEW FOR FACTORS INFLUENCING ON SHORT TERM OUTCOMES.

We define short-term outcomes as those which happen before 5 months after injury, which is a good discriminative cut-off point for all reviewed papers.

Richmond et al. studied 109 injured patients 18 year old or over. Central nervous system injured patients were excluded. Mean ISS was 15.5 ± 9.9. Risk factors for having Sickness Impact Profile score at 3 months from injury ≥ 20 were high levels of intrusive thoughts, defined as Impact Events Scale score ≥ 20 (OR 2.9), maximum injury involving extremities (OR 2.9) and failing to graduate from high school (OR 3.4) (Richmond 1998).

In another publication they studied 38,707 injured patients, aged 65 or above, injured by any mechanism. Functional Independence Measure at acute care discharge was 16,3 ± 0.03. Length of acute care stay was 11.5 ± 0.07 days (Richmond 2002).

Grossman et al. compared functional independence *at discharge* between > / < 80 y.o. patients. Highest levels of independence for both subgroups were in the areas of expression and social interaction and lowest were in locomotion (Grossman 2003).

Wang et al. followed-up 81 patientes injured in a MVC, at 1 and 4 weeks after the event. Quality of life variability was determined by the presence of depression (45% variability), anxiety (4% variability) and PTSD (6% variability) (Wang 2005).

REVIEW FOR FACTORS INFLUENCING ON LONG TERM OUTCOMES.

Batistella et al. described a cohort of 93 surviving trauma patients aged 75 years of age or over. Mean ISS for all included patients was 9.4 (SD 7.7). 35% had no difficulty with any ADL at an average of 5-years after injury. The authors didn't have information on pre-injury functional status (Battistella 1998).

Braithwaite et al. described 158 living patients aged ≥ 15 years with ISS > 15, injured by any mechanism. Disability at 5 years from injury was assessed using the Bull Disability Scale. Head injuries contributed substantially to all grades of disability. Injuries to the pelvis and limbs accounted for 45% of the disability scores overall and for 60% of the moderate and severe disability scores. If brain and spinal cord injuries were excluded, pelvic and limb injuries accounted for 82% of the disability scores overall and 90% of the moderate and severe disability scores (Braithwaite 1998).

Fern et al. compared a group of 54 trauma patients with multiple extremity injuries (MEI) with another group of 18 trauma non-MEI control patients (trauma control, TC). Patients were 16 to 80 years, with any type of blunt trauma mechanism. Patients with neurologic deficit because of head or spinal cord trauma were excluded. MEI patients scored lower in all SF-36 scales than TC patients. These differences were significant in Physical Functioning. Possible significant differences (after Bonferroni) were Role disability due to physical problem, Social Functioning and Vitality. Patients within MEI group with lower maximum AIS were better on most of the SF-36 scores than subjects with higher maximum AIS (Fern 1998).

Grossman et al. compared a group of 65 to 79 years of age injured patients with other group of 80 years of age or above. The highest levels of independence for both groups were in the areas of expression and social interaction, whereas the lowest were in locomotion. Octogenarian patients had a tendency toward modified dependence (requiring supervision or direct assistance) in locomotion and transfer but were relatively independent even at high levels of injury in areas of expression and social interaction. Patients 65 to 79 years demonstrated increased levels of independence for feeding and locomotion except at high levels of injury (Grossman 2003).

Holbrook et al. prospectively studied prognostic factors for discapacities in 1,048 injured patients over 18 years of age, at 12 and 18 months follow up. Patients were over 18 years old, with a GCS score on admission $\geq$12, admitted at least 24 hours, injured by any mechanism. They surveyed the Quality of Well Being Scale (mean for adult healthy population 0.81 ± 0.17). At 12 month follow-up there were very high levels of functional limitation (QWB score $0{,}67 \pm 0{,}13$). Only 18% of patients had scores above 0.80. There was no improvement in functional limitation at the 18 month follow-up. After multiple regression analyses, Post-injury depression, post-trauma stress syndrome, negative change in social satisfaction, serious extremity injury and intensive care unit length of stay were identified as significant independent predictors of poor Quality of Well Being Scale at 12 months form injury (Holbrook 1999).

MacKenzie et al. studied 473 injured patients aged 16 to 45 years, injured by any mechanism (44% by MVC). Patients with severe brain injury were excluded. Follow up at 6 months was possible for 389 (82%) of them. They found that the maximum AIS of upper and lower extremities and spinal cord injury carry considerable more weight when predicting functional status at discharge and 6 months after discharge than do the AIS scores of injuries to any other body region. ISS was not a good predictor of functional disability (MacKenzie 1986).
Risk factors for not *returning to work* one year after injury were severe head or spinal cord injury. Low one-year employment rates were also noted for individuals whose most severe injury was to one ore more extremities. Personal income, educational level and social network (presence of one or more confidants) were important correlates of post-injury employment status (MacKenzie & Shapiro 1987).

At 1 year follow up of the population in MacKenzie 1986, they had complete functional follow up of 479 patients. *Functional limitation* was dependent on the body region of the principal injury and on its severity. Specifically, those reporting largest self-care limitations were those with severe injuries to the spine or to the head. Factors influencing *return to work* were type and severity of trauma, higher educational level, white collar employment, higher pre-injury income and the presence of supportive individuals among family or friends (MacKenzie 1988).

Van Aalst et al. retrospectively studied a population of 54 patients of age 65 year and older, alive blunt trauma injured patients with ISS > 16. Follow up time was not similar in all cases (mean 2,82 years). Of those alive at the time of interview 16,7% regained their preinjury level of function, and 67% returned to independent living, but no factor for this outcome was studied (van Aalst 1991).

Michaels et al. compared different scores at 6 and 12 months on two groups of patients aged over 18: patients with multiple injuries who have orthopedic injuries (Ortho patients) and non-Ortho patients. The total number of patients was 165. Follow-up at 6 months was 75% (n=124) and 51% at 12 months (n=83). They found differences between both groups in the following items, being worse in patients with orthopedic injuries in: Bodily pain, Physical function, Role physical, Mental Health, Role emotional, Social Function, SIP work score, Beck Depression inventory score, Impact of Events score, Missisipi PTSD score, increased use of Sedatives, analgesics, cocaine and alcohol and those treated for alcohol and other drugs abuse (Michaels 2001).

Inaba et al. retrospectively studied a group of 128 injured people over 65 years (54% of whom were injured in a MVC), at 2,8 years after the injury. They compared it with the Canadian SF-36 age-adjusted norms. There was a significant decrease in seven of the dimensions and no effect in Bodily Pain. The effect was bigger in Physical Functioning and Role limitations due to physical health problems (Inaba 2003).

Maraste et al. followed-up 230 patients injured in a MVC for 3.5 to 4 years. They assessed participants with the EuroQol. One year after the event 38% of the non-fatal adults were suffering of some functional disability, pain and distress. Adults suffering from long-term loss of health decreased to 23% on average 3.7 years after the event (Maraste 2003).

Ameratunga et al. conducted a case-control study. He compared 218 patients injured in a MVC with 254 controls. SF-36 at 5 and 18 months were assessed. Among the group of drivers reporting worsened health (cases and controls), prospectively ascertained SF-36 scores revealed greater reductions in physical health in those admitted after the crash in comparison with controls. (Ameratunga 2006).

Others studies have assessed outcomes in elderly injured patients but lack some quality (Carrillo 1993).

Very few studies concentrate exclusively on injuries secondary to MVCs (Ameratunga 2004). The only studies exclusive of elderly people are those of Richomnd et al., Batistella et al., Grossman et al., Van Aalst et al. and Inaba et al.

Concluding, ISS has been shown to be a predictor for disability. Factors shown to independently influence on long term outcome after injury are mainly location of the maximum AIS. Injuries to the head, extremities and spine have been shown to be the most important predictors of disability whereas abdominal and thoracic injuries –if survivable-, are associated with little functional disability (MacKenzie 1987) but associated with higher mortality. It can be appreciated that factors influencing on discapacities are different for those influencing on mortality. In fact, Richmond et al. showed that having the maximum AIS location on any extremity or pelvic girdle there was less risk for death (OR 0.58), compared to having the maximum AIS injury on head or neck.

In the c*onclusions* section the advantages and disadvantages of the different studies' designs are discussed.

Table 8. Summary review for factors influencing on outcome. Alphabetically sorted.

Autor - year	*A: Eligible* *B: Began follow-up* *C: Discharge follow-up* *D: End-observation FU*	*Follow-up*	*Inclusion criteria*[1]	*MOI*[2]	*PF if used to stratify*	*Measured Outcomes for which PF where studied*	*Design*
Ameratunga 04	A 305 cases, 424 controls B 292, 368 C D 218, 254	5, 18 months	MVC	MVC 100%	ISS	SF-36 Global health indicator	CCS[3]
Battistella 98	A 279 B C 225 (81%) D 93 (33%)	4 yrs (min)	> 75 yrs Hospitalized & discharged alive	Not stated	Age, sex GCS ISS, RTS MOI Hospital LOS[4] Pre-existing diseases Discharge disposition	Survival Domestic arrangements Subjective health ADL (Katz) IADL	R
Braithwaite 98	A 212 B C 170 (80%) D 158 (75%)	5 yrs	Age > 15 Any injury ISS > 15 Any MOI		Anatomic injuries	Bull disability scale Return to work	P
Carrillo 93	A B C 82 D 78	1-3 yrs	Blunt injuries > 65 yrs		None	Their own	P
Fern 98	A[5] MEI 71/ TC 26 B C MEI 54 / TC 18 D	MEI 2,12 yrs TC 2,05 yrs	16-80 yrs Survivors Blunt trauma (any MOI) Mental competence No neurologic deficit Survivors		MEI vs TC Maximum AIS	LOS Resource intensity weight SF-36 Return to work	R

[1] If available, in this order: age, severity, **MOI**, neurologic, included deaths, other

[2] MOI: mechanism of injury

[3] CCS: Case control study, P: prospective, R: retrospective

[4] Length of stay

[5] MEI: Multiple Extremity Injuries, TC: Trauma Control

Autor - year	*A: Eligible* *B: Began follow-up* *C: Discharge follow-up* *D: End-observation FU*	*Follow-up*	*Inclusion criteria*[1]	*MOI*[2]	*PF if used to stratify*	*Measured Outcomes for which PF where studied*	*Design*
Fitzharris 07	A 242 B 68 C D 64 (12 m), 62 (8 m)	2.8 months	18-59 y.o. no head, spinal cord, head AIS≥3 admitted to hosopital exclusion criteria of severity		AIS, ISS GCS	SF-36 Health Assessement Quest. Functional Disability Index VAS pain ADL	P
Grossman 02	A 32,588 B C D 32,588	In-hospital	> 65 y.o. Not hip fractures Not intubated at admission GCS ≥ 4 at admission	64% fall	Pre-existing conditions	30-day mortality in hospital	R
Grossman 03	A 43,297 B C D 43,297	In-hospital	> 65 y.o.	MVC 24,5% Blunt 98%	67-79 vs >80	Mortality Complications FIM at discharge	P
Gubler 97	A 9424 cases, 37,787 ctrl. B C D 9,424 cases, 37,787 ctrl.	5 year	Elderly (≥ 67 y.o.) Hospital discharge after trauma	Not stated	Age, sex, race Charlson index	Mortality at 5 years	CCS-R
Holbrook 99	A 1,042 B C 806 (77%) 12 m C 780 (74%) 18 m D	6, 12, 18 m	> 18 yrs GCS ≥ 12 Any MOI LOS > 24h		Depression PTSD Social isolation Extremity injury ICU LOS	QWBS FDS (ADL)	P
Inaba 03	A 171 D 128	Mean 2.8 y. Range 1.5, 4.5	≥ 65 y.o. Discharged from hospital	MVC 54%		SF-36	CCS
MacKenzie 86	A 754 B 597 (473 no brain inj.) C D 389	6 months	16 – 45 No brain injury Discharged from trauma center	MVC 44%	Maximum AIS ISS	ADL IADL Mobility	P
MacKenzie 87	A 754 B 597 C D 486 (12m)	6 m, 1 year	Hospitalized 16-45 y.o.	MVC 63% Assault 21% Falls 16%	AIS Socioeconomic Type of work Income Social support	Return to work	P

Autor - year	*A: Eligible* *B: Began follow-up* *C: Discharge follow-up* *D: End-observation FU*	*Follow-up*	*Inclusion criteria*[1]	*MOI*[2]	*PF if used to stratify*	*Measured Outcomes for which PF where studied*	*Design*
MacKenzie 88	A 597 B C D 479 (80%	6 months, 1 yr	16-45 yrs Survivors Any mechanism	NS	AIS ISS Education Income Social support Work	ADL Return to work	P
MacKenzie 89	A 27,069	In-hospital	≥ 15 Not in-patients deaths			Hospital LOS	P
MacKenzie J Trauma 02	A 1,587 B C D 1,230	1 year	Members of Pennsilvania Study on Functional Outcomes Following Trauma	MCV 94%	head AIS Orthopedic injury	SF-36 Cognitive function scale (COG)	P
Maraste 03	A 476 B 230 C D 230	3.5 – 4 y.	Hospitalized	MVC 100%	-	EuroQol Index of Health Related QL	P
McGwin 00	A B C D102 cases, 408 controls	6 years	> 70 y.o. Hospitalized		Health status ADL IADL Nagi Disability Scale	Death	CCS
Michaels 01	A 165 B C D (6m) 124 (75%) D (12m) 83 (81%)	6, 12 months	> 18 y.o.		Ortho vs. non-ortho	SF-36 SIP work score Beck depression inventory score Impact Events Scale Missisipi PTSD score Medication Drugs abuse	P
Morris J Trauma 90	D 199.737	In-hospital	15 - 85 Trauma discharges	Trauma	ISS	Mortality *in-hospital*, not later	P
Richmond 97	A B C D 109 (100%)	3 months	Non CNS Serious injury			SIP	P

Autor - year	*A: Eligible* *B: Began follow-up* *C: Discharge follow-up* *D: End-observation FU*	*Follow-up*	*Inclusion criteria*[1]	*MOI*[2]	*PF if used to stratify*	*Measured Outcomes for which PF where studied*	*Design*
Richmond 98	A 228 B 123 C D 109	3 months	≥ 18 y.o. ≥ 3 days in hospital Any MOI excluded CNS injury		AIS ISS Cardiovascular complications	SIP IES SSQ	P
Richmond 02	A 38.707 B C D 38,707	In-hospital	Severily injured (hospitalized) ≥ 65 MOI any		ISS Complications MOI Surgery Most severly injured region Number regions injured	Mortality Complications Discharge placement FIM	P
Richmond 03	A B C D 63 (100%)	2 ½ yrs	Non CNS Serious injury	37% MVC		SIP IES Social support Questionnaire Network subscale	P
Sluys 05	A 246 B C D 205	5 years	Hospital admissions ≥ 15 y.o. ISS ≥ 9 Deaths excluded	93% blunt 63% MVC (blunt)	ISS Age Hospital / ICU LOS Recurreng injury Surgery Information	SF-36	P
Taylor 02	A 7,117 B C D 7,117	In-hospital	Blunt trauma ≥ 65 yrs Not burns LOS > 24hrs	NS (mainly blunt)	65-74 vs 75-84 vs >85 Shcock GCS RR Sepsis Renal failure	Mortality ICU LOS Hospital LOS	P
Tornetta 99	A 326 B C D 326	In-hospital	> 60 y.o. Blunt trauma	73% MVC	GCS AIS / ISS Transfussion Fluid requirement	Mortaliy Complications	R
Van Aalst 91	C 98 (93%) D 48 (46%)	2,8 yrs	Geriatric Blunt trauma ISS > 16			Functional ability (20) Independence (10) …	R

Autor - year	*A: Eligible* *B: Began follow-up* *C: Discharge follow-up* *D: End-observation FU*	*Follow-up*	*Inclusion criteria*[1]	*MOI*[2]	*PF if used to stratify*	*Measured Outcomes for which PF where studied*	*Design*
Wang 05	A B C D 81 (1 week) 64 (6 weeks)	1, 6 weeks	18 – 65 y.o. hospitalized no brain or spinal cord injury no sever pre-morbid condition no previous phsychiatric disorder	MVC 100%	Depression (for PTSD)	PTSD reaction index Beck Depression inventory State anxiety disorder Medical outcomes study quest.	P

OBJECTIVES

SPECIFIC AIM 1.

To validate the self-reported incidence of MVCs of participants in the SUN cohort. We will compare the answers in the questionnaire with a second answer to a mailed letter (test-retest reliability) and with the information found in their clinical records (criterion validity). Principal hypotheses to test include:

Hypothesis 1a. The test-retest study will show a good agreement between the answer to the questionnaire and the second answer to the mailed letter.

Hypothesis 1b. The criterion validity study will show a good agreement between the answers to the questionnaire and the information found in the clinical records.

SPECIFIC AIM 2

To determine how MVC's influence on the HRQL in participants of the SUN cohort. Principal hypotheses to test include:

Hypothesis 2a. Participants suffering a MVC will have a worse HRQL status prior to crash than participants not suffering a MVC.

Hypothesis 2b. Participants suffering a MVC will have a bigger decrease in HRQL than participants not suffering a MVC.

SPECIFIC AIM 3.

To characterize the long-term sequelae of motor vehicle crashes among elderly MVC-injured participants in the NSCOT cohort. In particular, we will evaluate the impact of motor vehicle crashes that require hospital admission along the following dimensions: (1) one-year survival; and (2) prevalence and characteristics of physical, psychological, and social sequelae among survivors. We will examine these outcomes in reference to what we know about the general population of elderly individuals so that we can better discern the impact of the injury per se. Principal hypotheses to test include:

Hypothesis 3a. Elderly MVC injured patients will have a higher *mortality* one year after the injury than their age-comparable counterparts in the US population.

Hypothesis 3b. Elderly MVC injured patients will have worse *physical health* than the general elderly US population at 12 months after the crash.

Hypothesis 3c. Elderly MVC injured patients will have worse *psychological health* than the general elderly US population at 12 months after the crash.

SPECIFIC AIM 4.

To determine the factors that influence mortality and the presence or absence of sequelae. The influence of socio-demographic characteristics; pre-injury health status (e.g., comorbidities, general health); injury characteristics (number of injuries, severity, body region affected); and acute care treatment on: (1) mortality and (2) the presence and type of sequelae 12 months post injury. The specific hypotheses to test are:

Hypothesis 4a. *Injury severity* will not be a significant factor in predicting worse outcomes among elderly MVC injured patients.

Hypothesis 4b. *Age* of the patient and *pre-injury health status* will be the most important effect modifier when examining the impact of injury on outcome among elderly MVC injured patients.

Hypothesis 4c. Elderly MVC injured patients with *head trauma* will have worse outcomes, even after controlling for other confounders, including injury severity.

Hypothesis 4d. Among elderly MVC injured patients without head injuries, patients with *lower extremity injuries* will have worse outcomes than patients with other types of injuries, even after controlling for other confounders, such as injury severity.

SPECICIF AIM 5

To pilot additional injury-related work in a cohort in relation to other types of injuries, such as physical activity related injuries. This aim is added as an example of other exposures leading to injuries, appart from MVCs, which is the global goal of the study.

Hypothesis 5a. Measure the risk of injury associated with different types of physical activity

MATERIALS AND METHODS

Materials

THE NATIONAL STUDY ON COSTS AND OUTCOMES OF TRAUMA (NSCOT).

The NSCOT is a multi-institutional prospective study involving over 5,000 trauma patients in the United States. Its main objectives are (1) to examine variations in treatment between Level I Trauma centers (TC) and non-trauma center hospitals, (2) assess the association of differences in care with survival and different functional and HRQL outcomes and (3) compare costs of treatment between TC and non-TC.

Fifteen Metropolitan statistical areas (MSA) with high volume on trauma were selected within the US. A random selection of trauma centers (TC) and non-TC was done within every MSA. From these, 18 TC and 51 non-TC agreed to participate in the study and received the approval from their institutions.

Participants' eligibility criteria were patients aged 18 to 65 years with at least one injury with AIS≥3 and those aged >65 years with any injury severity. Some other exclusion criteria were detailed. Patients were recruited during 18 months, from July 1, 2001 to November 30, 2002.

For eligible patients, a two stage sampling was done

- 1. ICD discharge diagnosis were computed to AIS. All patients fulfilling elegibility criteria were included.
- 2.a. All hospital deaths were selected (n = 1,438). Detailed medical record review excluded 290 of these (1,104 deaths enrolled in the study).
- 2.b. A stratified random sample of 16,760 patients discharged alive was done. The stratifying criteria were (1) age </≥ 65, (2) ISS ≤/>15, (3) head injury AIS ≥3 / head AIS <3 + extremity injury AIS ≥ 3 / other with at least one injury AIS ≥ 3. A quota sampling strategy was used to enrol approximately 3,000 participants aged <65 and 1,300 participants aged ≥65, evenly distributed across trauma center type, severity and principal body region injured.

Finally 8,021 live discharges were invited to participate in the study. From these, 4,087 were located, accepted, gave permission to assess their medical record and were eligible after reviewing the medical record.

Participants were followed-up at 3 and 12 months after injury.

Outcomes assessed incluye a wide set of health-related measures. Functional outcomes included were the Activities of Daily Living, Instrumental Activities of Daily Living, the Glasgow Outcome Scale, Musculoskeletal Function Assessment and return to usual major activity. Quality of life outcomes were SF-36, the Functinal Capacity Index, SF-6D, Health Utility Index and the EuroQol. Other specific outcomes were the Chronic Pain Grade Scale, the Center for Epidemiologic Scale for Depression, the cognitive subscale of the Sikness Impact Profile and the Posttraumatic Disorder Checklist.

Treatment provided to the participants was also assessed, including pre-hospital, hospital and postacute care.

Further details and a thorough description of the development of the NSCOT has been published elsewhere (MacKenzie 2006, 2007).

THE SEGUIMIENTO UNIVERSIDAD DE NAVARRA (SUN).

The Seguimiento Universidad de Navarra (SUN) cohort is an open enrolment prospective cohort of university graduates. It started at the end of year 1999. Participants answer a baseline questionnaire (Q0) assessing multiple exposures such as nutritional habits, physical exercise, and other risk factors. Every two years the participants answer to follow-up questionnaires (i.e., Q2, Q4, Q6 and Q8) assessing changes in exposures and new events of interest. To keep the questionnaires as brief as possible, some issues are asked in every questionnaire whereas others are asked in alternating times. A more concise questionnaire (Qb) is sent since September 2006 to participants who have not answered to any of the follow-up questionnaires. A more detailed description of the cohort development is available elsewhere (Martínez-González 2002, 2008, Seguí-Gómez 2006).

Methods

SPECIFIC AIM 1.

To validate the self-reported incidence of MVC's of participants in the SUN cohort.

Participant's follow up was done through mailed questionnaires. Information about previous MVC was gathered both from the baseline (Q0) and the first two follow-up questionnaires (Q2 and Q4); this is, two and four years after the baseline questionnaire. The follow up questionnaires included MVC related questions, specifically in Q2 two questions were made: "Since you answered the first questionnaire in this study, have you suffered any of these circumstances: (1) a MVC requiring hospitalization of at least 24 hours, (2) other MVC without hospitalization?. In Q4 the questions were (1) the same as in Q2 and (2) "have you suffered other MVC without hospitalization but with work leave?". Incidence of MVC and work leave was derived out of these questions.

For this re-test reliability and criterion validity study we chose as inclusion criteria: (1) residents of Pamplona's metropolitan area, (2) participants who had stated not to have had any MVC hospitalization in the baseline questionnaire (to avoid MVC's occurring prior to enrollment in the cohort), (3) participants who had not left in blank the questions regarding MVC in either Q2 or Q4 follow-up questionnaires and (4) participants who had not left in blank the question regarding MVC-related work leave in Q4.

There were 842 participants who fulfilled the selection criteria. We invited the selected participants to participate in this reliability and validity study through letters (up to three consecutive letters were sent in case we had no answer to the first one). These letters were sent during year 2005. In these letters, we asked them again on MVC and work leave to assess repeatability. Specifically, they had to check -if appropriate- the statement "I confirm I had a MVC since I participate in the SUN study" and also they had to say for how long they had been on work leave. Patients were also asked for their consent to access their clinical notes -which we considered the gold standard- to validate their answers.

MVC, regarding search through clinical notes, was defined in this study as any crash sustained as an occupant of a motor vehicle or as a pedestrian or cyclist being struck by a motor vehicle occurring during the same time frame in which the patient was participating in the cohort study. Regarding search through clinical notes for evidence for MVC-related work leave, we defined it as an occupant of a motor vehicle or as a pedestrian or cyclist being struck by a motor vehicle and requiring at least a one day work leave permit.

Two blinded and trained research assistants made a manual and systematic assessment of the clinical notes of those who gave consent. Subjects lost to follow-up were excluded from the analysis. Differences between those who consented and those who did not were analyzed with independent means' comparison and Pearson's χ^2 as convenient. We compared answers between written questionnaires and answers to this study's invitation letter, and between the former and the clinical notes in those who gave consent. Repeatability and criterion validity were assessed using Cohen's kappa statistic. Kappa coefficients were labelled as suggested by Landis et al. (Landis 1977). We calculated sensitivity, specificity and positive or negative values for the mailed questionnaire using the clinical notes as the gold standard. Results are graphically plotted as suggested by Bangdiwala et al. (Bangdiwala 2008).

SPECIFIC AIM 2

To determine how MVCs influence on the HRQL in participants of the SUN cohort.

MVC events were assessed in each SUN questionnaire. Since Q2, this is done through two questions framed as follows "Since you answered the [previous] questionnaire, have you suffered... 1) a motor vehicle crash requiring hospitalization of at least 24 hours?" and 2) ...other MVC without hospitalization but with work leave?". The SF-36 was assessed for the first time in Q4 and then again in Q8. Thus, for a complete follow-up, at least 8 years should have elapsed since the participant initially had answered the baseline questionnaire.

In this study, we have selected participants who had answered Q0 at least 8 years and 9 months before the time of analysis. The additional nine month from eligibility date is used to avoid selection biases related to the inclusion of participants of each wave who respond very early to the follow-up questionnaire because they may tend to be being overly conservative in their health-related behavior. From these we excluded participants who had had a MVC at Q4 or previously. SF-36 values at Q4 were compared between those who subsequently reported suffering a MVC and those who did not report such event over the same period of time (from Q4 to Q8). We also compared changes in the SF-36 scores from Q4 to Q8 between the two groups: those which declared a incident MVC after Q4 and those declaring not to have had any MVC after Q4.

Differences in SF-36 scales can be assessed along two concepts: clinical and statistical differences. Clinically significant differences are defined as a 5-point difference in the 0-100 scale (Ware 1993), whereas statistically significant differences were defined as 2-tailed $p<0.05$. Statistical analyses included:

i) paired comparisons of mean within-subject differences in SF-36 change from Q4 to Q8
ii) between-subject (those who had a MVC versus those who had not) differences in baseline SF-36 (Q4) and
iii) between-subject (MVC versus no MVC) differences in change in SF-36 (change from Q4 to Q8).

Regression models for differences in the change of SF-36 dimensions' between the two groups were done to adjust differences for age, sex and the pre-injury corresponding SF-36 dimension.

SPECIFIC AIM 3 & 4.

3. *To characterize the long-term sequelae of motor vehicle crashes among elderly MVC-injured participants in the NSCOT cohort.*
4. *To determine the factors that influence mortality and the presence or absence of sequelae.*

All participants in the NSCOT cohort ≥65 year old and injured in a MVC were included for the present study.

Participants were weighted as to represent the complete set of elegible population.

Descriptive analysis was done for outcomes variables for which a general population reference was available (Specific aim #3).

Mortality differences between groups were compared using the direct standardization method of rates.

As of the many outcomes measured in the NSCOT cohort, we included eight. (1) Mortality at 12 months; (2) SF-36, a general health scale (Ware 1998); (3) Activities of daily living (ADL) items including bathing, eating, transfer, toilet, dressing and walking (Katz 1963); (4) Social functioning (Simonsick 1998); (5) Depression, which was assessed using the Centre for Epidemiologic Studies Depression Scale Revised, CES-D (Cole 2000). Major depression episodes were identified as defined in DMS-IV. Lastly, three preference-based measures were obtained; (6) SF-6D, a single index measure based on people's preferences based on SF36, whose score ranges from 0 (worst) to 1 (best) (Brazier 1998, 2002); (7) The Health Utility Index 3 (HUI3), which is a preference based system for measuring health status producing utility scores defined such that score for dead is 0 and the score for perfect health is 1, allowing for negative values (-0.36) (Horsman2003); (8) Lastly, the EuroQol, a generic measure of health status that provides a single index value which also ranges from 0 to 1 (Rabin 2001). Only outcomes at 12 months are detailed.

Deaths in the NSCOT group after discharge were identified by interviewing a proxy or through a match with the National Death Index. Mortality rates for U.S. general population were obtained, from the National Center for Health Statistics (Hoyert 2005).

The SF-36v2 US GP norms were obtained from the 1998 National Survey of Functional Health Status, available at www.sf-36.org. ADL from US GP were obtained from the 2004 National Health Institute of Statistics (NHIS) available at www.cdc.gov. Preference-based HRQL US general population norms (SF-6D, EuroQol and HUI3) are those provided by Fryback et al. (Fryback 2007).

Comparisons for preference-based HRQL measures were done first including those alive at 12 months and then also including those dead at 12 months.

For the specific aim #4, the outcomes of interest were SF-36 summary scores and the preference-based HRQL measures (SF-6D, FCI, HUI3, EuroQol).

Multivariate regession analysis was done to adjust for age, sex, Charlson index, injury severity (NISS), head trauma (AIS <3 / ≥3), spine injury (AIS <3 / ≥3), lower extremity injury (AIS <3 / ≥3) and center trauma (TC / non-TC).

Outcomes comparing participants with or without lower extremuty injuries (AIS <3 / ≥3) were done excluding participants with maximum head AIS > 1.

SPECICIF AIM 5

To determine the association between physical activities' practice and incidence of injuries in the SUN cohort.

In the baseline questionnaire, participants are asked to provide a categorical value to the time invested in 17 physical activities (e.g. walking, cycling, various sports and others as listed in Appendix 5, Tables 1 and 2) in the previous year. They are to report both on time spent on a weekly basis (10 categories from never to 11 h/week) and on the number of months in 1 year that they participated in each activity. These questions on exercise frequency have been validated and shown to correlate to actual metabolic equivalents (METs) (Martínez-González 2005).

Participants were classified according to whether they participated or not in a particular activity and to the average time spent in this participation. Average MET consumption per each activity was derived from the Compendium of Physical Activities (Ainsworth 2000), and it defines the ratio of energy for each physical activity to the metabolic rate while sitting quietly. The number of average

METs in each activity was weighted by the weekly and monthly participation in that activity thus rendering a value of total physical activity (MET-hours) in a week (METs-h/week).

In the 2- and 4-year follow-up questionnaires participants were asked whether there had been any changes in their physical activity habits. In addition, whether any participant sustained a sports-related injuries that required medical treatment (the outcome of interest) was asked in all follow-up questionnaires (Q_2, Q_4 and Q_6). A specific operational definition of 'medical treatment' was not provided in the mailed questionnaires to participants; however, the requirement that the sports-related injury was diagnosed by a medical doctor was specified twice in the questionnaire.

Since the cohort is an open one, participants vary in how long they have been participating. Thus, we searched in every participant's follow-up questionnaire, and it could be that a participant had only 2-year follow-up data, 2- and 4-year follow-up data or 2-, 4- and 6-year follow-up data. If a sport injury was reported in several follow-up questionnaires, we included for analysis only the earliest one, i.e. we considered the individual subject and not the event as the unit of analysis.

The relationship between participation (yes/no) in each particular activity and the incidence of a sports-related injury that had required medical treatment was assessed using Cox proportional hazards regression. Each activity was examined separately, i.e. we did not consider the different activities as mutually exclusive. Therefore, every participant was included in all the categories of the physical activities in which he or she participated. Follow-up time was defined as time from the baseline assessment to the occurrence of a sports-related injury or to the last available follow-up questionnaire if no incident injury occurred. This assessment was done for men and for women separately, as previous studies show that the effects of sports on the incidence of injuries are different in men than in women (Knowless 2006, Parkkari 2004, Messina 1999). The following variables were included for adjustment: age (quintiles), body mass index (BMI) (continuous) and METs-h/week spent in other activities (continuous), i.e. to assess the association between participation (yes/no) in a specific activity and injury risk we assessed the METs-h/week spent *in the rest of activities* and adjusted for that variable (continuous). Alternatively, we also conducted another analysis adjusting instead for participation (yes/no) in each of the other activities (with a dichotomous variable for each of the other activities), without adjusting for METs-h/week.

For some activities (only those associated with a high absolute rate of injury in the crude analysis and only if at least 5% of men or 5% of women participated in them), we also performed a more detailed assessment of the relationship between the weekly time spent in each of these activities (four categories: 0, 0–0.5, 0.5–2 and >2 h) and the risk of incident injury. In these analyses we adjusted for age, BMI and for the sum of the total weekly time spent in leisure-time physical activities (continuous).

RESULTS

Briefly, in this section we report the results which are in more detail presented in the Appendix.

SPECIFIC AIM 1.

To validate the self-reported incidence of MVCs of participants in the SUN cohort.

> The accepted publication of this aim is attached in the Appendix, paper #1, with the title *"Validation of self-reported motor-vehicle crash and related work leave in a multipurpose prospective cohort"*, in press at the *International Journal of Injury Control and Safety Promotion*.

As of June 3rd 2005, there were 4,331 participants eligible for 4-year follow-up, from these 3,507 had completed the second follow-up questionnaire (Q4) (retention rate 80.9%) and 842 out of these fulfilled selection criteria. From these, 119 had reported to have had an incident MVC after the beginning of the observation. Of the 723 that reported not having had a MVC a random sample of 264 was selected for this study purposes (sampling rate 36.5%).

These were invited to enroll in the study (Appendix #1, Fig. 1). From these, 312 answered to the letter (81,4 % response rate) and 263 of these gave consent to access their clinical notes. Of those who consented, we were able to find the clinical notes of 223 participants. Four participants returned their consent too late and are not included in our study (Appendix #1, Fig. 1).

Comparison between patients who answered to the letter and those who did not show that the proportion of patients who reported to have had a MVC in the follow-up questionnaires was not different (Appendix #1, Table 1).

Table 2 shows a similar comparison but for those participants who answered the letter by stratifying on whether they consented to the clinical notes' search. There were no differences in age or sex distribution. The proportion of patients who reported to have had a MVC in the questionnaire was not different between those who gave consent and those who did not (Appendix #1, Table 2).

Re-test and criterion validity calculations were done weighting those who hadn't had a MVC or work leave as to represent the 100% of the original cohort's participants reporting not to have had these events. For re-test calculations the final weighted population was 696 for the MVC question and 620 for the work-leave question. For the criterion-validity analysis, the final weighted population was 497 for the MVC question and 446 for the MVC-related work-leave question.

Re-test reliability of the questionnaire respect to the answer in the letter regarding MVC is summarized in table 3. The percentage of agreement was 88.6%, with Kappa value 0.55. Sensitivity was 55.2%, specificity 95.3%. Positive predictive value was 70.3% and negative predictive value was 91.4% (Appendix #1, Table 3).

Table 4 summarizes re-test reliability of the questionnaire in respect of the answer in the letter regarding work leave. The percentage of agreement was 97.1%, with Kappa value 0.53. Sensitivity was 45.8%, specificity 99.2%. Positive predictive value was 68.8% and negative predictive value was 97.8% (Appendix #1, Table 4).

Criterion validity for MVC-related is detailed in table 5. Percentage of agreement was 86.3% and Cohen's Kappa value was 0.25. Sensitivity was 45.7%, specificity 89.4%, positive predictive value was 24.6% and negative predictive value was 95.6% (Appendix #1, Table 5).

Table 6 details criterion validity for work leave. Percentage of agreement was 96.4% and Cohen's Kappa value was 0.25. Sensitivity was 37.5%, specificity 97.5%, positive predictive value was 21.4% and negative predictive value was 98.8% (Appendix #1, Table 6).

These results are graphically represented in figures 2 and 3 (Appendix #1). The agreement chart provides a visual assessment of agreement by comparing areas based on the cell frequencies from contingency tables. The row and column marginal totals determine rectangles within the larger square determined by the sample size. The larger the darkened area within the rectangles, the larger the degree of agreement between the diagnostic test and the correct diagnosis.

SPECIFIC AIM 2.

To determine how MVCs influence on the HRQL in participants of the SUN cohort.

> The publication of this aim is attached in the Appendix, paper #2, with the title *"Longitudinal assessment of quality of life and its change in relation to motor vehicle crashes"* under second review in the *Journal of Trauma*.

There were 5,786 eligible participants who had entered the cohort 8 years and 9 months before the present analysis. The overall retention rate for these participants of the SUN cohort was 91.1%, as seen in Figure 1. Those who had died (n = 27) or had answered any of the previous questionnaires (n = 1,358) were not considered lost to follow-up. There were 4,738 participants who had answered Q8. Of these, we further excluded those who had had a MVC at Q0, Q2 or Q4 (n = 357) and those who had not answered any of the SF-36 questions at Q4 (i.e., missing pre-event SF-36 values) (n = 172). Final analysis included 3,361 participants (Appendix #2, Figure 1).

Their mean age was 40.0 years (95% CI 39.6, 40.3). There were 37.6% men and 62.4% women. Sixty four participants reported at least one MVC during the follow up period.

Some participants did not answer some of the SF-36 related questions. Missing values in Q4 through SF-36 scales ranged from 2 to 32 participants (0.0005 to 0.009% of all possible values), whereas in Q8 these missing values ranged from 0 to 91 participants (0.0 to 0.02% of all possible values). No imputation method was used, missing cases were treated as so and complete-subject analyses was done. Thus, the specific number of cases included in the comparisons varies slightly from comparison to comparison. Because of these exclusions, the sample size ranges from 61 to 64 in participants with a MVC and between 3,119 to 3,287 participants with no MVC (Appendix #2, Table 1).

The SF-36 average and 95% CI scores for both Q4 and Q8 according to the incidence of MVC over the 4 year follow-up are shown in Table 1 along with the *P* values of the paired *t* test of the within-subject Q4 vs Q8 comparisons for both groups (having or not a MVC). Among patients who eventually suffered a MVC there seems to be a decline of SF-36 scores along all physical dimensions together with an increase in mental health dimensions, but none of these changes reached clinical or statistical significance. In contrast, among participants who were free of MVC after the follow-up period, a decline on Physical Functioning and Bodily Pain did not reach clinical significance but reached statistical significance. In addition, there seemed to be improvements on mental health dimensions that also reached statistical significance while lacking sufficient clinical magnitude (Appendix #2, Table 1).

These changes are further evaluated on the last two columns of Table 2, where the individual differences in scores are summarized. Although none of the differences reached the 5-point benchmark for clinical relevance (the closest we get to this was a 3.6 drop in Bodily Pain), all estimates were larger for patients who suffered a MVC over time than among those who did not, even though it was in this group that the differences in Physical functioning and Bodily pain reached significance again and the improvement on mental health dimensions reached statistical significance (Appendix #2, Table 2).

Table 2 also presents the individual differences in SF-36 scores at baseline between individuals who suffered a MVC and those who did not. Patients who did not suffer any MVC over this period had clinically better Bodily Pain and Mental Health scores, and these differences were statistically significant. The same comparison at Q8 showed that patients who did not have any MVC were clinically better than those who suffered a MVC on Role Physical, Bodily Pain, General Health and Role Emotional scores, and these differences were also statistically significant but not clinically better of (less than 5 points in difference) in Mental health and the Physical component scores.

For each SF-36 dimension we performed two linear regression analyses using the change in dimension-specific differences for each score as the dependent variables. The main independent variable was whether the subject had a motor vehicle crash during the four year follow up period or not. In one of the regression models we adjusted for age at baseline and sex whereas in the second model we also adjusted for the Q4 values of the SF-36 for that dimension. Table 3 summarizes the coefficients and 95% CI of these models. Even though the majority of point estimates showed a negative effect, that is, sustaining a MVC decreased the Q8 scores of all SF-36 dimensions, the models that only adjusted for age and sex never reached statistical significance, while the models adjusting for Q4 values of SF-36 not only showed coefficients with larger effects (in fact three of the coefficients were above the 5 point clinical significance benchmark), but they also reached statistical significance for some other dimensions, such as in Role Physical, Bodily Pain, General Health, Role Emotional and Physical Component Score (Appendix #2, Table 3).

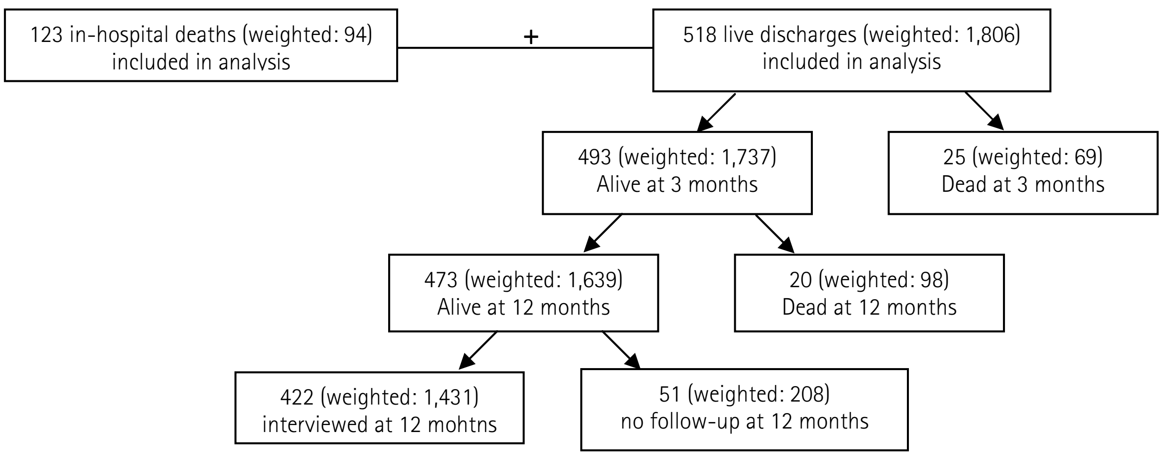
SPECIFIC AIM 3.

To characterize the long-term sequelae of motor vehicle crashes among elderly MVC-injured participants in the NSCOT cohort.

The draft paper of this aim is attached in the Appendix, paper #3, with the title "The effect of injuries on mortality and health related quality of life in people over 65". This paper includes all NSCOT participants 65 year old or over injured by any mechanism (not only MVC). The ensuing paragraphs select findings in the MVC injured victims.

All results are presented in weighted population and are mostly descriptive. Out of the 1,900 patients aged 65 or over suffering a MVC, 163 had died at 3-months follow-up and 261 at 1-year follow-up. At 12 months follow-up 1,639 patients were alive (Fig 1).

Figure 1. Selected NSCOT participants' follow-up flow chart.



Sociodemographic and injury characteristics data for elected patients both for unweighted and weighted are summarized in Table 9. Although participants are over 65 years old, over 47% of them had a Charslon Index Score of 0. At Emergency Department, very few of them were in shock or had a severe head injury as reflected in the motor GCS. New Injury Severity Score was less than 16 for 37.4% of them. Only 10 of them had some degree of spinal cord injury (Table 9).

Table 9. NSCOT patients' characteristics for weighted and unweighted sample

	Unweighted n = 641 Frequency	Proportion	Weighted n= 1,900 Proportion	(95% CI)
GENDER				
Male	317	49.5	54.4	(47.7, 61.0)
Female	324	50.5	45.6	(38.9, 52.2)
AGE				
65 – 74	339	52.8	57.3	(50.5, 63.8)
75 – 84	302	47.1	42.6	(36.1, 49.4)
RACE OR ETHNIC GROUP				
Hispanic	64	9.9	10.7	(7.5, 15.1)
Non Hispanic white	503	78.5	80.4	(75.2, 84.5)
Non Hispanic nonwhite	74	11.6	8.9	(6.4, 12.2)
HEALTH INSURANCE				
No insurance	14	2.1	2.5	(2.5, 6.2)
Private + Medicare	410	66.1	67.2	(61.0, 72.8)
Medicare	212	33.0	29.3	(23.9, 35.2)
Private only	-	-	-	
Medicaid	3	0.5	0.3	(0.0, 1.0)
Other	2	0.3	0.6	(0.0, 4.3)
CHARLSON INDEX SCORE				
0	295	46.0	47.0	(40.3, 53.9)
1	158	24.7	24.4	(19.3, 30.4)
2	86	13.4	11.1	(8.2, 14.8)
≥3	102	15.9	17.3	(11.5, 25.1)
BMI ≥40				
No	463	72.2	85.8	(82.0, 88.9)
Yes	8	1.3	1.5	(0.6, 3.2)
Missing	170	26.5	12.6	(9.2, 16.2)
COAGULOPATHY				
No	629	98.1	95.4	(83.3, 98.8)
Yes	12	1.9	4.5	(1.1, 1.6)
FIRST ED ASSESSMENT OF SBP <90 mm Hg				
No	602	93.9	95.5	(91.5, 97.7)
Yes	39	6.1	4.4	(2.2, 8.4)
FIRST ED ASSESSMENT OF PUPILS ABNORMAL				
No	1,574	87.0	96.0	(94.3, 97.2)
Yes	154	12.9	3.9	(2.7, 5.6)
FIRST ED ASSESSMENT OF MOTOR GCS SCORE				
6	540	84.3	89.3	(86.4, 91.6)
4-5	36	5.6	4.0	(2.5, 6.3)
2-3	5	0.8	0.6	(0.3, 1.3)
1 (not chemically paralyzed)	26	4.0	1.8	(1.1, 2.7)
Chemically paralyzed	34	5.3	0.4	(0.2, 0.6)
FIELD MOTOR GCS SCORE				
6	533	83.1	88.5	(80.6, 89.4)
4-5	37	5.8	4.4	(2.6, 7.1)
2-3	16	2.5	2.5	(1.0, 5.9)
1 (not chemically paralyzed)	28	4.4	2.6	(1.4, 4.6)
Chemically paralyzed	27	4.2	4.8	(2., 8.9)
NEW INJURY SEVERITY SCORE				
<16	263	41.0	37.4	(31.4, 43.8)
16-24	157	24.5	28.9	(23.1, 35.6)
25-34	139	21.7	24.1	(17.8, 31.7)
>34	82	12.8	9.4	(6.5, 13.3)
INJURY SEVERITY SCORE				
<16	343	53.6	53.6	(46.7, 60.5)
16-24	167	26.0	28.5	(22.9, 34.8)
25-34	91	14.2	14.3	(9.0, 22.1)
>34	40	6.2	3.3	(21.3, 5.3)

	Unweighted n = 641 Frequency	Proportion	Weighted n= 1,900 Proportion	(95% CI)
MAXIMUM AIS SCORE, OVERALL				
≤2	164	25.6	20.5	(16.4, 25.5)
3	279	43.5	46.8	(40.1, 53.7)
4-6	198	30.9	32.5	(25.9, 39.9)
MIDLINE SHIFT				
No	612	95.5	97.9	(96.6, 98.7)
Yes	29	4.5	2.0	(1.2, 3.3)
OPEN SKULL FRACTURE				
No	638	99.5	99.1	(96.4, 99.8)
Yes	3	0.5	0.8	(0.1, 3.5)
≥2 LONG-BONE FRACTURES / AMPUTATIONS				
No	588	93.5	93.5	(89.5, 96.0)
Yes	53	6.5	6.4	(3.9, 10.4)
FLAIL CHEST				
No	623	97.2	98.6	(97.2, 99.3)
Yes	18	2.8	1.3	(0.6, 2.7)
ANY SPINAL CORD INJURY				
No	401	97.6	97.9	(95.2, 99.1)
Yes	10	2.4	2.0	(0.8, 4.8)
EMS LEVEL AND INTUBATION				
ALS. intubated	38	5.9	5.4	(3.1, 9.4)
ALS. not intubated	450	70.2	76.1	(70.6, 80.9)
BLS	131	20.5	15.8	(12.1, 20.5)
Not transported by EMS	22	3.4	2.4	(1.4, 4.2)

ALS: Advanced Life Support
BLS: Basic Life Support
EMS: emergency medical service

Anatomic distribution of injuries, as described using AIS is detailed in table 10. Near 20% of participants had a head MaxAIS ≥4. Conversely, very few had a severe MaxAIS in spine, extremities or abdomen. Considering the different anatomic regions independently, there is a general tendency to a low severity of injuries.

Table 10. Anatomic distribution of injuries.

	Unweighted n = 641 Frequency	Proportion	Weighted n= 1,900 Proportion	(95% CI)
MAXIMUM AIS SCORE HEAD				
≤2	460	71.8	65.5	(57.1, 71.3)
3	61	9.5	14.0	(8.5, 21.9)
4-6	120	18.7	21.5	(16.4, 27.5)
MAXIMUM AIS SCORE SPINE				
≤2	580	90.5	90.3	(85.2, 93.7)
3	55	8.6	8.7	(5.4, 13.7)
4-6	6	0.9	1.0	(0.3, 2.8)
MAXIMUM AIS SCORE LOWER EXTREMITY				
≤2	493	76.9	76.5	(70.3, 81.6)
3	148	23.1	23.5	(18.3, 29.6)
4-6	0	0	0	
MAXIMUM AIS SCORE UPPER EXTREMITY				
≤2	574	89.5	90.6	(87.2, 93.2)
3	67	10.5	9.4	(6.8, 12.7)
4-6	0	0	0	
MAXIMUM AIS SCORE THORAX				
≤2	425	66.3	71.3	(63.9, 77.6)
3	141	22.0	21.6	(15.5, 29.4)
4-6	75	11.7	7.0	(5.1, 9.4)
MAXIMUM AIS SCORE NECK				
≤2	636	99.2	99.5	(98.6, 99.8)
3	4	0.6	0.4	(0.1, 1.3)
4-6	1	0.2	0.1	(0, 0.3)
MAXIMUM AIS SCORE ABDOMEN				
≤2	594	92.7	92.1	(82.9, 96.5)
3	30	4.7	2.9	(1.4, 5.9)
4-6	17	2.6	4.9	(1.3, 16.3)
MAXIMUM AIS SCORE FACE				
≤2	629	98.1	98.4	(96.8, 99.2)
3	12	1.9	1.5	(0.7, 3.1)
4-6	0	0	0	
MAXIMUM AIS SCORE EXTERNAL				
≤2	638	99.5	99.5	(98.3, 99.8)
3	0	0	0	
4-6	3	0.5	0.5	(0.1, 1.6)

Mortality incidence proportion at 12 months follow-up was 13.8%. Mortality rates were compared with the direct standardisation method, using the US standard population data (Hoyert 2005). The standard mortality rate ratio was 1.3 for men and 2.3 for women (Table 11). So, this injured population died more than their age and gender general population counterparts, particularly women.

Table 11. Mortality rate differences between the weighted NSCOT cohort and the US general population (US GP) using the direct rates standardization method.

	Weight[1]	NSCOT Rate (10^5)	Standardized rate	US GP age adjusted rate[2]	
MEN					
65-74	0.066037	7,738,9	511.0		
75-84	0.044842	19,414.8	870.6		
Sum			1,381.6	991,7	Rate ratio = 1.3
WOMEN					
65-74	0.066037	9,512.7	628.2		
75-84	0.044842	22,298.8	1000.0		
Sum			1628.2	705,4	Rate ratio = 2.3

1. Population weights used in Hoyert 2005, page 45.
2. Mortality rates for the US GP were obtained from Hoyert 2005, page 7.

As for *HRQL outcomes*, in most of SF-36 dimensions there were clinically relevant differences between the injured group and the general population, being the scores better in the general population. The magnitudes of the differences were bigger in physical scales, were bigger in men than in women and were bigger in people 65 to 74 years of age than in those 75 to 84. Smaller differences were found in mental scales. This is stated in terms of clinical significance on account that 5 is a relevant difference (Table 12). Results are presented as descriptive information.

Table 12. SF-36 dimensions for US GP and NSCOT cohort, stratified for age and sex.

Age 65-74	MEN			WOMEN		
Dimension	US GP	NSCOT	Difference	US GP	NSCOT	Difference
PF	45,48	38,2	**7,28**	43,63	38,8	4,83
RP	46,04	37,1	**8,94**	45,09	35,5	**9,59**
BP	48,41	43,7	4,71	47,33	42,4	4,93
GH	48,16	44,1	4,06	48,6	48,4	0,2
VT	51,94	45,4	**6,54**	51,28	45,6	**5,68**
SF	50,28	47,7	2,58	49,92	46,8	3,12
RE	48,8	44,9	3,9	48,48	45,6	2,88
MH	53,98	49,9	4,08	51,66	50,7	0,96
PCS	45,13	37,9	**7,23**	44,34	37,9	**6,44**
MCS	53,66	51,1	2,56	52,78	51,7	1,08

Age 75-84	MEN			WOMEN		
Dimension	US GP	NSCOT	Difference	US GP	NSCOT	Difference
PF	39,62	35,3	4,32	37,22	37,3	-0,08
RP	39,67	34,4	**5,27**	40,44	38,2	2,24
BP	46,28	43,1	3,18	44,87	43,4	1,47
GH	44,28	41,1	3,18	46,32	46,4	-0,08
VT	47,85	42,1	**5,75**	47,89	44,9	2,99
SF	45,56	45,7	-0,14	46,15	46,2	-0,05
RE	43,59	39,8	3,79	43,61	45,4	-1,79
MH	50,84	50.0	0,84	50,41	51,1	-0,69
PCS	40,38	35,7	4,68	39,78	38,0	1,78
MCS	50,04	48,8	1,24	50,57	51,4	-0,83

Injured population had more difficulties in their *activities of daily living* compared to general population. Around 10% of injured people had difficulties in four or more ADL and 2.6% in the US GP (Table 13).

Table 13. Proportion and participants needing help in ADL both for NSCOT cohort and US GP for the same age range.

ADL[1]	NSCOT				US GP[2] (n = 10,758)	
	Unweighted (N = 641)		Weighted (N = 1,900)			
	n	%	%	(95% CI)	n	%
0	204	48.5	48.3	(40.3, 56.5)	10,121	94.08
1	84	20.0	16.1	(11.8, 21.5)	150	1.39
2	60	14.3	17.6	(10.5, 28.1)	140	1.30
3	24	5.7	7.9	(4.1, 14.5)	62	0.58
4	18	4.3	4.5	(2.5, 8.0)	73	0.68
5	13	3.1	1.9	(1.0, 3.8)	97	0.90
6	17	4.1	3.3	(1.8, 5.9)	115	1.07
Missing	221					

1. Number of ADL in which help is needed.
2. Data of US GP from the 2004 National Health Institute of Statistics (National Center for Health Statistics (2005). Data File Documentation, National Health Interview Survey, 2004. National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland. http://www.cdc.gov)

Social isolation was measured using the questions described by Simonsick et al. (Simonsick 1998). They reported results from a survey in women over 65 years old, which we compared with the NSCOT women's population (Table 14). Data suggest that there is a tendency for more social contact in injured people in comparison with general population regarding social contact, but they less frequently leave home.

Table 14. Social isolation outcome comparison between NSCOT weighted population and other cohort's published data. Two specific outcomes are assessed: (1) how often the person has contact with non-household members and (2) how often does the person leave home. Figures are percentages (Simonsick 1998).

	In person social contact with non-household members		Frequency leaves home	
	Simonsick 98[1]	NSCOT[2] (weighted)	Simonsick 98[3]	NSCOT[4] (weighted)
< 1 time/week, %	23.4	13.8	16.6	18.6
1 - 3 times/week, %	46.0	49.7	17.1	55.9
4 - 6 times/week, %	12.8	12.3	18.0	7.4
≥ 7 times/week, %	17.7	24.1	48.3	17.9

1. Specific question not stated. Defined as face-to-face contact, in a typical week, with friends, neighbours or relatives living outside of the household.
2. Asked as, How often do you get together with friends, neighbours or relatives?
3. Asked as how often during a typical week, weather permitting did the patient leave his home.
4. Asked sequentially. First: during the past week, weather permitting, did you go outside your home, but stay in your neighbourhood? Then: about how many times in the past week did you go outside your home, but stay in the neighbourhood? Of those asked,18.4% refused to answer.

Among NSCOT participants, there were 39 mayor *depression* episodes (2.5%).

Post-traumatic stress disorder was present in 15% of weighted population (n = 1,407).

Regarding *preference-based HRQL measures*, for people alive and dead at 12 months, SF-6D unweighted mean was 0.50 (95% CI 0.41 to 0.44) and weighted was 0.59 (95% CI 0.55 to 0.62). Fryback et al. provided general population values which show the difference between that and the injured population of the same age (Fryback 07). There were differences in both groups but even bigger in the older group of age (Table 15).

HUI3 at 12 months was 0.59 (95% CI 0.55 to 0.63, n= 1,130) for weighted population, 0.62 and 0.52 in the 65-74 and 75-84 year old population stratum respectively. HUI in the US GP is 0.80 in the 65 to 74 year old population and 0.75 in the 75-84 year old population.

EuroQol at 12 months for non-weighted population was 0.58 (95% CI 0.54 to 0.62, n=1,136) for the weighted population, 0.61 and 0.53 in the 65-74 and 75-84 year old population stratum respectively. EuroQol in the US GP is 0.86 in the 65 to 74 year old population and 0.84 in the 75-84 year old population.

The results when dead participants at 12 months were not included showed smaller differences but still present (Table 15b).

Table 15. Preference based measures outcome for NSCOT cohort and US GP (Fryback 2007).

A. Including those dead at 12 months follow-up (scored 0).

	Unweighted NSCOT Mean (95% CI)		Weighted NSCOT Mean (95% CI)		US norms[1]
SF-6D	0.50 (0.41 to 0.44)	n = 590	0.59 (0.55 to 0.62)	n = 1,692	
65-74	0.56 (0.43 to 0.60)		0.64 (0.60 to 0.68)		0.78 (SD 0.01)
75-84	0.42 (0.37 to 0.46)		0.52 (0.45 to 0.58)		0.76 (SD 0.01)
HUI3	0.44 (0.40 to 0.48)	n = 360	0.59 (0.55 to 0.63)	n = 1,130[2]	
65-74	0.52 (0.48 to 0.57)		0.62 (0.58 to 0.66)		0.80 (SD 0.01)
75-84	0.34 (0.28 to 0.39)		0.52 (0.47 to 0.58)		0.75 (SD 0.01)
EuroQol	0.43 (0.40 to 0.47)	n = 365	0.58 (0.54 to 0.62)	n = 1,136	
65-74	0.51 (0.46 to 0.56)		0.61 (0.56 to 0.65)		0.86 (SD 0.01)
75-84	0.35 (0.29 to 0.40)		0.53 (0.47 to 0.58)		0.84 (SD 0.01)

B. Not including those dead at 12 months follow-up.

	Unweighted NSCOT Mean (95% CI)		Weighted NSCOT Mean (95% CI)		US norms[1]
SF-6D	0.69 (0.68 to 0.71)	n = 422	0.70 (0.67 to 0.72)	n = 1,430	
65-74	0.70 (0.68 to 0.72)		0.70 (0.67 to 0.74)		0.78 (SD 0.01)
75-84	0.68 (0.66 to 0.71)		0.69 (0.65 to 0.72)		0.76 (SD 0.01)
HUI3	0.70 (0.68 to 0.71)	n = 228	0.69 (0.67 to 0.72)	n = 959[2]	
65-74	0.72 (0.70 to 0.74)		0.70 (0.67 to 0.74)		0.80 (SD 0.01)
75-84	0.66 (0.63 to 0.69)		0.67 (0.64 to 0.69)		0.75 (SD 0.01)
EuroQol	0.68 (0.67 to 0.70)	n = 233	0.68 (0.65 to 0.71)	n = 966	
65-74	0.69 (0.67 to 0.72)		0.68 (0.64 to 0.73)		0.86 (SD 0.01)
75-84	0.67 (0.63 to 0.70)		0.67 (0.64 to 0.71)		0.84 (SD 0.01)

1. US norms provided by Fryback et al (Fryback 07). US GP norms last age stratum includes ages 75 to 89 and could bias comparisons undersizing the difference.
2. Figures vary because successful follow-up was different within outcomes.

SPECIFIC AIM 4.

To determine the factors that influence mortality and the presence/absence of sequelae.

Mortality

Mortality was studied as incidence proportion at one year after the injury. AIS (</≥3) at anatomic regions did not show statistical significance but for neck. Risk for death increased with age, commoribidities and injury severity.

Tabla 16: Logistic regression for mortality at 1 year after injury.

	N	OR	95% CI
Age			
65-74	1090	Ref.	
75-84	810	3.7	1.7, 7.8
Charlson index			
1	895	Ref	
2	465	1.0	0.4, 2.4
3	211	1.6	0.6, 4.3
>3	329	5.7	2.1, 15.1
NISS			
<16	712	Ref.	
16-24	551	5.8	2.3, 14.6
25-34	458	6.8	2.7, 16.6
>34	179	16.0	5.7, 44.8
Neck Maximum AIS			
<3	1,892	Ref.	
≥3	8	10.6	1.0, 110.8

Also adjusted for sex and trauma center type, thorax MaxAIS </≥3, abdomen MaxAIS </≥3, head MaxAIS </≥3.

Physical HRQL

Table 17 summarizes the adjusted effetcs of different factors on HRQL at 12 months. There is bigger effect produced by the presence of a spinal MaxAIS ≥3 over all other factors. This effect is greater in these physical dimensions than in mental quality of life (Table 18). Other factors also show a signficant effect. Effects of factors assessed are similar in the SF-36 Physical component score and in the FCI. Age did not have impact in physical outcomes. Lower extremity injury didn't have a significant factor on physical health, either when only patients with head maximum AIS ≤1 were selected for analysis.

Table 17. Impact of factors in physical HRQL.

	SF-36 PCS		FCI	
	Change[1]	95% CI	Change[1]	95% CI
Age (65-74 vs 75-84)	-0.6	-3.7, 2.4	-1,8	-4.7, 1.01
Charlson index	**-3.8**	-5.6, -2.1	-2.9	-4.4, -1.4
NISS	-1.6	-3.7, 0.5	-1.4	-3.2, 0.4
Head trauma AIS ≥ 3	3.2	-0.7, 7.3	-0.1	-4.1, 3.8
Lower ext. injury AIS ≥ 3	-1.3	-5.3, 2.6	0.01	-4.2, 4.2
Spinal MaxAIS >=3	**-8.7**	-13.6, -3.8	-4.4	-9.0, 0.1

1. Coefficient of regression model.
Charlson categorized as 0 / 1 / 2 / >3
NISS categorized as <16 / 16 – 24 / 25 – 34 / >34
Adjusted for variables specified in the column and also for sex and Trauma center level.

Mental HRQL

Again, spinal MaxAIS ≥3 is found to be a mayor negative factor for mental health. These effects are detected in the SF-36 Mental component score. Participants who had lower extremity injuries with AIS≥3 have a better adjusted mental health. Severe head trauma (AIS ≥3) –for those who survived-had a modest effect on SF-36 MCS.

Table 18. Impact of variables of interest in mental HRQL.

	SF36 MCS Change[1]	95% CI
Age (65-74 vs 75-84)	-1.5	-4.4, 1.3
Charlson	-0.5	-2.1, 0.9
NISS	0.1	-1.5, 1.9
Head trauma AIS ≥ 3	-3.8	-7.6, 0.2
Lower ext. injury AIS ≥ 3	**4.3**	0.5, 8.1
Spinal MaxAIS ≥3	**-7.3**	-13.6, -1.0

1. Coefficient of regression model.
Charlson categorized as 0 / 1 / 2 / >3
NISS categorized as <16 / 16 – 24 / 25 – 34 / >34
Adjusted for variables specified in the column and also for sex and Trauma center level.

Preference-based measures

As seen in table 19, the same conclusions can be driven when preference-based measures are analyzed. Spinal MaxAIS ≥3 remains as the principal factor. Preference-based measures have the particularity that their range of values is from 0 to 1. This small scale may make it difficult to appreciate the effects, but still they are there.

Table 19. Impact of variables of interest in preference-based HRQL measures

	SF-6D		HUI		EuroQuol	
	Change	95% CI	Change	95% CI		
Age	-0.01	-0.05, 0.03	**-0.04**	-0.08, -0.01	-0.02	-0.06, 0.01
Charlson	**-0.03**	-0.05, -0.01	**-0.01**	-0.03, -0.003	**-0.04**	-0.06,-0.02
NISS	-0.01	-0.03, 0.01	-0.01	-0.03, 0.004	**-0.02**	-0.04, 0.002
Head trauma	0.002	-0.05, 0.05	-0.02	-0.06, 0.01	**-0.05**	-0.09, -0.01
Lower ext. injury	0.01	-0.03, 0.06	0.01	-0.02, 0.05	-0.02	-0.06, 0.02
Spinal MaxAIS ≥3	**-0.15**	-0.23, -0.08	**-0.07**	-0.13, -0.01	**-0.08**	-0.14, -0.02

1. Coefficient of regression model.
Age as 65-74 vs 75-84
Charlson categorized as 0 / 1 / 2 / >3
NISS categorized as <16 / 16 – 24 / 25 – 34 / >34
Adjusted for variables specified in the column and also for sex and Trauma center level.

SPECICIF AIM 5.

To determine the association between physical activities practice and incidence of injuries in the SUN cohort

The publication of this aim is attached in the Appendix, paper #5 with the *title "Risk of injury according to participation in specific physical activities: a 6-year follow-up of 14,356 participants of the SUN cohort"*, published in the *International Journal of Epidemiology*.

Data from 15,859 participants recruited up to November 2005, who had answered any of the three follow-up questionnaires (Q_2, Q_4 or Q_6), were analysed. Participants lost to follow-up were 1,503. Thus, the retention rate was 90.5%. Among those participants with 6-year follow-up (n=7,087), only 2.2% (158) failed to return one or two of their intermediate (2- or 4-year) follow-up questionnaires. Among those participants with only 4-year follow-up (n=4,029), only 3.8% (155) failed to return their intermediate (2-year) follow-up questionnaire. In all these cases we used the last available questionnaire. The average age of participants was 38.1 years [standard deviation (SD) 12.1] although people up to 85 years old were included. Mean total leisure-time METs-h/week was 24.5 (SD 22.2). In the SUN cohort, 11.5% of participants experienced a physical activity-related injury after a median follow-up of 4.6 years. Table 1 shows the distribution of participants according to their total leisure-time physical activity (categories of METs-h/week) and to participation (yes/no) in specific activities. Mean age and BMI were computed within strata of each physical activity (Table1, Appendix #5).

Participation in cycling, running, tennis, soccer and athletics was predominantly done by men, whereas aerobics and gymnastics were more frequent among women. Players in team sports (including soccer) were younger, whereas those participating in gardening, walking or gymnastics were older. Mean BMI was lower among participants in almost every activity when compared with non-participants. Table 2 presents the incidence rate of injury according to total leisure-time physical activity (categories of METs-h/week) and to the participation (yes/no) in specific activities. A monotonically increasing trend in risk was observed for METs-h/week. Specific activities have been ranked in the table according to their injury-associated rates for men and women considered together (Appendix #5, last column of Table 2). Participants in soccer, team sports other than soccer (basketball and handball), athletics, and sailing exhibited higher rates of injury. However, these estimates were crude and participation in sailing was observed only in a very small proportion of our cohort (1.8%). Walking, gardening and aerobics were associated with the lowest crude rates.

Cox regression models were adjusted to evaluate the relationship between participation in each activity and the risk that a participant may experience a sport related injury (Appendix #5, Table 3). Among men, when we adjusted for METs-h/week in other activities, three sports stood out to have particularly strong harmful associations for injuries: soccer, other team sports and athletics. Other activities with a significantly higher risk among men were skiing, running and tennis (Table 3). Sailing was associated with a higher risk among men, but only 84 men in our cohort reported to participate in this sport. Among women, team sports [adjusted hazards ratio (HR) 2.04, 95% confidence interval (CI) 1.45–2.87] and skiing (2.02; 1.67–2.45) were the two sports with the highest risk. Running was also associated with a high risk among women. We used the estimates for men and women considered together with adjustment for all activities (entering all of them as dichotomous variables in the same model) to rank activities from the highest to the lowest risk (Appendix #5, Table 3, last column).

Table 4 presents the HR for incident sports-related injury according to the weekly time of exposure to total physical activity and to the time spent in specific activities. We included in this assessment only those activities associated with a higher risk and with 5% of either men or women participating in them. Among men, a monotonically increasing dose–response trend was observed for four activities: soccer, other team sports, athletics and running. Among women this trend was apparent only for athletics and tennis (Appendix #5, Table 4).

DISCUSSION

GENERAL DISCUSSION

Studies' design

The terms *retrospective vs. prospective*, can be understood in three ways regarding they refer (a) to the timing of recording of exposure and the occurrence of disease, (b) to the timing of accumulated person-time with respect to the stuy's conduct or (c) to the timing of events under study in relation to the time the study begins or ends. In any case, the terms should clarify wether the outcome could influence information in the study. This is, a study susceptible of recall bias is retrospective. For example, on one hand not all case-control studies involve recall and on the other prospectively recorded information might have a retrospective component to its inclusion in a study if inclusion depends on disease occurrence (Rothman 2008).

We have presented two prospective cohorts. In the case of the SUN cohort all data were recorded prospectively, even HRQL status *before* the injury had occurred. This offers a unique oportunity to have pre-injury health information avoiding bias. In the case of MVCs this is especially praiseworthy as the inmense research done taking into account pre-injury health status obtains the information after the event. Exceptions to this are the particular case of the validation study (aim #1), in which the information in the clinical notes was prospectively –not systematically though- recorded but retrospectivelly collected, and also, in the NSCOT, patients were prospectively selected but pre-injury comorbidities and health status were retrospectively collected.

The SUN cohort is a multipurpouse cohort and injury rates prevent from enough sample size, for the time being, to evaluate factors influencing long term outcomes for MVC. Thus the value of combining data from the SUN cohort with the NSCOT, in which factors influencing outcomes after injury are evaluated.

Another important issue in cohort studies is the collection of exposure. The *measure of exposure* in the diffent studies has varied. In the NSCOT cohort all exposures (MVCs) were acute and no induction time definition has been set, as we find this is unnecesary. The same applies to the SUN cohort (aim #1 and #2). Conversely, in the study studying the association between injuries and physical activities (aim #5), exposure was measured as intensity with which the participant practiced each sport regarding time within a weekly schedule and estimated METs associated. Time during which exposure occurrs and time at risk of exposure effects were put on a level. To make results simpler, we studied the incidence of injury regarding the participant practiced or not a specific sport, as a dicotomic variable adjusting for METs-h/week invested *in the other* physical activities.

Case-control studyes are a more efficient version of the corresponding cohort study. Cases are the same cases as would ordinarily be included in the cohort study and controls are selected from the source population. This way, the sampling of controls from the population that gave rise to the cases affords the efficiency gain of a case-control over a cohort design in which the controls provide an estimate of the prevalence of the exposure and covariates in the source population (Rothman 2008).
As said, NSCOT and SUN cohorts are prospective (in the NSCOT, preinjury information is retrospectively collected) but in both –for aims #1, #2 and #3- not all the elegible population was selected for our analyses. This might resemble a case-control study, but it is not the case. In aim #1 all participants having a MVC were selected, but only a random sample of those not having a MVC was selected. In the NSCOT cohort, all elegible deaths were selected but only a stratified random sample of patients discharged alive was selected. In both cases, final data were weighted by the *sampling rate* as to represent the 100% of the elegible population.

Follow-up

Participants *lost to follow-up* raise a concern for bias, as quitting the cohort could be associated either to exposure or outcome. Within cohort studies it should be assumed that loss to follow-up is a non-random phenomenon. In this case, seriously biased estimates of the measures of association with low levels of loss to follow-up can be found, even with 20% loss to follow-up (Kristman 2004).

In the NSCOT group, in the worse circumstance, 51 participants of those discharged alive, were lost to follow-up (90.1 % retention rate). This figure varied for the different outcomes assessed as completeness of surveys varied from patient to patient. In the SUN cohort, the retention rates for studies #1, #2 and #5 were 80,9%, 91.1% and 90.5 respectively. This places the follow-up in a good position.

Confusion

A confounding factor is an extraneous or surrogate risk factor associated with the exposure under study in the source population not affected by the exposure or the disease. To observe effects, we should ideally have assessed outcomes in the same population when they have a MVC and compare the outcomes in the same population if they hadn't had the MVC. We have to observe differences between two different populations, one exposed and the other unexposed. Here is when confounding comes into play, because the differences observed may not be related only to the difference in exposure, but also to differences in other characteristics, as the populations compared are not the same (Rothman 2008).

The best way to account for differences in extraneous factors is randomization of exposure allocation, in which association between exposure allocation and extraneous factors will be random, and so, variation in the outcome across exposure groups that is not due to exposure effects can be adscribed to these random associations and hence can be justifiably called "chance variation". This is, though, not feasible when dealing with nocive exposures, which are obviously unlikely subject of experimental designs.

Confusion in these studies has been tackled stratifying for confounding factors through multivariable analysis (aims #2, #4 and #5).

Bias

Selection bias in prospective studies are present when participants are selected depending on their exposure status and in case-control studies when cases or control selection depends on their exposure levels.

In the NSCOT group a sampling was done for patients discharged alive, but selection bias was intended to be avoided by a staged random selection. In the SUN cohort, the same applies to the validation study, as sampling of "controls" was random. For the outcome's study (aim #2) and physical-activity-related injury risk (aim #5) participants were selected regardless their exposure level.

In the NSCOT, death on arrival was an excluding condition (patients had to be alive at least 24 hours). This is so because the main objective of the cohort was to assess the efectiveness of trauma center type treatment. Therefore, patients in which significant treatment could not be given had to be excluded. This necessarily excludes patients with top mortality injuries, for which treatment is presumably helpless to provide any effect.

Information bias is that in which participants are misclassified in their exposure or their outcome. It can be either non differential, when it does not depend on the actual values of other variables, or differential, when it depends on them.

Retrospectively collected information's validity is jeopardized by *detection bias*. This is the case of clinical notes reviewed for study #1. The fair (not *moderate*) agreement between the answers to the questionnaire and the clinical records hints that they might not be a valid source of information (one of the few available, though). In Navarre there is no trauma registry and there is no protocolized system for data collection after a MVC. Therefore, an opportunity for bias appears. For example, it might be that low-severity injuries could not be recorded, leaving the initiative of appraisal to the health personnel. We assessed age, sex and MVC incidence differences between those who answered to the letter and those who didn't, also between those who consented to search in their clinical notes and those who didn't. We found no relevant differences. It would be interesting to further investigate differences in injury severity, but we had no means to assess this in a systematic method.

A potential presence for *recall bias* from participants is present when patients are asked about their pre-injury health status. They tend to overrate their previous abilities and tend to rate lower than the general population. This bias is avoided in the SUN cohort by its all-prospective design.

Proxy responses

Proxy-completed responses in interviews may systematically affect responses. This is particularly worrisome in the elder population as this might be a more frequent problem. A recent review found that proxy-completed responses tend to more accurately report conditions that are less private and more observable, but tend to underestimate less observable conditions such as emotional and affective states, also SF-36 dimensions tend to be lower and tend to over report disabilities for people ≥ 65 y.o. (Ellis 2003). In the SUN cohort, the questionnaires do not assess who actually answers to it. As this cohort is mostly young, it can be surmised that the questionnaire is answered by the participant himself.

In the NSCOT, interview at 12 months follow-up cohort was answered by a proxy in 19.1% of cases.

Competing risks of death.

Cause-specific survival analysis is based on the assumption of proportionality of risks and on the absence of competing risks of death. Kaplan-Meyer's stimates assumes that participants are censored either because they finished the follow-up or because they died because of the event of interest. When patients are censored because of other reasons (deaths due to other diseases) the interpretation of survival with Kaplan-Meyer stimates or Cox regresion model is no longer tenable (Martínez-González 2008). Other statistical methods have been developed to analyse survival when competing risks of death are present (Llorca 1999, 2004).

In the present study, competing risks could be present. Regarding mortality in the NSCOT cohort – specifically in participants with low severity of injuries- some could have died because of other reason than the injury itself. In an intermediate concept, the injuries could have boosted death because of other pre-event morbid condition, this is, patients with worse pre-injury health would have a worse survival. The ultimate cause of death of participants in the NSCOT cohort was registered, but not wether the patient's death could have been assigned to a cause other than the injury itself, so a survival analysis taking into account competing risk was not done.

The same applies for aim #5. It could be that participants could be injured because of other reason. To avoid competing risks, the question in the survey clearly asked wether the injury was related to sport's practice.

External validity

The conclusions obtained from the associations found in these studies can be generalized to that population with the same carachteristics. Our NSCOT cohort selection represents a population injured in a MVC.

The SUN cohort sample in aim #1 was limited to Pamplona metroplolitan area. Other agreement values could have been obtained if clinical information systems had been assessed in other provinces in Spain. We had to limit research to Pamplona for feasibility reasons.

Conclusions from aim #5 can be applied to the general population. Certainly the SUN cohort has the particular trait of being comprised by university graduates mainly in the 4th- 5th decade of life, but range of values for age is wide. We don't think university graduates have different physical characteristics to those of the blue-collar population.

Missing values

Missing data magement can be done in different ways: 1) complete-case analysis, 2) missing-indicator method, 3) overall mean imputation, 4) simple imputation and 5) multiple imputation. Only this last option gives accurate estimates. In multiple imputation, missing data are predicted using other known characteristics. There are three types of missing data: (a) *missing completely at random*, in which the set of subjets with no missing data is a random sample from the source population, (b) *missing not at random*, in which missing values depends on information that is not observed and (c) *missing at random*, in which missing data are considered random conditional on other known participant's characteristics, but complete cases are not a random sample of the source population (Donders 2006).

In aim #2 there were very few participants with missing values through SF-36 scales. We discarded any imputation in this case, all the more reason being it the dependent variable of interest.

In the NSCOT, multiple imputation techniques were used for certain variables. No missing data on patient outcomes or hospital treatment were imputed (MacKenzie 2007). We did not use imputed datasets for our analysis, as none of the imputed variables was used in them.

In aim #5, time to event or end of follow up was imputed in 278 of the 14,356 participants (1.9%) as the median of the follow up time of the group with a random factor.

SPECIFIC AIM 1.

To validate the self-reported incidence of MVC's of participants in the SUN cohort.

Surveillance of motor vehicle crashes can be done through different data sources. In any case it must be kept in mind that there is not a perfect agreement between the event and the different information sources (self-reports, on-road assessment, ambulance records, emergency department records, hospital records or state crash databases) and what actually happens. This is due to the fact that some of the data sources are not necessarily involved in the process that evolves after a MVC and that some of them fail to register the mechanism of injury. National data sources provide the most thorough data for the general population. On the other hand, targeted cohorts on motor vehicle crashes allow for a deeper insight in events, risk factors and outcomes. There is a duty to study the validity of the source information of MVC events, as it can be concluded from the variability of agreement between different sources. Regarding self-reported MVC, the question is whether it really happened. The first way to assess this is to test-retest the participant asking him twice the same question. A second way is to assess whether the participant is really answering to what is intended to be asked in the question (criterion validity) contrasting the self-reported information to that of a gold-standard. In this second aspect there are several options which depend on what is taken as the gold standard. In this study we took the clinical notes as our source of information.

We initially thought that the health centre's clinical notes would be the reference standard as Primary Health Care is a well established institution in Spain, a country with a National Health Insurance system in place for several decades. The information system in most regions, including

Navarra, where Pamplona is located, is integrated and electronic, making available telemetric access both to outpatient and in-hospital clinical notes and documents since 1999 onwards. In addition, sick (and maternity) leaves have to be signed by the primary health physician (or similar if the patient has work insurance). This is so for employees and self-employed workers. Therefore it was expected that a patient's work leave would be recorded in the clinical notes, with the caveat that it should have been self-stated by the patient to the primary health care physician.

Given the administrative structure of medical electronic records, only participants living in Pamplona's metropolitan area were selected because direct access to their clinical notes was otherwise not possible. This selection could have been spread to other regions but we found this selection criteria provided enough subset sample for a re-test reliability and a criterion validity study. The proportion of reported MVC in the original cohort questionnaires was not statistically different between patients who answered to the letter inviting them to join our data quality study and those who didn't answer (Appendix #1, Table 1). Only one participant who had not answered to the letter had abandoned the study.

The agreement charts are designed so that the frequencies in the diagonal cells from the contingency table determine darkened areas of perfect agreement within the rectangles and the unshaded areas within the rectangles represent the off-diagonal cells entries of disagreement (Bangdiwala 2008). Thus, regarding test-retest calculations, there is more agreement in questions regarding work leave than in questions regarding MVC (Appendix #1, Fig 2). The same happens in the criterion study (Appendix #1, Fig. 3).

However seemingly low agreement values, these findings need to be put into perspective with others in the literature. Our repeatability findings on MVC are slightly lower, but consistent with those previously reported by us in a study where a subset of participants of the SUN cohort were assessed using a telephone interview (Alonso 2006). In this previously published study we only included cases followed up for two years. The two questions assessed were "Since you answered the first questionnaire in this study, have you suffered one of these circumstances: (1) a MVC injury requiring hospitalization of at least 24 hours (yes/no, if yes, tell us month and year); (2) other MVC injury not requiring hospitalization (yes/no, if yes, tell us month and year)". Our group found a Cohen's Kappa statistic of 0.63. Sensitivity was 83%, specificity 77 %, positive predictive value 74% and negative predictive value 89%. Our current findings over a longer follow-up period yield agreement rates slightly lower, possibly in relation to forgetfulness of the event with a longer follow up period and the different source of information. Interestingly, our current criterion validity findings are not that different from those published by others. Norrish et al. assessed validity of self-reported hospital admission with an admission computerized database. They found that only 58% of patients recalled all of their admissions and 16% recalled none of their admissions (Norrish et al., 1994). Arthur et al. presented data regarding self-reported MVC. Kappa index calculated from the data provided in the paper is 0.25, a value not far from ours (Arthur 2005). We found only two studies showing better values: Begg et al. found that 86% of the participants in their study were able to recall unintentional injury in the previous three years, having the health system database as their gold standard (Begg 1999). Koziol-McLain et al. assessed re-test reliability of self-reported injury and found a Cohen's Kappa coefficient of 0.80 (95% CI 0.52 to 1.0) (Koziol-McLain 2000).

Validation exercises in other exposures and events reveal interesting numbers and interpretations. For example, validation studies for other health topics within the SUN cohort present results similar to ours. Alonso et al. found an intraclass correlation coefficient of 0.35 when validating self-reported high-blood pressure (Alonso 2000). Martinez-Gonzalez MA et al. found a Kappa index of 0.25 for self-reported physical activity during leisure time (Martínez-González 2005). Only self-reported weight yielded very satisfactory results, with a Kappa index of 0.91 (Bes-Rastrollo 2005). Validation studies in the Nurses' Health Study for a dietary questionnaire yielded a mean of correlation coefficient between the dietary records and a questionnaire of 0.52 (Salvini 1989). Analogous values are reported in the Health Professionals Follow-up study, where they studied correlations between two food-frequency questionnaires and diet records ranged from 0.45 to 0.74 (Hu 1999).

Our current findings reveal that participants are not perfectly consistent in their reporting of (supposedly) major events, such as a MVC. Very interestingly, the self-report and official data sources do not agree perfectly either. This may be due to different factors worth of discussion.

The validity of the clinical notes should also be assessed. The fact that there is not perfect agreement between self-reported answers and reviewed clinical notes may be due to the fact that health center's clinical notes are indeed not a good gold standard. Interestingly, in Spain less than 50% of hospital admissions have E codes for mechanism of injury (Work group on traffic accidents impact measure on health in Spain), the WHO coding system meant to identify these events. Information on motor vehicle crash involvement is supposedly recorded in an administrative variable related to the source of payment (medical care for crash victims is meant to be covered by vehicle insurance instead of the national health system funds). Yet, this administrative variable is not included in the electronically available files that represent the medical history of a patient. Yet, hospitalization data is, in principle, one of the very few data sources we can rely on to document this type of events. These facts emphasise the importance of registering hospital discharges as a means for further research. Furthermore, this is a call for public institution to enhance the development of trauma registries in Spain, where none has been developed.

Agreement between cohort participants and clinical notes is worse regarding work leave. Possible factors leading to this include that the primary health physician was not in charge of the participant's work leave paperwork or that self-employed participants take "official" work leave but actually go to work -and this is what they report in their answers to us. Interestingly, many health interviews around the world use the work leave related question to measure incidence of injuries in the population (Warner 2005), although we are not aware of any specific validation exercise on these questions.

Another issue regarding validation of self-reported health events is the *recall period*. It has been previously thoroughly disclosed that percentage of recall declines as time increases between event-time and recall-time (Warner 2005, Harel 1994). Yet, we would like to highlight that the longest recall period for all of our participants was four years.

It should be noted that the *magnitude of kap*pa is influenced by two factors. One is the *prevelence index*, which is the absolute difference proportion (between positive and negative) of agreeded classifications. If the prevalence index is high, chance agreement is also high, and kappa is reduced accordingly. The effect of prevalence is greater for large values of kappa than for small values. Second, the *bias index*, which is the difference proportion of disagreeded classifications. When there is a large bias index, kappa is higher than when bias index is low or absent. The effect of bias index is greater when kappa is small than when it is large (Byrt 1993; Feinstein 1990). In the present case, as seen in Appendix 1, Table 7, there are both large prevalence indexes and low bias indexes, which should back a more optimistic interpretation of the kappa values obtained. Furthermore, this conclusion is also suported by the difference between tha kappa values and the maximum attainable kappa values (Dunn 1989).

In conclusion, even though our findings regarding Kappa and positive predictive values are below what one may have preferred, they seem to be within the bulk part of other validation and repeatability items often cited in the scientific literature. Thus, for the time being we propose to include this information in epidemiological studies to identify motor vehicle injury risk factors. Motor vehicle injuries amount to a large loss of health burden to our society; pending future evidence that demonstrates a more efficient system to characterize and investigate them, we must rely on a combination of methods, including self-reported events, administrative databases and others.

SPECIFIC AIM 2.

To determine how MVC's influence on the HRQL in participants of the SUN cohort.

This paper presents the first analysis that we are aware of to report pre-injury self-stated health related quality of life in people who will eventually suffer injuries. This is thanks to the prospective nature of the SUN cohort study. Our findings reveal that those who will be involved in a MVC are slightly worse off at baseline than those who will not be involved in MVC over the same 4-year follow-up. These pre-event differences were only statistically significant for Bodily pain and Mental Health (Appendix #2, Table 1, first column). However, this trend is seen in all SF-36 scales. Explanation of this fact requires further studies, which should address possible differences in co-morbidities, medication, life style and other medical and mental conditions between groups. For example, we have already demonstrated that patients with worse health habits, such as smoking, report worse SF-36 in this cohort (Gutierrez-Bedmar 2009).

Previous publications have assessed how different morbid conditions put a person in a higher risk to have a MVC (Vaa 2003). Therefore it is plausible to say that people who will sustain a MVC are less healthy than their counterparts. This hypothesis, though, has been seldom concluded from a longitudinal study.

Our findings also reveal that among those suffering motor vehicle crashes, their worsening in HRQL is more significant, -not only from a statistical point of view, but also with clinical criteria-, than the change that happens in those not suffering a MVC over this period of time too.

Last, but not least, our findings highlight the importance of controlling for pre-event SF-36 scales' values. These should be regarded as confounding factors above and beyond the confounding effects of age and sex.

Results from differences adjusted for age, sex and preinjury SF-36 scales show clinically relevant differences for Role physical, Bodily pain and Role emotional and statistical differences for General health and Physical component score. The other specific dimensions also have a negative trend for those who had a MVC (Appendix #2, Table 3).

The decline in SF-36 scores within subjects suffering a MVC were bigger in all physical scales than in their counterparts, but statistical significance was not found, possibly because of a lack of statistical power due to the low sample size of this subgroup. Statistical significance was found for smaller differences within subjects not suffering a MVC because of the higher sample size.

The main strength of this study is its longitudinal design and the characteristics of its participants, which provide validity to the data. It is possible that the relatively low number of MVC incident cases prevented us from finding more differences. This, together with the evaluation of the possible explanations for the differential states at baseline merits further analyses as more cohort participants reach the sufficient follow up time (i.e., Q8) to allow for a larger sample size. This should occur within the next couple of years due to the open enrolment nature of the SUN cohort.

We excluded early respondents to the questionnaires (those who answered in less than nine months). In order to obtain conservative estimates, this has been our policy in our publications of the SUN cohort. This decision emerges from the impression that early respondents and late respondents have different baseline characteristics as it has been suggested in other publications. As an example, Manjer et al. studied differences between early and late respondents to a personal invitation to participate in a study regarding nutrition and cancer. Those who responded late were more prone to be men, older, be in comparatively unfavourable socioeconomic situation and were characterized by a high prevalence of current smoking, obesity, weight change, and prevalent disease (Manjer 2002).

The clinical implications of the study are large since it is commonly believed that -as MVC's victims tend to be younger than other types of patients-, their health status is equal or even better than that of the general population. This has overrated the health recovery expectancies based on the fact that –as the MVC injured population would be younger- they would have a bigger physiological stock. However, what our study suggests is that MVC-injured patients are worse off than their counterparts that will not be involved in MVCs and that when those crashes occur, their health status deteriorates even faster.

We did not assess injury severity in this cohort beyond the fact that, at least, the participant was on a work leave because of the MVC. However our results show a global impact of MVCs in health.

In sum, the clinical relevance of this study is to know i) that MVC-injured people are –previously to the event- worse than those who will not have a MVC, mainly in Bodily pain, Role emotional and Mental health and ii) that after the MVC they worsen more in Role physical, Bodily pain and Role emotional. This is particularly relevant in clinical settings since the current expectations for full recovery among young injured individuals may be overestimating the health state that injured patients had prior to the event. The implications of our findings reach beyond the clinical world into the policy arena since the societal burden of injuries has been traditionally estimated considering the full-health state of injured individuals, and thus, some of the current burden estimates may indeed be overestimations.

SPECIFIC AIM 3.

To characterize the long-term sequelae of motor vehicle crashes among elderly MVC-injured participants in the NSCOT cohort.

Injuries in elderly people carry not only an increase in mortality rate, but also a handicap in health related quality of life, as shown in the outcomes assessed in this study. We have found differences in all outcomes in the elderly injured population in comparison with the general population of the same age. This could be assessed at one year after injury in mortality, SF-36, ADL, social functioning, SF6D, HUI3 and EuroQol.

Regarding mortality, our study yields similar results to that of previous ones although different mortality measures hinder direct comparisons. For instance, Batistella et al. did not include in-hospital mortality in their study, which could have biased their findings towards a "healthier" group (Batistella 1998). Gubler et al. and McGwin et al. also showed the increased risk of mortality produced by injuries (Gubler 1997, McGwin 2000).

SF-36 is one of the most common outcomes used for assessment. Our results agree with those of McCarthy (McCarthy 1995), MacKenzie (MacKenzie 2002) and Sluys (Sluys 2005), although these included younger people in their studies. In all these three, the biggest effect was seen in SF-36 physical dimensions, and within these, in role limitations due to physical health (RP), as in our study, even though the time when SF-36 was measured after the injury differs between the papers reviewed and ours. Within physical scales, both Physical-Functioning and Role-Physical with Bodily pain and Physical Component Summary have been shown to be the most valid SF-36 dimensions for measuring physical health. These are in fact (except for Bodily Pain) the most affected SF-36 scales. Inaba et al. showed the effect on SF-36 scales confirming what was known for younger population (Inaba 2003).

Battistella found that 35% of elderly trauma patients had no difficulty with ADL at an average of 5-years after injury. This cannot be compared to our 1-year follow-up. Yet their inclusion criteria was patients aged 75 or over (Battistella 1998).

Social functioning is not a major affected facet of injured elderly. This may be due to an increase in "passive" social aspects. The social outcome shows that the NSCOT population is not really isolated after injury. The high frequency of refusal to answer to the frequency of leaving home, however, jeopardizes the validity of these questions.

Prevalence of a major depression episode in general population over 65 years of age is estimated to be 2% (Fountoulakis 2003). Major depression episode in this elderly NSCOT subgroup was 2,5%. Thus, no great differences between injured and general population have been shown.

We have not found reports of prevalence of PTSD in general US population. PTSD incidence of younger patients in this same NSCOT cohort was bigger (13.5 percent in this 65-84 subset versus 20.7 percent in the <65 years groups of age). This may may be due because the younger group was more severely injured (mean weighted ISS 17.1 vs 14.9) (Zatzick 2008).

Generally, for preference-based HRQL measures, comparison of the NSCOT cohort with US GP norms available shows more than a big decrease in health (Table 5). Specifically, SF-6D differences with general population norms were bigger in the 65-74 group of age than in the 75 -84 group.

Grootendorst et al. showed that HUI mean differences of 0.03 of bigger are clinically relevant (Grootendorst 2000). We have found a difference of 0.3, which shows the size of the effect of injuries both in the elder population. This fact is confirmed by the differences found in EuroQol (Table 15).

Summarizing, this study sheds some more light in the situation of elderly injured people. Specifically, we have reported outcomes that previously had not been addressed: social functioning, depression and a set of preference based HRQL measures.

This study shows that mortality is not the only outcome affected by injuries in elderly people. The burden of discapacities it carries stirs not only to enhance primary prevention by also to study the factors that lead to a worse outcome within this subpopulation of elderly people to toil for a improvement in their quality of life.

The advantages of this study lie on its prospective design and its sample size. But, this study is not free of objections. We made comparisons assuming the potential bias that result from the fact that the questions for ADL done both in the NSCOT and in the NHIS do not exactly match. ADL surveyed in the NSCOT included seven items: bathing, dressing, eating, transfer, toilet, walk and continence. For each item, three questions were done in the telephone survey: (1) By yourself, that is without the help from another person or special equipment, do you have difficulty [item]? (2) Do you use special equipment to [item], such as [special equipment example]?, (3) Does anyone usually help you in [item]? Walking was assessed with a more complete set of questions. If the patient answered affirmatively to any of them he/she was assigned that needed help in that ADL. As stated, ADL from US GP were obtained from the 2004 National Health Institute of Statistics (NHIS) available at www.cdc.gov. In that survey, ADL questions were asked as "Do you/does [alias] need the help of other persons with [item]?" (items were: bathing/showering, dressing, eating, getting in/out of bed or chairs, using the toilet including getting to the toilet). Walk in the NHIS survey was asked as "Because of a health problem, do you have difficulty walking without using any special equipment?" Continence was not included in the NHIS survey, so we didn't include NSCOT results about continence in the comparison.

Another factor which could bias downwards the effect of injury is that some of the U.S. population data we used presumably would include injured people.

On the other hand a factor that should be kept in mind is that data for ADL, SF-36, social functioning and depression from the general population were not surveyed in the same period of time as NSCOT data.

Our NSCOT patients are not meant to be representative of general population, but they present a wide enough array of injury types and injury severities to spread conclusions the injuries in the elderly population. We reckon this representativity is not jeopardized with 11.1% of participants lost to follow up at 12 months.

Specific Aim 4.

To determine the factors that influence mortality and the presence/absence of sequelae.

Data on the effect of injuries in elderly people are really scarce. Richmond et al. studied a large cohort of trauma patients over 65 y.o. but follow-up was only until hospital discharge (Richmond 2003). Bastistella et al. described another cohort of 93 patients over 75 y.o. but they didn't do any inferential study (Batistella 1998). Van Aalst et al. did a retrospective study of 54 patients (Van Aalst 1991). Grossman et al. followed up another large cohort of elder trauma patients, but again, only during hospitalization (Grossman 2003). Current knowledge of the effect of trauma on elderly people comes from observations in the adult population extended to the elderly. This lack of valid data also implies that we cannot compare –on a solid ground- our results with those previously reported.

This NSCOT selected cohort provides novel data regarding the effect of MVC specifically in the elder population, not only on a descriptive ground, but also studying how some factors can modify the outcome. In specific aim #3 we have seen the global negative effect of MVCs in comparison with their general population counterparts. Here we discuss modifying factors for this effect.

Within physical HRQL, we have seen that effects are similar in the SF-36 Physical component score and in the FCI. It should be noted that SF-36 is a psychometric health status and FCI is a preference-based measure. Besides, FCI includes within physical dimentions, some specific musculoskeletal and basic physiological details which SF-36 ignores. On the other hand FCI doesn't assess pain. Despite these differences both scales detect similar effects through the factors studied.

We surmised that age would be a major negative prognostic factor. Although this trend is seen, it didn't reach clinical relavance. This is in contrast with the previous repeated finding that, for the same injury severity, elder people tend to have worse outcomes than younger.

Within mortality, age, Charlson index and NISS showed to influence survival at 12 months after the injury. Maximum AIS through different injury locations had no major influence save an AIS≥3 in the neck. This must be due to the most severe injuries in this region: those that affect the great vessels and perforation of esophagus or larynx.

Pre-injury health status –as measured by Charlson index- showed a significant effect in physical outcomes. This effect was lower, but also with a negative trend in mental HRQL.

We also reckoned that –differently than in the adult population-, injury severity would not be a major predictor for a worse outcome. In fact NISS showed to have no major influence in any of the outcomes.

Head trauma (AIS≥3) did not influence outcomes. The trend even hints to be positive. In the whole weighted population 35% of patients had head AIS ≥3. This does not represent the trauma spectrum in the US. This is precisely a consequence of the stratified sampling strategy targeted to have valid results. This trade-off of validity for representativity is necessary as representativity can be looked for only if there are valid results. This rules out that the lack of statistical significance is due to lack of sample size in groups. As it has previously been described in the adult population, head injury is a principal factor for survival but in our cohort crude survival at 12 months for participants with head AIS <3 vs ≥3 was 12% and 16% respectively. Conversely, head AIS ≥3 has an impact on SF-36 MCS, but lower than spinal MaxAIS ≥3.

Similar observations apply for lower extremity injuries, from which we expected a major impact on outcomes.

Our findings regarding spinal MaxAIS >=3 and discapacity are in agreement of those reported by MacKenzie et al. (MacKenzie 1986, 2002) regarless they were assessed in an adult population.

Preference-based measures provide a different approach on outcome assessment. Standard physicometric methods provide numerical assessment to reflect individual's health status and can discriminte among levels of health status. These measures are useful in measuring changes in health status over time, predicting future health outcomes and discriminating among individuals with different diseases, but these measures do not reflect the value patients place on the various attributes of health being measured. Another difference is that preference-based measures have an interval scale. Preference-based measures apply a 0 score to the dead health status and 1 to perfect health (Neumann 2000).

The importance of effects shoud rely on the knowledge of how much change is clinically relevant and how HRQL measures are able to detect the effects of injuries on health. In this regard, FCI was developed to measure the capacity of persons to perform certain tasks necessary for everyday living and not the performance of socialliy defined works, thus FCI should be less sensitive to personal and enviromental influences.

Summarizing, our results can't be compared to others, as there is no similar prospective cohort with the same characteristics and outcomes assessment. Spinal MaxAIS ≥3 is the major factor affecting HRQL both in physical and mental dimentions. Severe head trauma –for those who survive- is also, but in a lower magnitude, a determinant for mental health in elder people injured in a MVC.

Specicif Aim 5.

To determine the association between physical activities practice and incidence of injuries in the SUN cohort.

Our findings show the close relation between some sports and injury; especially team sports showed a strong injury risk both among men and women. Physical activity is in general a healthy habit; however, the risk of injury associated with the participation in some activities needs also to be taken into account. Specifically, among men, a higher risk of injury in participants in soccer, other team sports and athletics was clearly apparent. On the contrary, walking, gardening, mountain hiking or swimming were not significantly associated with a higher risk of injuries. As for women, team sports other than soccer had an enormous detrimental association to injuries when the participation was 40.5 h/week. Both in men and women, to replace other sports by activities such as walking or gardening would reduce the risk of injury. The failure to find any association between soccer and injury in women could be explained by the fact that soccer is only seldom practiced in Spain by women. It must be considered that soccer is one of the most popular sports among men in Spain. As in other countries, soccer is also common among women, the lack of association between soccer and injury in our female participants might not be applicable to other countries. In any case, conclusions about soccer from this article should be generalized to those of team sports in general.

It seems clear that both in men and in women, team-based sports had a strong effect on injury incidence and thus, prevention efforts should be focused on them. Our results are similar to those of Parkkari et al., who found that commuting and lifestyle activities have low risk for injury, whereas the risk was higher in squash, contact and team sports. Interestingly, in their study, the absolute incidence of injuries was higher in commuting and daily living activities, as they were performed so often (Parkkari 2004).

Previous reports have been focused solely on specific sports and their conclusions are therefore limited only to the specific sports which the research addressed. Messina et al. selected 100 high-schools to survey the incidence of injury in the varsity teams. From these, 80 of the schools answered for the girl's teams and 75 for the boy's teams. They found that the risk of injury during a competitive game was higher than during usual participation and that females had greater risk of knee injuries (odds ratio 2.3) (Messina 1999). Powell et al. studied the incidence of injuries in students participating in high-school sports and found higher incidence of injuries in males for various sports and higher risk for knee injury in girls (Powell 2000). Finch et al. prospectively followed up 1,512 non-professional players of hockey, Australian football, basketball and netball. Injury rates were highest in Australian football and lowest in netball. In addition, lower limb injuries were twice as common as those to the upper limb (Finch 2002). In comparison with these previous studies, our cohort allows a more comprehensive assessment of the risk associated with a wide variety of sports.

The precision of the results of the study may be limited by (i) the lack of studies validating the self-reported injury, (ii) the failure to record severity of injury and (iii) we do not know exactly in which sport did the injury occur—only that it did and the type and frequency of exercise that participants undertook. Furthermore, the number of people practicing some sports was relatively low and the frequency of those practicing it very often was even lower. However, we consider that these limitations do not influence on the validity of our results. The participants' quality as university graduates make it possible to surmise a significant validity of the factors and the outcome assessed in this study (Tortosa 2008). Other outcomes in the SUN Project have already been validated (Martínez-González 2005, Alonso 2005). Data validity may also be threatened by a possible recall bias for those who had injuries, who may be more likely to differentially remember information on their physical activities. However, we have recorded information on physical activities at the baseline questionnaire (Q_0), before the incidence of injury occurred to avoid such bias.

Strengths of the study are its prospective design, which provides an adequate cause–effect temporal sequence, making it possible to point out team sports (including soccer) as the principal risk factor for injury in physical activity and, on the other hand, the protective effect of other daily life physical activities, such as walking or gardening. Also the relatively large sample (in comparison with previous reports) provides sufficient accuracy to the estimates of the effects.

Overall, this study points to a relationship between some sports and a higher injury incidence; most of all in team-based sports. We acknowledge the healthy effects of physical activity, but this study shows that not all of them are similar. This should be transferred to the population targeted recommendations of physical activities as good for health, stressing that it is better to participate in moderate physical activities, in agreement with the World Health Organization recommendations (Worl Health Organization 2004).

Future research should be focused on the effect of each particular physical activity on the severity of injuries, and for risk factors—other than the physical activity—for more significant injuries, especially those risk factors which are modifiable. Also the study of the effect of each particular physical activity on general health would enlighten the conclusions made in this study.

Conclusions

Specific aim 1.

To validate the self-reported incidence of MVC's of participants in the SUN cohort.

1. In the SUN cohort, test-retest reliability is moderate both for self-reported incidence of MVC and MVC-related work leave.
2. In the SUN cohort, criterion validity is fair both for self-reported incidence of MVC and MVC-related work leave.

Specific Aim 2.

To determine how MVC's influence on the HRQL in participants of the SUN cohort.

3. In the SUN cohort, participants who eventually suffered a crash had a worse health status before the MVC than those who did not suffer a MVC.
4. They lost even further health following the injurious event.

Specific Aim 3.

To characterize the long-term sequelae of motor vehicle crashes among elderly MVC-injured participants in the NSCOT cohort.

5. Elderly MVC injured people have higher *mortality* a year after the injury than their age-comparable counterparts in the US population.
6. Elderly MVC injured people have worse *physical health* than the general elderly US population 12 months after the crash.
7. Elderly MVC injured people have worse *psychological health* than the general elderly US population at 12 months after the crash.
8. Elderly MVC injured people have more *limitations in their daily lives* than the general elderly US population at 12 months after the crash.

Specific Aim 4.

To determine the factors that influence mortality and the presence / absence of sequelae.

9. Age, comorbidities and injury severity are prognostic factors for mortality.
10. *Injury severity* is not a significant factor in predicting disabilities among elderly MVC injured patients.
11. *Age* of the patient was not either an important factor for disabilities.
12. Head trauma is not a clear factor for a worse outcome after a MVC.
13. The presence of spinal MaxAIS ≥ 3 is the principal determinant of outcome for physical and mental health.

SPECICIF AIM 5.

To determine the association between physical activities practice and incidence of injuries in the SUN cohort.

14. Soccer, other team sports, skiing, athletics, running and tennis were associated with a high risk of injuries among men.
15. Team sports, skiing, running, athletics and tennis were associated with a high risk of injuries among women.
16. Walking, gardening, swimming or gymnastics did not noticeably increase the risk of injury in this cohort.
17. Messages addressed to the general population promoting the participation in physical activity to prevent chronic disease should emphasize these lower-risk activities.

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APPENDIX