Universitat de Girona

A CROSS-SECTIONAL STUDY COMPARING OSTEOPOROSIS IN TWO POPULATIONS OF CHILDREN WITH AND WITHOUT JIA

FINAL DEGREE PROJECT

A cross-sectional study with a control group.

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1. ABBREVIATIONS

BMD	BONE MINERAL DENSITY
JIA	JUVENILE IDIOPHATIC ARTHRITIS
OP	OSTEOPOROSIS
DXA	DUAL-ENERGY X-RAY ABSORPTIOMETRY
VF	VERTEBRAL FRACTURES
ILAR	INTERNATIONAL LEAGUE OF ASSOCIATIONS OF RHEUMATOLOGY
RF	RHEUMATOID FACTOR
ERA	ENTHESITIS-RELATED ARTHRITIS
JPA	JUVENILE PSORIATIC ARTHRITIS
ESR	ERYTHROCYTE SEDIMENTATION RATE
DMARD	DISEASE-MODIFYING DRUG
NSAIDs	NON-STEROIDAL ANTI-INFLAMMATORY DRUGS
IAGCs	INTRAARTICULAR GLUCOCORTICOIDS
OI	OSTEOGENESIS IMPERFECTA
MAS	MACROPHAGE ACTIVATION SYNDROME
ISCD	INTERNATIONAL SOCIETY FOR CLINICAL DENSITOMETRY
JADAS	JUVENILE ARTHRITIS DISEASE ACTIVITY SCORE
VAS	VISUAL ANALOGUE SCALE
WBLH	WHOLE BODY LESS HEAD
ESR	ERYTHROCYTE SEDIMENTATION RATE

2. ABSTRACT

BACKGROUND: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Today, thanks to early diagnosis and the therapeutic options available to us, its comorbidities have been substantially reduced. Even so, we do not know the current incidence of some of them. Especially those that occur silently, such as low bone mineral density (BMD) for chronological age or even childhood osteoporosis(OP).

OBJECTIVES: The aim of this study is to evaluate the prevalence of low BMD for chronological age/OP in patients diagnosed with JIA and in their different subtypes of JIA and to compare it with healthy paediatric patients. We also want to study the variables that may be associated with low BMD/OP in patients with JIA and define phosphocalcium analytical parameters, including vitamin D, and markers of bone turnover in these patients.

DESIGN AND PARTICIPANTS: This study is designed as a cross-sectional study comparing two populations of patients with and without JIA. It is an observational and multicentre study, consisting of JIA patients followed up in the Paediatric Rheumatology Unit of 7 referral hospitals in Catalonia and their control group, consisting of the patient's relatives (siblings or cousins aged 5-16), adjusted for age, sex, weight and height, who wish to participate in the study.

METHODS: 134 patients will be recruited with a consecutive non-probabilistic sample method. Recruitment of patients will last 2 years. They will be divided into two groups depending on the presence or absence of JIA. BMD in children is measured at the lumbar spine (LS) or whole body less head (WBLH) using DXA adjusted by age, sex and height by Z-score. This, together with knowledge of previous fractures, allows us to assess the presence or absence of osteoporosis.

KEYWORDS: Juvenile idiopathic arthritis, childhood osteoporosis, low bone mineral density in children, risk of fractures in children.

3. INTRODUCTION

3.1. JUVENILE IDIOPATHIC ARTHRITIS

3.1.1. CONCEPT

Juvenile idiopathic arthritis (JIA) is the **most common** rheumatic disease in children (1) JIA unifies all forms of chronic childhood arthritis, affecting not only joints, but also extra-articular structures such as eyes, skin, and internal organs. This condition can lead to disability and even associated fatal. JIA is defined as the presence of arthritis of unknown etiology that begins before the age of 16 and persists for at least 6 weeks (2)

3.1.2. EPIDEMIOLOGY

It is the **most common childhood chronic rheumatic disease** and causes **much disability.** In high-income countries, it has a yearly incidence of 2–20 cases per 100. 000 population and a prevalence of 16–150 cases per 100.000 population (2)

A multicentre study conducted in Catalonia, Spain, reported an annual incidence rate of 6.9 cases per 100.000 inhabitants and a prevalence rate of 36-44 cases per 100.000 inhabitants. (3)

Between the different categories of JIA, the most common is oligoarthritis (27-56% of all subtypes), followed by rheumatoid factor (RF) negative polyarthritis (11-28%), systemic-onset JIA (4-17%) and arthritis related enthesitis (ARE) (3-11%) Psoriatic arthritis and FR positive polyarthritis are the least frequent categories (approximately 5% each) (2)

Subtype of JIA	Frequency	Sex ratio
Systemic arthritis	**4-17%**	**F=M**
Oligoarthritis	**27-56%**	**F>>>M**
Rheumatoid-factor(+) polyarthritis	**2-7%**	**F>>M**

Rheumatoid-factor (-) polyarthritis	**11-28%**	**F>>M**
Enthesitis-related arthritis	**3-11%**	**M>>F**
Psoriatic arthritis	**2-11%**	**F>M**
Undifferenciated arthritis	**11-21%**	**-**

Table 1: Frequency and sex distribution of the International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis (JIA). Modified from (2)

3.1.3. CLASIFICATION

The International **League of Associations for Rheumatology (ILAR)** classifies subtypes of autoimmune inflammatory disorders, based on the **number of joints affected**, the presence of **systemic symptoms,** and the **detection of rheumatoid factor** (RF). JIA is divided into the sub-forms: oligoarticular (persistent or extended), polyarticular (RF-negative or RF-positive), systemic (sJIA), psoriatic arthritis and enthesitis-related arthritis, with each differing in genetic susceptibility and severity of arthritis. (2)

Any arthritis that does not fit into these categories or corresponds to more than one subtype is considered as **undifferentiated**(4)

SYSTEMIC ARTHRITIS

Systemic arthritis is quite distinct from other subtypes. The disease arises as often in boys as in girls and does not show a preferential age at onset. Onset in adults (known as adult-onset Still's disease) is rare.

Diagnosis of systemic arthritis requires:

1. Presence of **arthritis accompanied or preceded by quotidien fever** of at least 2 weeks' duration **plus one or more of the following**:
2. Typical evanescent, non-fixed erythematosus **rash** (that characteristically coincides with fever peaks); (Fig 1) **hepatomegaly or splenomegaly, generalized lymphoadenopathy, or serositis**.

   Myalgias and abdominal pain can be intense during fever peaks.

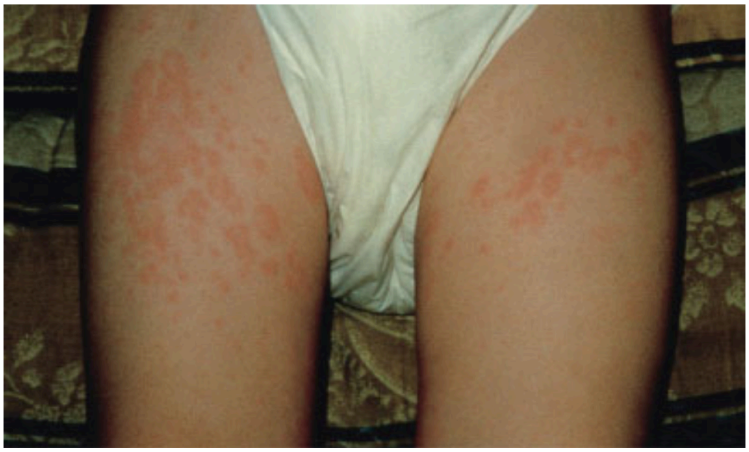

Fig 1. Typical evanescent, non-fixed erythematosus rash in systemic JIA. Extracted from (5)

Arthritis is often **symmetrical and polyarticular**, and could be absent at onset and develop during the disease course.(2)

Laboratory investigations show **leucocytosis** (with neutrophilia), a very high **erythrocyte sedimentation rate** (ESR) and **C-reactive protein concentration**, and **thrombocytosis**. **Anaemia** is common and is microcytic, and is different and more severe than the anaemia of chronic disease seen in adult rheumatoid arthritis. The anaemia seems mostly related to interleukin-6-induced iron sequestration in the reticuloendothelial system. (6)

About 5–8% of children with systemic juvenile idiopathic arthritis develop a life-threatening complication known as **macrophage activation syndrome** (MAS). (7)

The syndrome is characterised by the sudden onset of sustained fever, pancytopenia, hepatosplenomegaly, liver insufficiency, coagulopathy with haemorrhagic mani- festations, and neurological symptoms. Laboratory features include raised triglyceride concentrations, low sodium concentrations, and markedly increased ferritin concentrations (8)

The **differential diagnosis** of systemic juvenile idiopathic arthritis can be difficult, especially at presentation, and includes bacterial or viral infection, malignancy, and other rheumatic diseases. In patients whose systemic features precede the development of overt arthritis, a definite diagnosis cannot be made until arthritis symptoms appear.(2)

OLIGOARTHRITIS

Oligoarthritis is the **most common form** of juvenile idiopathic arthritis (JIA) at onset. It is characterized by involving **4 or fewer joints** in the first 6 months. Depending on the number of affected joints after the first 6 months, we differentiate two groups: **persistent oligoarticular JIA** (never involving more than 4 joints) and **extended oligoarticular JIA** (more than 4 affected joints after the first 6 months of disease)(9).

This form, which is typical of children and is not seen in adults, is characterised by **asymmetric arthritis**, **early onset** (before 6 years of age), **female predilection**, high frequency of positive **ANAs**, and high risk of **iridocyclitis** (Fig 2)

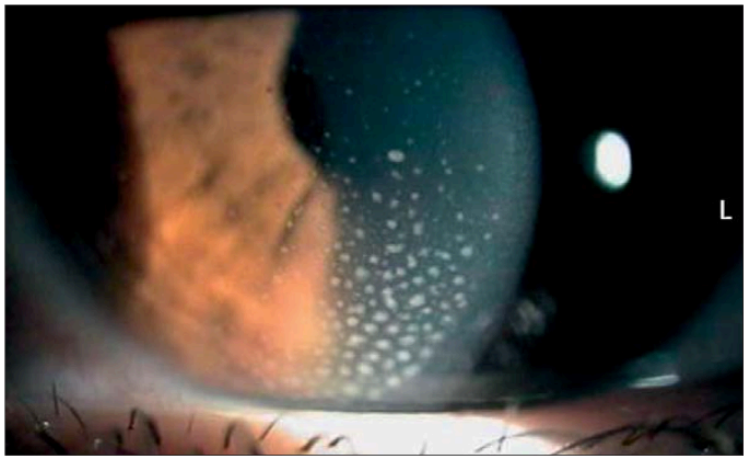

Figure 2: **Iridocyclitis in oligoartritis** Slit-lamp examination shows flare in fluid of anterior chamber and keratic precipitates on posterior surface of cornea. Extracted from (2)

Oligoarthritis is mainly a disease of the **legs**, with the knee joint being mostly affected, followed by the ankles. In about 30–50% of cases, one joint is affected at presentation. Acute-phase reactants are often normal or moderately increased, although in some instances ESR can be quite high. ANAs are detected in substantial titres in about 70–80% of patients, and they represent a risk factor for iridocyclitis.(2)

RHEUMATOID-FACTOR-POSITIVE POLYARTHRITIS

RF-positive polyarthritis is defined as an arthritis that affects **five or more joints** during the first 6 months of disease, and which includes the presence of an **IgM RF** on at least two occasions more than 3 months apart.

The typical presentation is a **symmetric polyarthritis** that affects the **small joints**

of the hands (Fig 3) and feet. The large joints, usually knees and ankles, can also be affected at onset, but usually in association with small joints. (2)

Extra-articular manifestations are rare, except for **rheumatoid nodules**, which occur in up to 30% of cases in the first year of the disease (10)

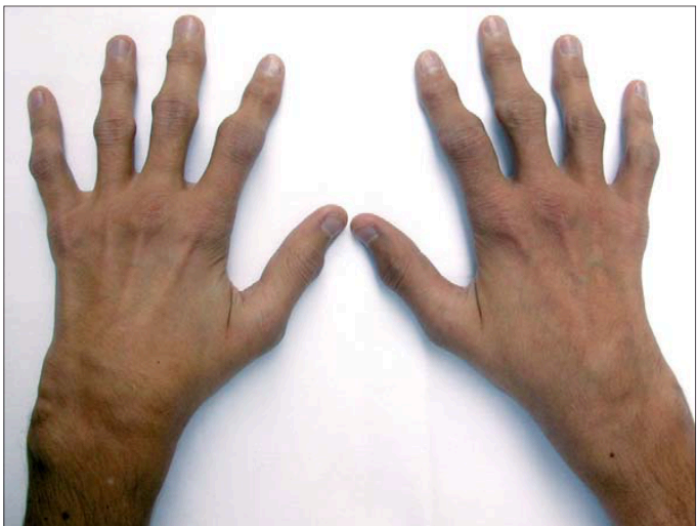

Figure 3: **Symmetric polyarthritis** affecting the metacarpophalangeal, proximal and distal interphalangeal, and radiocarpal joints. Extracted from (2)

RHEUMATOID-FACTOR-NEGATIVE POLYARTHRITIS

RF-negative polyarthritis is defined as an arthritis that affects **five or more joints** during the first 6 months of the disease in the **absence of IgM RF**. (2)

It is probably the most heterogeneous group. At least three distinct subsets of RF-negative polyarthritis can be identified:

The first is a form with asymmetric polyarticular involvement of early onset, between 2-4 years of age, clinically similar to the JIA extended oligoarticular subtype, but with involvement of more than 4 joints in the first 6 months. Predominantly in girls, antinuclear antibody (ANA) is usually positive and is at high risk of developing chronic anterior uveitis. They are associated with HLADRB1*0801.

The second subtype has symmetrical joint involvement of large and small joints, onset is between 6 and 12 years of age, is associated with negative ANAs and elevated acute phase reactants, and has a variable course and prognosis.

Finally, the **third subtype**, called dry synovitis, is characterised by minimal inflammation of the joints but with significant stiffness, leading to rapid development of contractures. Sedimentation rate and other inflammatory parameters are normal or slightly elevated. This subtype often responds poorly to treatment and may follow a destructive course. (10)

ENTHESITIS-RELATED ARTHRITIS

Enthesitis-related arthritis (ERA) is characterised by a predominance of the **males**, a **late age of onset,** and the involvement of **entheseal structures and the axial skeleton**. (11)

ERA patients most are mostly **HLA-B27 positive**. The most common sites of enthesitis are the calcaneal insertions of the Achilles tendon, plantar fascia, and tarsal area.

Arthritis commonly affects the joints of the **lower extremities,** typically asymmetrically. **Hip involvement** is common at disease presentation. About half of patients have four or fewer joints affected throughout the entire course of the disease.(2)

One of the most frequent extra-articular manifestations is **acute anterior uveitis**, occurring in up to 7.8% of patients with ERA

Classification: arthritis and enthesitis, or arthritis or enthesitis and 2 or more of the following: (11)

- Presence or history of sacroiliac pain or inflammatory lumbosacralgia
- HLA-B27 positive
- Onset of arthritis in males over 6 years of age
- Acute anterior uveitis (symptomatic)
- History of HLA-B27-associated diseases in a first-degree relative (father or mother) or full sibling (brother or sister)

PSORIATIC ARTHRITIS

It is defined as the presence of arthritis of 6 weeks or more duration in children under the age of 16 years and psoriasis, or arthritis plus at least one of the following clinical signs: (11)

- Dactylitis.(Fig 4)
- Nail pitting or onycholysis.
- History of psoriasis in a first-degree relative (father or mother) or full sibling (brother or sister)

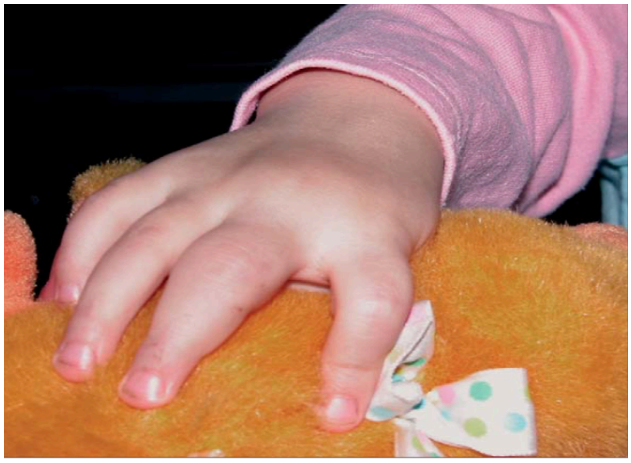

Figure 4: **Dactylitis** in a girl with psoriatic arthritis. Extracted from (2)

It usually has 2 peaks of incidence: the first in early childhood (2-3 years), with a female predominance, and the second in late childhood or pre-adolescence (12-13 years), with no gender predominance.

JPA has great clinical variability and can present with **peripheral or axial involvement**, although there are 3 classic patterns: polyarticular, oligoarticular and spondyloarthritic (more common in adolescents and HLA-B27-positive males).

The most common form is **asymmetric oligoarthritis** in small and large joints (knees, ankles and interphalangeal joints).

UNDIFFERENTIATED ARTHRITIS

Undifferentiated arthritis does not represent a separate subset, but includes patients who do not satisfy inclusion criteria for any category, or who meet the criteria for more than one. (2)

Table 2. *International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis(JIA). Edmonton 2001 criteria. Extracted from (12)*

JIA Category	Definition
Systemic arthritis	Arthritis in ≥1 joint with daily fever of ≥2 weeks duration plus ≥1 of:
	1. Evanescent, erythematous rash
	2. Generalized lymph node enlargement
	3. Hepatomegaly and/or splenomegaly
	4. Serositis
	Exclusions: a, b, c, d (see footnote)
Oligoarthritis	Arthritis affecting 1 to 4 joints during the 1st 6 months of disease.
Persistent	Affecting ≤4 joints throughout the disease course
Extended	Affecting a total of >4 joints after the 1st 6 months of disease
	Exclusions: a, b, c, d, e
Rheumatoid factor negative polyarthritis	Arthritis affecting ≥5 joints during the 1st 6 months of disease; a test for rheumatoid factor is negative.
	Exclusions: a, b, c, d, e
Rheumatoid factor positive polyarthritis	Arthritis affecting ≥5 joints during the 1st 6 months of disease; ≥2 tests for rheumatoid factor ≥3 months apart are positive in the 1st 6 months of disease.
	Exclusions: a, b, c, e

Psoriatic arthritis	Arthritis and psoriasis OR arthritis plus ≥2 of:
	1-.Dactylitis
	2. Nail pitting or onycholysis
	3. Psoriasis in a 1st degree relative
	Exclusions: b, c, d, e
Enthesitis related arthritis	Arthritis and enthesitis OR arthritis OR enthesitis plus ≥2 of:
	1. Sacroiliac joint tenderness and/or inflammatory lumbosacral pain
	2. Presence of HLA-B27 antigen
	3. Acute anterior uveitis
	4. History of spondyloarthritis or acute anterior uveitis in a 1st degree relative.
	Exclusions: a, d, e

Exclusions: a. psoriasis or a history of psoriasis in the patient or a 1st degree relative; b. arthritis in an HLA-B27 positive male beginning after the 6th birthday; c. spondyloarthritis, enthesitis related arthritis, or acute anterior uveitis OR a history of one of these disorders in a 1st degree relative; d. presence of IgM rheumatoid factor on ≥2 occasions ≥3 months apart; e. presence of systemic JIA in the patient

3.1.4. HISTOPATHOLOGY OF JIA

The main hallmark of JIA is **joint inflammation with tissue destruction.** (13)

The **chronically inflamed synovium** and involvement of associated muscle and soft tissues can eventually **lead to degeneration of the osteocartilaginous structures**, which are the primary cause of functional disability in JIA.(14) For this reason, in paediatric rheumatology it is of great importance to follow osteocartilaginous degeneration (15)

Within the synovial joint, the **synovial membrane thickens** in response to uncontrolled proliferation of synoviocytes and immunocompetent cells, including T-cells, B-cells, natural killers, neutrophils, macrophages, dendritic cells and plasma cells that infiltrate the sublining layer of the synovium (Fig. 5)(13)

Hyperplasia and hypertrophy of the synovium causes intra-articular hypoxia, increasing the production of proangiogenic mediators and initiating **pathological angiogenesis**(16)

Leading to increased concentrations of vascular endothelial growth factor (VEGF), a potent endothelial cell (EC) mitogen, its soluble receptors-1 and -2 (sVEGF-R1, sVEGF-R2), and osteopontin, a chemotactic factor that activates mononuclear cells. Angiopoietin-1 (Ang-1), another pro-angiogenic EC mitogen with a role in stabilization of newly formed vessels was also shown to be up-regulated in JIA.

New blood vessel formation within the synovium increases blood supply and the migration of pro-inflammatory cells into the joint, forming a **pathological synovium**, known as ‘pannus’ (1) (Fig. 5).

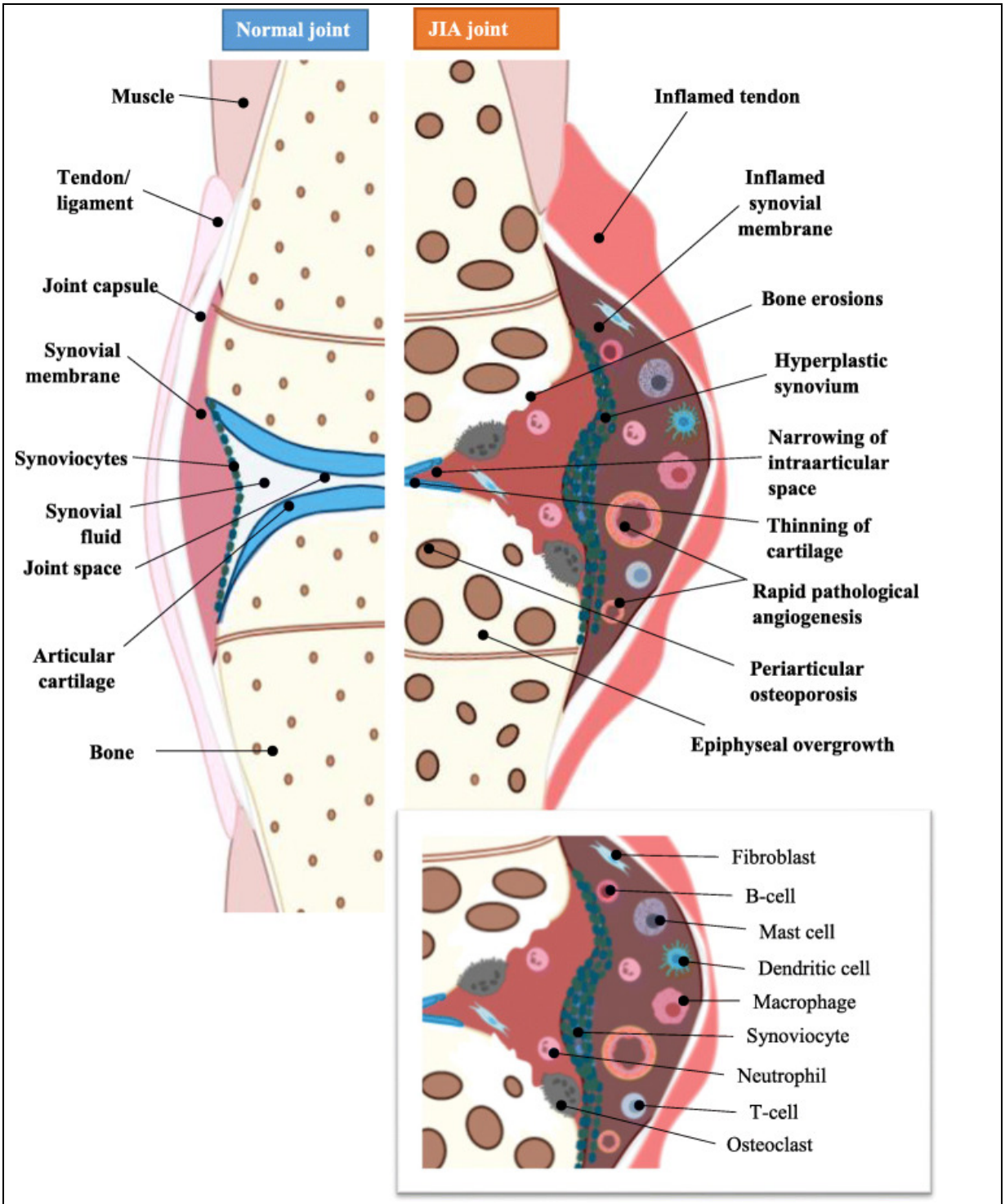

Fig 5. Schematic diagram showing the differences between the normal and JIA joint. The pathological process within the JIA synovial joint is characterised by uncontrolled proliferation of synoviocytes resulting in increased number of layers and thickening of the synovial membrane; rapid pathological angiogenesis; formation of pathological synovium, "pannus", with uncontrolled growth and invasive properties; accumulation of granulocytes, macrophages, plasma cells, lymphocytes and the production of inflammatory mediators, provoking synovitis. Extracted from (1)

3.1.5.ETIOLOGY

The cause and trigger of chronic arthritis in JIA remain unclear. **Abnormal immune responses** triggered by the interactions between **environmental factors** in a **genetically susceptible individual** are speculative. (17)

Some environmental factors such as **antibiotic exposure, infections and caesarean deliveries**, are possible potential risk factors; however**, breastfeeding and household siblings** are possible protective factors.(18)

The following **infectious viruses** (Epstein-Barr virus, Parvovirus B, Rubivirus, Hepatitis B virus) and **bacteria** (Salmonella, Shigella, Campylobacter, S. pyogenes, B. henselae, M. pneumoniae, Chlamydophila pneumonia) have been reported as causal factors provoking JIA (19).

Based on familial aggregation studies and the concordance rate of 25% to 40% in monozygotic twins, **genetic factors play a significant role**.
Specific **HLA alleles and non-HLA genes** may be susceptible to specific JIA subtypes and uveitis (20).

3.1.6.PATHOGENESIS

The **imbalance of regulatory T cells**, Th1 (IFN-gamma secreting T cells), and Th17 (interleukin -17 secreting T cells) of **adaptive immunity** is a characteristic of most JIA subtypes. IL-17 induces proinflammatory cytokines and matrix metalloproteinases, resulting in **joint damage** in **oligoarthritis, polyarthritis, and psoriatic arthritis**. (21)

In **ERA**, IL-23 is a crucial cytokine that leads to inflammation through IL-17 and tumor necrosis factor (TNF), and new bone formation through IL-22.(22)

In contrast, the critical immunopathophysiology of **systemic arthritis** is persistent activation of **innate immunity**, including monocytes,(23) macrophages, and neutrophils(24).
As a result, **innate proinflammatory cytokines** such as IL-1 beta, IL-6, and IL-18 contribute to symptoms and signs of systemic arthritis. (25)

3.1.7. TREATMENT

NON-PHARMACOLOGICAL TREATMENT

It is essential, as a chronic process, to ensure **adequate caloric and nutritional intake**, paying special attention to calcium and vitamin D supplementation.

Physical and occupational therapy play a fundamental role in the triple aspect of improving range of motion, relieving pain and preventing disability. (26)

PHARMACOLOGICAL TREATMENT

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**

Their proven effects in controlling joint pain and stiffness mean that they are used in the initial treatment and in association with second-line drugs.

- **Corticosteroids**

In general, their use tends to be **limited** in the oral route (prednisone or prednisolone) and parenterally (methylprednisolone) **due to their known side effects**. However, they are **useful in systemic JIA**, for the treatment of fever and serositis, and in **polyarticular forms** as a bridging therapy with other drugs. They are also used topically in the treatment of uveitis.

Intra-articular triamcinolone acetonide is used. Its beneficial effects have been clearly proven.

- **Synthetic disease-modifying drugs**

Methotrexate. This is the main disease-modifying drug (DMARD) used in the treatment of JIA. It is a folic acid analogue with anti-inflammatory and immunomodulatory action.

Sulphasalazine. Appears to be effective in polyarticular and oligoarticular forms and oligoarticular forms and perhaps in ERA. Not useful in systemic forms where it may increase toxicity.

- **Biological disease-modifying drugs**

TNF- α antagonists. TNF-α antagonists are typically prescribed for patients who have arthritis that is unresponsive to standard therapy or who have clinical and radiological indications of active sacroiliitis despite undergoing adequate NSAID therapy. Some of the most commonly used TNF-α antagonists include etanercept, adalimumab, and infliximab.

Interleukin-1 antagonists. This group includes a receptor antagonist (anakinra), a fusion protein (rilonacept) and a human anti-IL-1b monoclonal antibody (canakinumab).

Interleukin-6 antagonists. Tocilizumab is a human anti-IL-6 monoclonal antibody. Preliminary clinical trials showed a rapid response in patients with systemic JIA, with a good safety profile. (26)

From 2019 to 2021, the **American College of Rheumatology** published recommendations for the treatment of JIA. (27,28)

According to this guidelines:

- Patients with oligoarthritis: **NSAIDs** are conditionally recommended as part of initial therapy for active oligoarthritis. **Intraarticular glucocorticoids** (IAGCs) such as triamcinolone hexacetonide are strongly recommended as part of initial therapy. **Conventional synthetic DMARDs** such as methotrexate are strongly recommended if there is an inadequate response. **Biologic DMARDs** are strongly recommended if there is inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD for active oligoarthritis.
- Patients with polyarticular JIA require initial **methotrexate** treatment. For those who do not respond adequately, and have a low disease activity intra-articular **glucocorticoid injection** is required, and for those who have a moderate/high disease activity **TNF-a antagonist** will be added.
- Patients with systemic JIA **Biologic DMARDs** (IL-1 and IL-6 inhibitors) are conditionally recommended as initial monotherapy for systemic JIA with or without macrophage activation syndrome (MAS), **NSAIDs** are also conditionally recommended as initial monotherapy **for systemic JIA without MAS**, while **glucocorticoids** are conditionally recommended as part of the

initial treatment of **systemic JIA with MAS.** Biologic DMARDS or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors.

- Patients with enthesitis-related arthritis: **NSAID** treatment is strongly recommended. Bridging therapy with a limited course of **oral glucocorticoids** (<3months) during iniciation or escalation of therapy is conditionally recommended. Using a **TNF-a antagonist** is conditionally recommended over methotrexate or sulfasalazine.
- Patients with psoriatic arthritis: **NSAID** is recommended initial treatment combined or not with **oral glucocorticoids** (<3months) during iniciation or escalation of therapy. **Conventional synthetic DMARDs** such as methotrexate are recommended if there is an inadequate response. (11)

Oligoarthritis

- 1. Initial active arthritis: non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoid inyection
- 2.No response: Methotrexate or biologic disease-modifying drug (DMARD)

Polyarthritis

- 1. Initial methotrexate treatment
- 2. If no response and low disease activity:intra-articular glucocorticoid inyection will be added.
- 3. If no response and moderate/high activity: TNF-a antagonist will be added.

Systemic arthritis

- 1. No macrophage activation syndrome (MAS): Biological DMARDs+-NSAIDs
- 2. MAS: Biological DMARDs +- Glucocorticoids.
- 3: If no response: change DMARDs

Enthesitis related-arthritis

- 1. Initial NSAID+- oral glucocorticoid
- 2. TNF-a antagonist if there is an inadequate response

Psoriatic arthritis

- 1- Initial NSAID+- oral glucocorticoid
- 2. Methotrexate if there is an inadequate response

Table 3. Summary of the main treatments for each type of JIA. Synthesised information from the **American College of Rheumatology guideline** JIA treatment.(27,28)

3.1.8. DISEASE COURSE

Significant **advances** have been made in the diagnosis and treatment of JIA over the last three decades. Clinical outcomes have remarkably improved, with most patients now able to **achieve disease control and remission**. However, it is worth noting that a considerable proportion of patients still experience ongoing disease activity. In fact, around **half of patients require active treatment throughout their adult lives**, whereas the attainment of **complete remission is only feasible in 20-25%** of patients. (29)

Comorbidities and complications emphasize JIA's significance as the primary paediatric rheumatological condition, which may persist with remissions and flares throughout life, causing connective tissue impairment and reduced quality of life. (2)

3.2. OSTEOPOROSIS

Osteoporosis is a disorder characterised by a reduction in bone mass and alterations in the microarchitecture of bone tissue, resulting in bone fragility and consequently in an elevated risk of fractures (30)

At present, osteoporosis is a public health problem in industrialised countries, affecting about 30% of women and 8% of men over 50 in Europe. (31) Although it has typically been considered an adult disorder, it is becoming increasingly clear that osteoporosis might be rooted in childhood and adolescence (32)

Osteoporosis is a major public health problem with serious long-term complications and increased morbidity that is largely unrecognised in children and young adults. (33)

According to the cause it is usually **classified in primary or secondary form:** (34)

Table 4. Causes of primary and secundary osteoporosis*. Extracted from (34)*

PRIMARY OSTEOPOROSIS
Ehlers-Danlos syndrome
Homocystinuria
Marfan's syndrome
Osteogenesis imperfecta
Idiopathic (juvenile) osteoporosis
SECUNDARY OSTEOPOROSIS
Inflammatory Diseases
Juvenile idiopathic artritis
Systemic lupus erythematosus
Inflammatory bowel disease
Chronic Immobilisation
Cerebral palsy
Meningomyelocele
Myopathic diseases (e.g. Duchenne, spinal muscular atrophy)
Nutritional, Intestinal and Malabsorption Disorders
Coeliac disease and other malabsorption syndromes
Schwachman-Diamond disease
Cystic fibrosis
Malnutrition; vitamin and mineral deficiency
Haematologic Disorders
Leukaemia
Thalassaemia
Endocrine Disturbances
Growth hormone deficiency
Sex hormone deficiency (e.g. hypogonadism, Turner's syndrome)
Hyperthyreosis
Cushing's syndrome
Anorexia nervosa
Secondary to Therapies with Adverse Effects on Bone Health
Following chemotherapy for childhood malignancy
Following solid organ or bone marrow transplant
Glucocorticoids, anticonvulsants, heparin, calcineurin inhibitors

Osteogenesis imperfect (OI) is the most prevalent form of **primary osteoporosis** in children. (35) **Secondary forms** of paediatric osteoporosis are caused by **adverse effects of systemic diseases and/or their treatment effect** on bone mass.

During the course of these chronic disorders in the secondary forms several factors may interact to determine osteoporosis, in addition to the direct bone adverse effects of the disease or its treatment. These factors include prolonged immobilisation, reduced time spent outdoors and possibly consequent vitamin D deficiency, hypogonadism, and poor nutrition. The inflammatory systemic diseases are characterized **by increased levels of proinflammatory cytokines** (such as tumor necrosis factor alpha, interleukin-1, and interleukin-6) that uncouple bone remodeling cycle, interfering with bone mass acquisition (36)

Glucocorticoid-associated osteoporosis is a frequent complication of childhood systemic inflammatory diseases and the most common form of secondary osteoporosis. (35)

It is important to note that **bone matrix mineralisation** takes place during these stages of life, and therefore subjects reach peak bone mass at the end of this growth phase. If this peak is not optimal, as can occur in chronic inflammatory diseases such as JIA, it will facilitate the development of **osteoporosis in adulthood**. This is why knowledge about bone health is so important in this disease. (32)

Furthermore, the incidence of childhood osteoporosis is increasing due to, among other factors, the increased survival rate of patients suffering from chronic diseases and the increased use of drugs that can damage bones(37) .

The **definition of osteoporosis** in children and young adults differs from the one in adults, as it is based not only on densitometric criteria alone but also on the occurrence of fragility fractures. (33)

In 2013, the **International Society of Clinical Densitometry** task force produced pediatric positions that **define pediatric osteoporosis** (38)

Based on these positions, osteoporosis in children is defined by:

The presence of a clinically significant fracture {vertebral fractures (VF)} or a significant fracture history and a low bone mineral density (BMD).

1. The finding of one or more vertebral compression fractures is indicative of osteoporosis in the absence of local disease or high-energy trauma regardless of the BMD Z-score.

2. In the absence of VF, diagnosing osteoporosis requires either the presence of a clinically significant fracture and a BMD z-score ≤ -2. Clinically significant fractures are defined as follows:

    - Two or more long bone fractures by age 10 years.
    - Three or more long bone fractures at any age up to 19 years.

OSTEOPOROSIS TREATMENT

A crucial aspect to consider when studying bone health in children is that this stage presents a **non-pharmacological therapeutic opportunity** to prevent deterioration in bone health, an increase in the number of fractures in adulthood and a deterioration in quality of life.

As a general guideline, **high-risk groups should undergo DXA** and spinal imaging screening from diagnosis or at a minimum age, based on the chronic illness's duration and severity and/or the frequency and nature of fractures (39). Meantime, precautionary measures should be taken to prevent, postpone, or treat osteoporosis.

Preventive measures

- Annual monitoring of **vitamin D status** is recommended during late winter or early spring, with hypovitaminosis D requiring treatment. To maintain optimum vitamin D and calcium status, it is important to ensure regular intake of 600-1000 IU of vitamin D and elemental calcium according to age, either through diet or supplements (40)
- Appropriate **hormonal therapy** is necessary to correct growth retardation, pubertal delay, or hypogonadism. (41)
- Effective management of the **underlying disease** is the optimal primary strategy to prevent secondary osteoporosis.(41)
- It is essential to optimize **nutritional status**, and for children with linear growth delay and osteoporosis risk factors, consideration should be given to supplemental enteral nutrition. (33)
- The close correlation between muscle force and bone formation is well-established (42), thus interventions to **enhance muscle force and power** should be integrated into the treatment plan for children with JIA. (43)
- **Glucocorticoid dose** should be kept to the minimum required and steroid-sparing agents, such as biological factors should be used instead, where appropriate. Non-steroidal therapies should be used, when possible, to maintain remission, once achieved. (33)
- In **inflammatory conditions**, consider treating inflammation with steroid-sparing techniques. Anti-inflammatory treatment with the tumor necrosis factor-alpha (TNF-alpha) antibody could be more suitable option in certain situations to manage inflammation. (33)

Medical treatment of osteoporosis.

In OI and other forms of primary osteoporosis, treatment with **bisphosphonates** is usually recommended as soon as osteoporosis is recognized.(44) However, in children with secondary osteoporosis, treatment with bisphosphonates is more controversial and should be reserved for cases where all other therapeutic measures have failed and there are severe, persistent fractures. These decisions need to be made by specialists in treating osteoporosis in children.(33)

4.JUSTIFICATION

Juvenile idiopathic arthritis (JIA) is the **most common rheumatological pathology of the childhood** (45) and can be a cause of associated morbidity, including **limitations in adult life**.(2)

It has been reported that up to 50% of **adult patients with a history of JIA have low BMD** that can lead to fractures, but these data are from more than 15 years ago.(43) Today, thanks to early diagnosis and the therapeutic options available to us, these comorbidities have been substantially reduced.

Even so, **we do not know the current incidence** of some of them. Especially those that occur quietly, such as low bone mineral density (BMD) for chronological age or even childhood osteoporosis(OP).

The greatest increase in bone mineral content (BMC) during life occurs during adolescence (46) and ceases in the mid-twenties. Young adults with **higher peak bone mass are likely to have a lower risk of developing osteoporosis** in later life. This is particularly important when there is a relative **impairment in bone formation**, such as occurs in **JIA**, which will have an accentuated effect during the adolescent years when bone acquisition would normally be at its maximum.

It is important for healthcare professionals to be knowledgeable about children's bone health, particularly those at risk of low BMD for chronological age/OP, such as JIA patients, in order to **recognise the window of opportunity for therapeutic strategies early in children's lives**, before peak bone mass is reached, as optimising bone strength accrual during growth is important to prevent fractures and deterioration in quality of life in these patients.(47)

As for the **control group** concerns there is not enough literature on bone health in healthy children and the associated factors that may influence their bone health, in both in children with and without JIA, and we should not forget that the childhood

age represents a unique opportunity for **prevention and treatment** of these diseases.

In addition, we use DXA to assess bone health, a non-invasive test with minimal radiation (1-6 µSv, equivalent to 1 day of natural background radiation of 7-21 µSv) and the scan is simple and fast (60seconds)(48)

Recently, recommendations have been published to **standardise the assessment of bone health** in paediatric patients at risk of developing low BMD for chronological age/OP, such as children with JIA(39). For this reason, and in the absence of recent studies which provide more comprehensive information on the bone health of these children, we propose this study.

In conclusion, we propose this study in view of recent recommendations assessing bone mineralisation in children at risk of osteoporosis, the lack of recent studies providing more comprehensive information on the bone health in JIA and non-JIA paediatric patients, and because of the window of opportunity for therapeutic strategies early in children's lives, before peak bone mass is reached, to prevent fractures and deterioration of quality of life in these patients.

5. HYPOTHESIS

5.1. MAIN HYPOTHESIS.

1. Patients with JIA have a higher prevalence of low BMD for chronological age/ OP than healthy patients.

5.2. SECONDARY HYPOTHESIS.

1. There are differences in the prevalence of low BMD for chronological age/OP between the different subtypes of JIA.
2. Bone health parameters are normal in healthy paediatric patients.

6. OBJECTIVES

6.1. MAIN OBJECTIVE

1. To analyse the prevalence of low BMD for chronological age/OP in patients diagnosed with JIA in Catalonia and compare it with healthy paediatric patients.

6.2. SECUNDARY OBJECTIVES

1. To evaluate the prevalence of low BMD for chronological age/OP in the different **subtypes of JIA.**
2. To study the **variables** that may be associated with low BMD/OP in patients with JIA.
3. To define **phosphocalcium analytical parameters**, including vitamin D, and markers of bone remodelling, in patients with JIA with and without low BMD for chronological age/OP

7. SUBJECTS AND METHODS

7.1. STUDY DESIGN

This study is designed as a **cross-sectional study** comparing two populations of patients with and without JIA.

It is an observational and multicentre study, composed of JIA patients followed up in the paediatric rheumatology unit of 7 referral hospitals in Catalonia and their **control group**, composed of the patient's relatives (siblings or cousins aged 5-16 years), who wish to participate in the study.

7.2. STUDY SETTING

The selection of the **referral centres** to participate in the study will be based on the following criteria:

1. Those centres that have the **capacity to perform a DXA** study from within the hospital centre or on an outsourced basis will be able to participate.
2. Those centres that have a **paediatric rheumatology** unit.

Based on the previous criteria the following centres will participate in our study:

1. Hospital Universitari Doctor Josep Trueta (Girona)
2. Hospital Sant Joan de Deu (Barcelona)
3. Hospital Universitari Vall d'Hebron (Barcelona)
4. Hospital Sant Pau (Barcelona)
5. Hospital Universitari Germans Trias i Pujol (Badalona)
6. Hospital Sant Joan de Déu de Manresa (Manresa)
7. Hospital Universitari Parc Taulí (Sabadell)

7.3. STUDY POPULATION

The population of this study will be **patients diagnosed with JIA** under follow-up in the paediatric rheumatology area of 7 referral hospitals in Catalonia who meet the International League of Associations for Rheumatology (ILAR) classification criteria for JIA (12) (Table 2), and their **control group** will be the patient´s relatives (siblings or cousins aged 5-16 years), who wish to participate in the study.

7.3.1. GENERAL INCLUSION CRITERIA

1. Who is between 5 to 16 years old
2. Who can speak and understand Catalan, Spanish and/or English
3. Who has an adequate level of awareness and ability to collaborate throughout the process

7.3.2. INCLUSION CRITERIA FOR JIA GROUP

1. Patients with a diagnosis of JIA fulfilling the ILAR clasification for one of the subtypes of JIA.
2. Patients followed up in the paediatric rheumatology unit of 1 of the 7 referral hospitals in Catalonia.

7.3.3. INCLUSION CRITERIA FOR CONTROL GROUP

1. Children aged 5-16 years who are relatives of JIA patients (siblings or cousins)

7.3.2. GENERAL EXCLUSION CRITERIA

1. Patients with **primary osteoporosis**
2. Patients diagnosed with other **diseases or osteotoxic treatments** that may be a cause of secondary osteoporosis other than JIA (Table 4)

7.4. SAMPLING

7.4.1. SAMPLE SIZE

The sample size was estimated using the **GRANMO software**.

Assuming a risk alpha of 5% and a risk beta of less than 20%, with a statistical power of 80% in a bilateral contrast, 67 subjects in the first group (AIJ patients) and

67 in the second group (control group) are needed to detect a difference equal to or greater than 15% between the two. **A total of 134 patients** will be needed for the study.
In the control group, a ratio of 0.02 is assumed because there is no literature of the prevalence of osteoporosis in children without JIA. However, this is estimated to be a low value. A loss-to-follow-up rate of 0% has been estimated.

7.4.2. SAMPLE SELECTION

Our sample will be obtained through a **consecutive non-probabilistic sampling**.

Parents/guardians of diagnosed JIA patients being followed up in the paediatric rheumatology unit of the above-mentioned referral hospitals who meet the ILAR classification criteria and who fulfil the inclusion criteria and none of the exclusion criteria will be offered the opportunity to participate in the study.

For the **control group**, during the same visit the parents/guardians of this JIA patients will be asked about the possibility of having relatives of the patient (siblings or cousins aged 5-16 years) who meet the inclusion criteria and none of the exclusion criteria participate in the study.

All such patients will be asked to participate and will be given a detailed verbal explanation of the study and the steps to be followed, as well as the information document and informed consent. (Annex 2) (Annex 3)

Healthcare professionals will emphasise the voluntary and confidential nature of patient participation.

7.4.3 ESTIMATED TIME OF SAMPLE RECRUITION

With regard to the **recruitment time**, a recruitment time of 1 year is estimated according to the controls carried out in children with JIA, which are carried out every 3 months, and the availability of DXA, which can be programmed in a period of less than 1 month.

7.5. VARIABLES AND MEASUREMENTS

7.5.1. INDEPENDENT VARIABLE

The independent variable is the **presence or absence of juvenile idiopathic arthritis (JIA)**, which is a dichotomous nominal qualitative variable (yes/no). The information about this variable has been described in detail in the introduction, and we will collect the presence or absence of JIA from the patient's medical records.

7.5.2. DEPENDENT VARIABLE

The dependent variable is the **development of osteoporosis**, a dichotomous nominal qualitative variable (yes/no), that depends on the **number of previous fractures** and the **BMD measured at the lumbar spine (LS) or whole body less head (WBLH) by DXA** and **adjusted by the Z-score,** which expresses the number of standard deviations (SD) by which the patient's BMD deviates from the mean of healthy controls of the same age, sex and height.

Based on the **International Society of Clinical Densitometry** Task Force (2013) and their definition of paediatric osteoporosis (38) a patient is considered to have osteoporosis if they meet one of the following criteria:

1. The presence of **one or more vertebral compression fractures** is indicative of osteoporosis in the absence of local disease or high-energy trauma regardless of the BMD Z-score.
2. In the absence of vertebral fractures, the diagnosis of osteoporosis is indicated by **both the presence of a clinically significant fracture and a BMD Z-score ≤ -2**.

   Clinically significant fractures are either:
   - Two or more long bone fractures by age 10 years.
   - Three or more long bone fractures at any age up to 19 years.

Vertebral fractures and BMD are measured as follows:

Vertebral fractures can be scored using the **Genant semiquantitative method** (Fig 6). This is a visual grading system for VFs detected on a vertebral fracture assessment (VFA) dual-energy X-ray absorptiometry (DXA) study. Each vertebra is individually assessed and graded from 0 to 3.

- Grade 0= normal
- Grade 1= mild fracture with 20-25% reduction in anterior, middle, or posterior height relative to the same or adjacent vertebra.
- Grade 2 = moderate fracture with 25-40% reduction in anterior, middle, or posterior height relative to the same or adjacent vertebra.
- Grade 3 =severe fracture with >40% reduction in anterior, middle, or posterior height relative to the same or adjacent vertebra.(49)

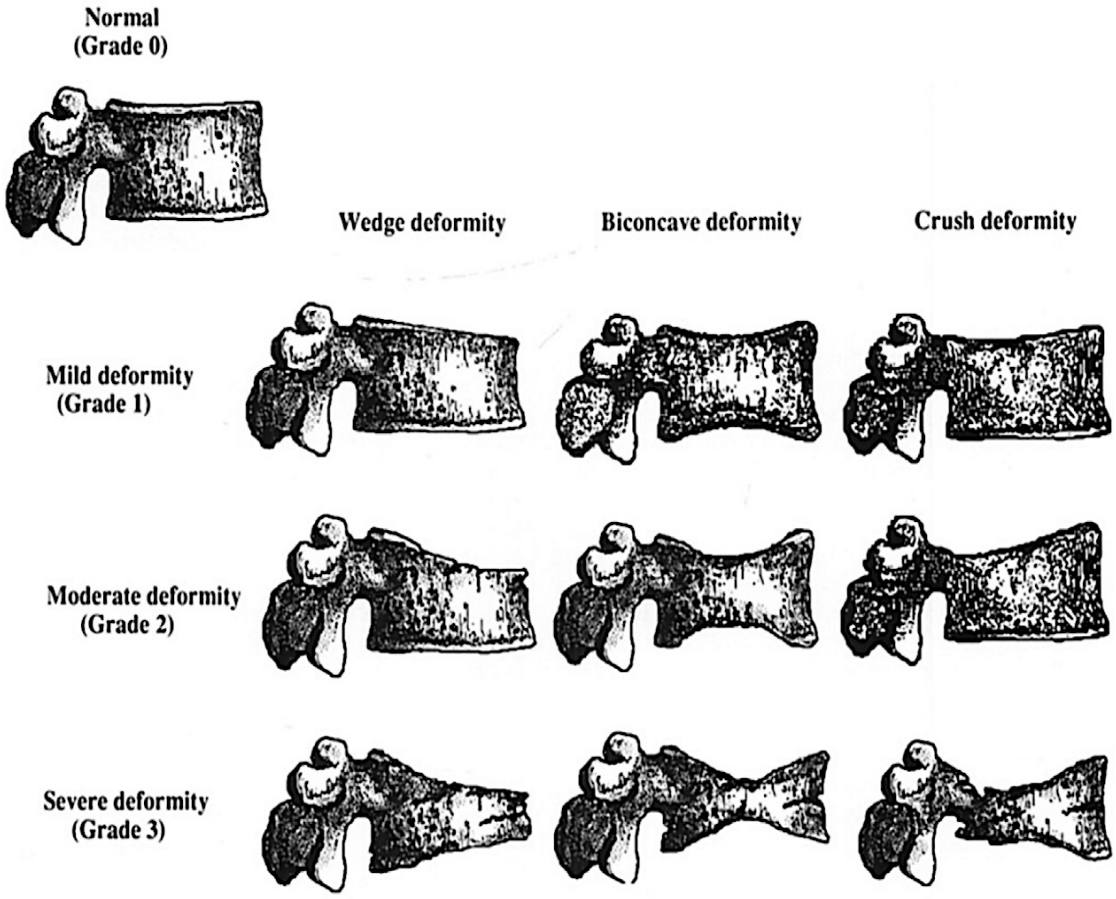

Fig. 6. Semiquantitative visual grading of vertebral deformities. Extracted from (49)

Measurement of BMD in children

Low BMD for chronological age is a densitometric concept and his study has been modified by the latest recommendations of the **International Society for Clinical Densitometry** (ISCD), which recommend dual-energy X-ray absorptiometry (DXA) of the lumbar spine or whole body (33) adjusted for age, sex and height by Z-score as the **method of choice** for measuring bone mineral density (BMD) in the paediatric age group. Low BMD for chronological age applies to the growing population when **the BMD Z-score is less than or equal to -2, adjusted for age, sex and height.**

DXA is a **non-invasive** test with minimal radiation (1-6 μSv, equivalent to 1 day of natural background radiation of 7-21 μSv) and the scan is simple and fast (60seconds)(48). DXA should be performed in children older than 5 years, as younger children are more difficult to cooperate, and there are no reference data for this age group.

The main confounding factor of DXA is that BMD increases as the bones get larger. (50) Thus, DXA may underestimate BMD in children with short stature or growth retardation and overestimate BMD in tall children, even though the volumetric BMD is equal. Therefore, the measurements should be corrected for height using appropriate methods and bone mineral apparent density (BMAD) for i-DEXA Lunar scanners or height-adjusted z-score (HAZ) for Hologic scanners are the preferred methods for correcting for short stature (51,52).

7.5.2. COVARIABLES

- Clinical and demographic variables
  - **Sex**: Phenotypic sexual characteristics of the patient. It is be expressed as “male” or “female”. *Important for adjustment in densitometry*.
    This variable will be collected from data collection form. (Annex 1) It is a qualitative nominal dichotomous variable.
  - **Date of birth**: Date of birth will be collected from the data collection form. (Annex 1) Age is *important for adjustment in densitometry*. It is a quantitative discrete variable.

- **Weight** is measured on a calibrated scale during the physical examination. It must be expressed in kg*. It is important for adjustment in densitometry.* It is a quantitative continuous variable.
- **Height:** is measured during the physical examination on a calibrated stadiometer. The value must be expressed in cm*. It is important for adjustment in densitometry.* It is a quantitative continuous variable.
- **Pubertal stage:** Puberty is the developmental process of physical changes as the body matures from childhood to adulthood. The staging system to describe these changes is **Tanner Staging**.

  The scale defines physical sexual measurements such as breast size, external genitalia, testicular volume and pubic hair development, we will define these parameters with a **physical examination** that will allow us to determine the pubertal stage,which goes from 1-5 calling pre-pubertal patients Tanner stage 3 or below, and pubertal patients Tanner stage 4 or above. It is a qualitative ordinal polytomous variable.

  This is relevant because the production of sex steroids at the onset of puberty is clearly **associated with an increase in the acquisition of bone mineral density during** this period.(53) This production has a protective effect on BMD and is associated with a reduced incidence of atraumatic fractures(54)

  Delayed puberty can result in reduced BMD and subsequent increased rate of fractures(33)
- **Family history of osteoporosis.** This variable will be collected from the data collection form. (Annex 1) First degree relatives affected (father or mother) or full sibling (brother or sister). It is a qualitative nominal dichotomous variable
- **Presence of previous fractures and number and location of previous fractures:** Previous fractures collected from the data collection form (Annex 1)

  It is a qualitative nominal dichotomous variable (Yes if fracture present or no fractures no present)

  (If yes, the number of fractures is a quantitative discrete variable and the location of fractures is a qualitative nominal polytomous variable)

- **Physical activity:** Documenting this is important because physical activity during the years of rapid growth adds bone mass to the periosteal surfaces which improves bone strength and reduces the risk of osteoporosis and future fractures.(47) Data will be collected from the validated PAQ-C questionnaire (55) which assesses physical activity in children up to 14 years of age (Annex 4) and the validated PAQ-A Questionnaire (56) which assesses physical activity in children over 14 years of age (Annex 5). The data were scored on a 5-grade scale, with 1 representing low physical activity and 5 representing high physical activity. It is a qualitative ordinal polytomous variable.

DEMOGRAPHIC VARIABLES	DEFINITION	TYPE OF DATA	CATEGORIES OR VALUES
Sex	Phenotypic sexual characteristics of the patient collected from the data collection form (Annex 1)	Qualitative nominal dichotomous variable	0: MALE 1: FEMALE
Date of birth	Collected from the data collection form (Annex 1)	Quantitative discrete variable	Day/Month/Year
Weight	Measured during the physical examination and collected in the data collection form (Annex 1)	Quantitative continuous variable.	Expressed in kg
Height	Measured during the physical examination and collected in the data collection form (Annex 1)	Quantitative continuous variable.	Expressed in cm
Pubertal stage	The staging system to describe these changes is Tanner Staging determinated by physical examination and	Qualitative ordinal polytomous variable	-Tanner 1 -Tanner 2 -Tanner 3 -Tanner 4 -Tanner 5

	collected in data collection form (Annex 1)		
Family history for osteoporosis	Collected from data collection form (Annex 1)	Qualitative nominal dichotomous variables	Yes/No
Previous fractures	Previous fractures collected from data collection form (Annex 1)	Qualitative nominal dichotomous variables (If yes, number of fractures quantitative discrete variables/ location of fractures qualitative nominal polytomous)	Yes/No Number of fractures (1,2,3..) Location of fractures
Physical activity	Collected from PAQ-C or PAQ-A Questionnaire to Assess Physical Activity in Children (Annex 4-5)	Qualitative ordinal polytomous variable	Scale from 1 to 5 1: Very low physical activity 5: Very high physical activity

- Variables related to JIA
  - **Subtypes of JIA:** Main clinical and laboratorial characteristics of JIA subtypes based on (ILAR) classification criteria (Table 2). Data collected from medical records. It is a qualitative nominal polytomous variable

    We consider 6 subtypes of JIA:

- Oligoarticular JIA
- Polyarticular JIA RF (-)
- Polyarticular JIA RF (+)
- ERA
- Psoriatic JIA
- Systemic sJIA

- **Date of diagnosis:** Data collected from medical records. It is a quantitative discrete variable.
- **Disease activity** was assessed using the JIA Disease Activity Score (JADAS) which is calculated according to the number of joints affected, the patient's and his family´s global assessment of disease activity on a visual analogue scale (VAS), the physician´s assessment of disease activity on the VAS and elevation of acute phase reactants (including assessment of C-reactive protein or ESR).(57) Disease activity is scored as follows: <1, inactive; ≥1 but ≤3.8, low activity; ≥3.8, high activity. It will be a qualitative ordinal polytomous variable.

VARIABLES RELATED TO JIA	DEFINITION	TYPE OF DATA	CATEGORIES OR VALUES
Subtypes of JIA	Main clinical and laboratorial characteristics of JIA subtypes based on (ILAR) classification criteria (Table 2)	Qualitative nominal polytomous variable	1- Oligoarticular JIA 2-Polyarticular JIA RF (-) 3- Polyarticular JIA RF (+) 4-ERA 5- Psoriatic JIA 6- Systemic sJIA
Date of diagnosis	Data collected from medical records	Quantitative discrete variable	Day-Month-Year
Disease activity	Measured by the JIA Disease Activity Score and collected in data collection form (Annex 1)	Qualitative ordinal polytomous variable	<1, inactive; ≥1 but ≤3.8, low activity; ≥3.8, high activity

- Variables related to JIA treatment:
    - Treatment with **glucocorticoids** is a qualitative nominal dichotomous variable that will be collected from medical records and is important to collect as a negative correlation has been found between bone mass and cumulative dose of glucocorticoids in children. (58) During childhood and adolescence, glucocorticoids may interfere with the physiological process of bone mass accumulation and cause a deterioration of peak bone mass, resulting in an increased risk of fracture in later life (33) although it is also true that more severely affected patients are more likely to be treated with glucocorticoids and the effect of disease severity (inflammation) and glucocorticoids is very difficult to separate (confounding effect). For this reason, I will include this variable in the multivariate analysis.
    - Treatment with **disease-modifying drugs** (DMARDs) (synthetic or biologic) is a qualitative nominal dichotomous variable that will be collected from medical records.

      Methotrexate, which is the most frequent DMARDs in children, can cause osteopenia in children patients with malignancies, but low-dose methotrexate used in inflammatory diseases did not influence negatively the bone mass.(59)
    - **Duration of glucocorticoid therapy** is a quantitative discrete variable that will be collected from medical records.
    - **Glucocorticoids average dose is a** quantitative continuous variable that will be collected from medical records.

VARIABLES RELATED TO JIA TREATMENT	DEFINITION	TYPE OF DATA	CATEGORIES OR VALUES
Treatment with glucocorticoids	Data collected from medical records	Qualitative nominal dichotomous variable	Yes/No
Duration of glucocorticoid	Data collected from medical	Quantitative	Days

therapy	records	discrete variable	
Glucocorticoids average dose	Data collected from medical records	Quantitative continuous variable	(Mg/kg/day of treatment)
Biological disease-modifying antirheumatic drugs (DMARDs)	Data collected from medical records	Qualitative nominal dichotomous variable	Yes/No
Synthetic disease-modifying antirheumatic drugs (DMARDs)	Data collected from medical records	Qualitative nominal dichotomous variable	Yes/No

- Densitometric variables (DXA)
  - **Vertebral BMD:** value of vertebral as BMD measured by DXA. It is a quantitative continuous variable.
  - **Vertebral Z-score:** Number of standard deviations from the mean value of vertebral BMD in the population of the same age, sex and height, where a result ≤ -2 means that vertebral BMD is low for the chronological age and a result ≥ -2 means that vertebral BMD is not low for the chronological age. It is a qualitative dichotomous variable.
  - **Whole body BMD without head:** value of whole body BMD measured in DXA. It is a quantitative continuous variable.
  - **Whole body Z-score without head:** Number of standard deviations from the mean value of whole body BMD in the population of the same age, sex and height, where a result ≤ -2 means that whole body BMD is low for the chronological age and a result ≥ -2 means that whole body BMD is not low for the chronological age. It is a qualitative dichotomous variable.
  - **Vertebral morphometry** using the Genant quantitative scale, is a visual grading system for vertebral fractures detected on a vertebral

fracture assessment (VFA) dual-energy X-ray absorptiometry (DXA). Each vertebra is individually assessed and graded from 0 to 3. Where 0 is normal; 1 is a mild fracture; 2 is a moderate fracture and 3 is a severe fracture. It is a qualitative ordinal polytomous variable. (Fig 6)

DENSITOMETRIC VARIABLES	DEFINITION	TYPE OF DATA	CATEGORIES OR VALUES
Vertebral BMD	Value of vertebral BMD measured in DXA	Quantitative continuous variable	Continuous numerical value
Vertebral Z-score	Number of standard deviations from the mean value of BMD in the population of the same age, sex and height	Qualitative dichotomous variable	≤-2: Low BMD for chronological age ≥ -2: No low BMD for chronological age
Whole body BMD without head	Value of whole body BMD measured in DXA	Quantitative continuous variable	Continuous numerical value
Whole body Z-score without head	Number of standard deviations from the mean value of BMD in the population of the same age and sex and height	Qualitative dichotomous variable	≤ -2: Low BMD for chronological age ≥ -2: No low BMD for chronological age

Vertebral morphometry	Visual grading system for vertebral fractures applying the Genant quantitative scale	Qualitative ordinal polytomous variable	Grade 0 Grade 1 Grade 2 Grade 3

- Analytical variables:

  - **Calcaemia and Vit D (25-Hidroxy-Vitamin D) determination:** *Nutritional variables are important modifiable factors that affect bone health.* Traditionally, supplementation with these 2 nutrients has been the mainstay of osteoporosis prevention. (47) Calcaemia is a qualitative polytomous variable and 25-Hidroxy-Vitamin D is a qualitative dichotomous variable. This data is collected from the blood sample.
  - **Phosphataemia:** is a qualitative polytomous variable collected from the blood sample and related to bone metabolism.
  - **Parathyroid hormone:** controls the level of calcium in the blood**.** It is a qualitative polytomous variable collected from the blood sample related to bone metabolism.
  - **Bone remodelling markers**. such as alkaline phosphatase which is related to bone metabolism. It depends on the age and it is a qualitative polytomous variable obtained from the blood sample.
  - **Acute phase reactants** (ESR value). **Only measured in JIA patients to assess the disease activity**. It is a qualitative dichotomous variable collected from the blood sample.

ANALYTICAL VARIABLES	DEFINITION	TYPE OF DATA	CATEGORIES OR VALUES
Calcaemia	Data collected from the blood sample	Qualitative polytomous variable	<8.5 mg/dL: hipocalcaemia; 8.5-10.2 mg/dL: normal calcaemia; >10.2 mg/dL

			: hipercalcaemia
25-Hidroxy-Vitamin D	Data collected from the blood sample	Qualitative dichotomous variable	Vit D deficiency: <20ng/mL Non- Vit D: deficiency: >20ng/mL
Phosphataemia	Data collected from the blood sample	Qualitative polytomous variable	<4.0 mg/dL: hipophosphataemia; 4.0-7.0 mg/dL: normal phosphataemia; >7.0 mg/dL :hiperphosphataemia
Parathyroid hormone	Data collected from the blood sample	Qualitative polytomous variable	<10.0 pg/mL: low levels; 10.0-55.0 pg/dL: normal levels; >55.0 pg/dL :high levels
Bone remodelling markers such as alkaline phosphatase	Data collected from the blood sample	Qualitative polytomous variable	Low values if: <273.47-871.44 U/L for 5-8 years: <215.04-893.69 U/L for 9-13 years <228.9-739.22 U/L for 14-18 years.
Acute phase reactants(ESR value)	Measured in JIA patients to asses the disease activity	Qualitative dichotomous variable	>10 mm/h: High value <10 mm/h: Normal value

7.6. DATA COLLECTION

DAY 1. STUDY INTRODUCTION

Patients with JIA are chronic patients who are followed up every 3 months by their paediatric rheumatology department.

During this follow-up, when the patient is scheduled for a follow-up visit, the co-investigator will proceed to **explain the study** to the patient's parents or legal guardians and **invite the patient to participate** in the study after ensuring that the patient meets the inclusion criteria and does not meet none of the exclusion ones.

Regarding to the study **control group**, the visit will be used to ask about the possibility of participation in the study by relatives of the JIA patient from 5 to 16 years of age who meet the inclusion criteria and does not meet none of the exclusion criteria. The importance of this control group for the study will be emphasised.

Parents or legal guardians will be informed of the details of the study at the visit, but in addition they will receive a **written information document** (Annex 2) containing all the relevant details about the study and **the informed consent form** (Annex 3). These documents can be read and referred to until the next visit. After this, a **second appointment** will be scheduled for the following week for them to inform us of their willingness to participate in the study.

DAY 2. CLINICAL COLLECTION FORM AND PHYSICAL EXAMINATION

The creation of a computerised database will be the first step towards proper information gathering. This will be a protected Excel database that you will only be able to access from the hospital. In order to anonymise the information in the study database, a numerical code will be assigned to each patient. Later, this data will be sent to the data collector who will collect all the information from all the co-investigators at the different hospitals.

The data will only be accessible to the researchers in charge of the study and will only be used for the purposes of the study.

If after reading the **information document** (Annex 2) the parents or legal guardians of the patient and the parents or legal guardians of the relatives of the patient, agree to participate in the study, they will be asked to **sign the informed consent form** (Annex 3).

During this visit, the co-investigator will perform an interview to collect the clinical information in the **clinical data collection form** (Annex 1) and will also perform a **physical examination** and collect certain information from the **patient's medical records**.

Confidentiality and anonymity of data will be emphasised.

DAY 3. DENSITOMETRY AND BLOOD SAMPLING SCHEDULE

In the following weeks, the patient is scheduled to visit the radiologist for a **densitometry scan** and a visit to the nurse for a **blood sample**. The procedures to be performed on the patient have been **described previously**.

The densitometry will be analysed by an expert radiologist and will also be used to assess whether or not the patient has low BMD for chronological. The blood sample will be analysed by the paediatric rheumatologist for markers of bone disruption or inflammation. This information is also collected and sent to the data collector.

DAY 4. RESULTS

The **results** will be presented to the patient's parents or legal guardians at the next follow-up appointment. At this time, we will evaluate the results.

If the results of the tests are positive for osteoporosis, the patient will be informed of the diagnosis and the therapeutic measures to be followed; if the results are negative for osteoporosis, the patient will be informed of his/her bone health status and advised on a series of measures to maintain this bone health.

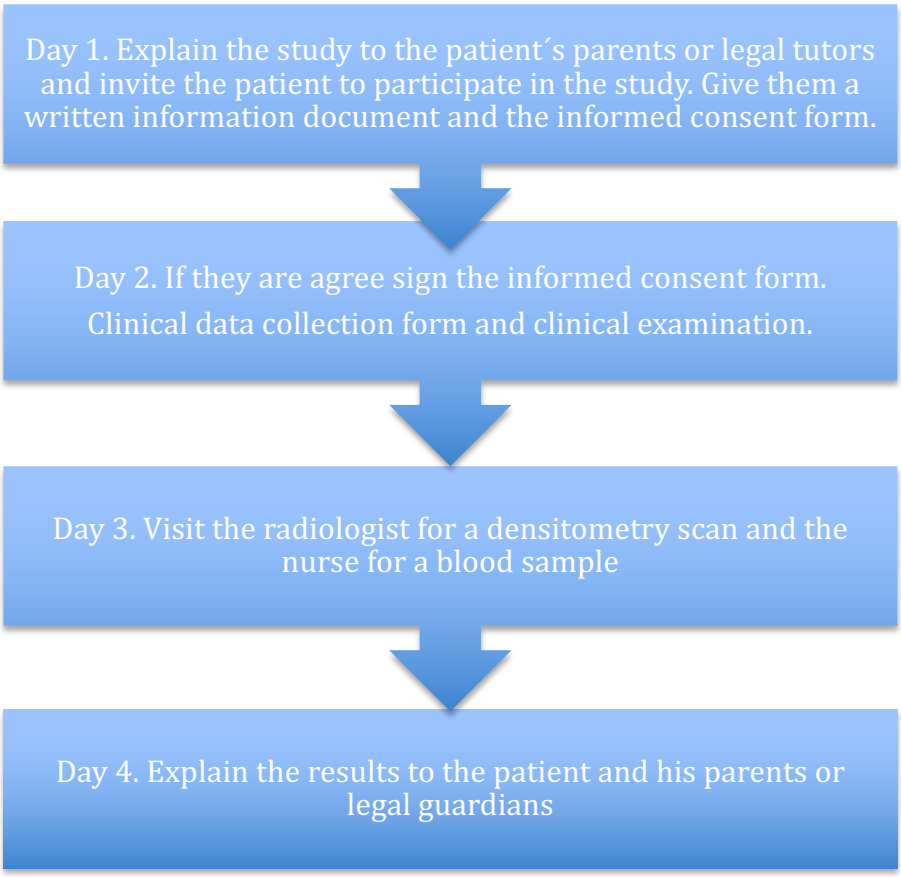

Fig 7. Data collection form summary.

8. STATISTICAL ANALYSIS

8.1. DESCRIPTIVE ANALYSIS

The dependent variable (development of osteoporosis) and the independent variable (presence or absence of JIA) are **qualitative** variables and will therefore be expressed in **proportions**. Proportions will also be used for **qualitative covariates**.

Mean, standard deviation, medians and interquartile range (IQR) will be used for **quantitative** covariates.

These analyses will be **stratified** by the groups defined by presence or absence of juvenile idiopathic arthritis (JIA). In addition, stratification will also be performed by the covariates.

8.2. BIVARIATE ANALYSIS

Chi-square or Fisher's exact test (if the expected number of cases in a cell will be lower than 5) will be used for the difference of proportions of the qualitative variables between the two groups (JIA and non-JIA)

Student's t test will be used to study if there are differences of the means, standard deviation, medians or interquartile range (IQR) of the quantitative variables between the two groups (JIA and non-JIA)

8.3. MULTIVARIATE ANALYSIS

All variables included in the previous analysis with a significance of $p < 0.2$ will be estimated by **logistic regression**. In order to assess the differences in the development of osteoporosis according to the AIJ and non-AIJ groups and to control for the covariates that may affect the results, to avoid possible confounding.

9. ETHICAL AND LEGAL CONSIDERATIONS

The principal investigator and co-investigators ensure that the study will be carried out in compliance with the human rights and the ethical considerations outlined in the World Medical Association **Declaration of Helsinki** on "Ethical Principles for Medical Research Involving Human Subjects" of 2013

This study adheres to the Principles of Biomedical Ethics by **Beauchamp and Childress of 1979**:

- ✓ Autonomy: Each participant will be provided with an **information document** detailing all the study information (Annex 2) In case they voluntarily agree to participate, an **informed consent** must be signed (Annex 3). They will have the right to withdraw at any time if they wish so.

  To ensure the **confidentiality** of the data, all patients will have assigned an identification number that will be recorded in the database for analysing the information in an **anonymous** way. The data will only be accessible to the researchers in charge of the study and will only be used for the purposes of the study.

  Participants will also have the right to access and remove their personal data from the database at any time.
- ✓ Beneficence: There are **no risks** of harm to the patient, as the tests required for the study are non-invasive and can be carried out very quickly and easily. On the other hand, as a **benefit**, we obtain knowledge of the JIA patient's bone health and the factors that may be related to it, which are very important as it is a fundamental period in which we can act to prevent future fractures and a reduction in the patient's quality of life.
- ✓ Non-maleficence: This principle is expected to be respected, so no harm will be caused to the patient, given the observational nature of the study.
- ✓ Justice: There is neither negative nor positive discrimination in the study. All patients meeting the inclusion criteria and none of the exclusion criteria and wishing to participate may enter to the study, avoiding any discrimination.

This research protocol will be evaluated by the Comitè Ètic d'Investigació Clínica (CEIC) of Hospital Universitari Doctor Josep Trueta and the other participating hospitals. In case of any objections, modifications will be done to achieve their conditions. Only after receiving their approval, the study will begin.

All the personal data from the patients included at the study database will be confidential according to **Regulation (EU)** 2016/679 of the European Parliament and of the Council of April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and the "**Ley Orgánica** 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales".

The researchers declare that there are no conflicts of interest in this study.

10. WORK PLAN AND CHRONOGRAM

10.1. Team members

The research team that will conduct this study will be composed of the following members:

- **Principal investigator**: is the person leading the study, an expert in metabolic bone pathology who is in contact with the coordinators of each hospital and ensures that everything goes as it should. Responsible for following tasks:
    1. Responsible for making a proposal for a working group.
    2. Responsible for the elaboration of the protocol and the bibliographic research.
    3. Responsible for the presentation of the protocol to the CEIC.
    4. Responsible for writing the conclusions and publication of the results.
- **Co-investigators**: investigators with scientific expertise and a particular commitment to metabolic bone pathology to help design the study and the bibliographic research. Each participant hospital will have one investigator responsible for coordinating and supervising his/her team.
- **A data manager**: responsible for the collection of the data, the anonymisation process and creating a database.
- **A statistical analyst**: responsible for the statistical analysis.
- **Collaborators**: the radiology team will be in charge of the performance and interpretation of the densitometry and the nursing team will be in charge of the collection of blood samples.

10.2. Working plan and chronogram

The duration of the study is expected to be approximately 2 years. The phases of the study will be carried out as follows:

STAGE 0: STUDY DESIGN (February-May 2023)

- First meeting (February 2023): The principal investigator meets with the team members to make a **proposal for a working group**.
- Once the team have agreed to participate in the study the principal investigator and the co-investigators will proceed to discuss the research project, perform **bibliographic research** and elaborate the **protocol**. (March 2023)

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL (June-September 2023)

- Presentation to CEIC: This protocol will be presented to the Comitè Ètic d'Investigació Clínica (CEIC) at Hospital Universitari Doctor Josep Trueta for its approval. Simultaneously, the protocol will be sent to the other participant hospitals Ethical Committee. The principal investigator is the main responsible.

STAGE 2: DATA COLLECTION (October 2023 – December 2024)

- At the beginning of this phase, all team members will meet at the reference hospital Hospital Universitari Doctor Josep Trueta to define their functions and to clarify their tasks to be carried out.
- The inclusion of the patients in the study will be a consecutive non-probabilistic sampling method, where the JIA patients of the 7 participant hospitals and their relatives will be recruited during the follow-up visits to the paediatric rheumatology area.
- Only patients who meet the inclusion and none of the exclusion criteria, and that have signed the informed consent will be included in the sample. All the personal data of the patients involved will be anonymised.
- The co-investigators of each centre will collect the information through the data collection form (Annex 1), the physical examination, the data from medical records and the blood sample taken by the nursing team. The radiology team will collect the densitometry data. All the data will be delivered to the data manager who will register and anonymise it into a database.

- During this stage, at least once a year, the principal investigator, and the work team will meet telematically via videoconference, to evaluate whether the protocol is being properly fulfilled.

STAGE 3: DATA ANALYSIS AND INTERPRETATION (December 2024 – May 2025)

- **Statistical analysis**. Once all data are obtained, a subcontracted statistician will process it performing a descriptive analysis, bivariate and multivariate analysis.
- **Statistical interpretation**. The final statistical analysis will be interpreted by the principal investigator and co-investigators of each participant hospital in a telematic meeting. Afterwards, the discussion and conclusion of the study will be elaborated.

STAGE 4: PUBLICATION AND DISSEMINATION OF THE RESULTS (May 2025-July 2025)

- During this final phase team members will meet at the reference hospital Hospital Universitari Doctor Josep Trueta to develop the final report and publish the results.
- Due to the nature of the paper, it is anticipated that it will be accepted for publication in an international rheumatology or paediatric journal, as well as in communication format for national congresses such as SERPE, SER, and SEIOMM, and European congresses such as EULAR or PRES.

10.3.Table 5. Chronogram.

STAGE	TASK	PERIOD																																	
		2023											2024												2025											
		F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
0. STUDY DESIGN	First meeting																																			
	Bibliographic research																																			
	Protocol elaboration																																			
1. ETHICAL EVALUATION	Presentation to CEIC																																			
2. DATA COLLECTION	Meeting to define the task of the team members																																			
	Participants recruitment																																			
	Data collection																																			
	Deliver data to the data collector																																			
3.DATA ANALYSIS AND INTERPRETATION	Statistical analysis																																			
	Statistical interpretation																																			
4.PUBLICATION AND DISSEMINATION OF THE RESULTS	Final report																																			
	Congress presentation																																			
	Publication																																			

11. BUDGET

11.1. Not included in the budget:

- **Investigation team:** the required profiles of researchers are covered and do not need to be budgeted for.
- **Resources available for the implementation of the project:** A prerequisite for the inclusion of hospitals in the study is that they have densitometry equipment and that the paediatric rheumatology department is part of their service so there is no need to be budgeted for.

11.2. Included in the budget:

Personnel

- **Statistical analysis**: the subcontracting of a statistician will be required for the statistical analysis of the data. It will be paid 40€/h, with an estimated total of 40h of work, so it will have a total cost of 1.600€.
- **Data collection**: data manager will be subcontracted to collect the data and create the database. The approximate salary will be 40€/hour and we estimate approximately 40 hours of work, so it will have a total cost of 1.600€.

Material and services

- **Densitometry**: as it is not a routine procedure, densitometry will be added as a separate expense, with a value of 40€ per densitometry, which will be applied to 134 children for a total value of 5360€, in addition to the extra work of the radiologists who will charge 40€ per hour and as they can perform a densitometry in approximately 5 minutes, the hours will be a maximum of 20 with a total expense of 800€.
- **Blood analysis**: as it is not a routine procedure, blood analysis will be added as a separate expense, with a value of 13€ per analysis, which will be applied to 136 children for a total value of 1.768€, in addition to the extra work of the nurses who will charge 28€ per hour and as they can perform a blood analysis in less than 5 minutes, the hours will be a maximum of 15 with a total expense of 420€.

Travel and meals

- **Two face-to-face meetings** will be held at Hospital Universitari Doctor Josep Trueta. The first meeting took place in the second stage, when the functions of each member were defined before the data collection, and the second in the fourth stage, when the final report and the dissemination of the results took place. It is budgeted 80€ to cover travel, and meal costs per person, per meeting. The other meetings will be held telematically via videoconference.

Publication and dissemination

- **Publication fees**: It is expected that a journal article presenting the main results will be published. It is assumed that the publication fee will be €1.500 but before submitting this article, English language proofreading will be required. So the total budget for the publication will be 1.800€
- **Dissemination of the results**: the principal investigator will present the study in national congresses such as SERPE, SER and SEIOMM and European congresses such as EULAR or PRES with 500-1000€ and 1.500-2.000€ per registration respectively. In addition, the travel, accommodation and meals will also be included (700€ in national congresses and 1.300€ in international congresses).

***Table 5**: Summary of the study budget.*

	PRICE	**QUANTITY**	**SUBTOTAL**
PERSONNEL			
Statician	40€/h	40h	1.600€
Data collector	40€/h	40h	1.600€
Radiologist	40€/h	20h	800€
Nurse	28€/h	15h	420€
MATERIALS AND SERVICES			
Densitometry	40€	134	5.360€
Blood analysis	13€	134	1.768€
PUBLICATION AND DISSEMINATION			
Meeting expenses	80€ 2 times = 160€	12	1.920€
International publication in scientific journal (open access)	1.800€	1	1.800€

National congress. Inscription fee, travel, diets and accommodation	1.200€	1	1.200€
International congress. Inscription fee, travel, diets and accommodation	2.800€	1	2.800€
		TOTAL:	19.268€

12. STUDY STRENGHTS AND LIMITATIONS

The strengths and limitations of the study are those of a **cross-sectional** study. These include:

- ✓ **Strength**: simple, easy, inexpensive and allows the generation of working hypotheses for future studies, which is highly valuable in the absence of previous literature of this kind, as in this study.
- X **Limitation:** It does not allow us to see the causality of an association, but the introduction of a control group is very useful to see not only the prevalence of osteoporosis in children with and without JIA, but also the prevalence of covariates in the two groups, which can give us useful information to further strengthen the basis of the study when it comes to carrying out a longitudinal study.
- X **Limitation**: All results from observational studies are potentially affected by **confounding bias**, resulting in an overestimation or underestimation of the true association. To reduce potential confounding, both bivariate and multivariate analyses are performed.

  A possible **information bias** is also considered as it is a multicentre study and the interpretation of the results may imply interobserver variability. To avoid this, at the onset of the study the team members will hold a meeting to define their tasks. During the study there will be some meetings to ensure the study is being well developed.

The strengths and limitations of the **sample selection** include:

- ✓ **Strength**: The addition of a control group will provide us with very important information about the bone health of the children. This is information that is currently not available in the literature.
- X **Limitation:** The selection of an adequate control group is the biggest difficulty, but we will select a population that is as similar as possible to the group of JIA patients, which will be the relatives of these patients.
- X **Limitation**: We will use a consecutive **non-probabilistic sampling method**, which implies the risk of selecting a sample that is not representative, leading to

a **selection bias**; we expect to minimise this bias by clearly defining our sample population.

The strengths and limitations of the **of the study variable** include:

- X **Limitation:** It is not a very common disease.
- ✓ **Strenght:** The study will contribute to a better understanding of the consequences of the disease. This will help to develop more appropriate therapeutic strategies to improve the quality of life of these patients.

13. FEASIBILITY

Investigation team: the necessary profiles of researchers are covered and do not need to be budgeted for. We have a working group whose objectives include the creation of new knowledge in the field of paediatric rheumatology. Several members of this working group from different hospitals have scientific experience, with related publications and a special commitment to paediatric metabolic bone pathology.

On the other hand it will be necessary to hire a data collector to collect the data correctly and a statistician to analyse the data as well. The non-routine work of radiologists and nurses will also incur additional costs, but the time needed to perform the tests is less than 5 minutes per patient, so the number of hours will be minimal.

Resources available for the implementation of the project: A prerequisite for the inclusion of hospitals in the study is that they have densitometry equipment and that the paediatric rheumatology department is part of their service so there is no need to be budgeted for. Once the equipment is in place, there will be an additional cost of 40 € per densitometry and 12 € per analysis for non-routine use of the equipment.

In conclusion, we consider this study to be feasible due to:

- X **Experience of the team members** in the study area
- X **The low budget** of the study
- X **T**he **availability of resources** to carry out the study.
- X The necessity of **non-invasive methods** to obtain results
- X Necessity of obtaining information in the **absence of previous knowledge**
- X The **low number of patients** required

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15.ANNEXES

15.1. ANNEX 1: DATA COLLECTION FORM

Fulla de recollida de dades de les variables demogràfiques i epidemiològiques dels pacients participants a l'estudi.

A les següents línies ompliu la informació que se us sol·liciti o marqueu la casella corresponent:

1. Codi numèric assignat: _____
2. Data(dia/mes/any): __/__/_____
3. Hospital:
   □ Hospital Universitari Doctor Josep Trueta (Girona)
   □ Hospital Sant Joan de Deu (Barcelona)
   □ Hospital Universitari Vall d'Hebron (Barcelona)
   □ Hospital Sant Pau (Barcelona)
   □ Hospital Universitari Germans Trias i Pujol (Badalona)
   □ Hospital Sant Joan de Déu de Manresa (Manresa)
   □ Hospital Universitari Parc Taulí (Sabadell)

4. Data de naixement (dia/mes/any): __/__/_____
5. Sexe:
   □ Home
   □ Dona
6. Antecedents familiars d'osteoporosi (familiars afectats de primer grau)
   □ Si
   □ No
7. Presència de fractures prèvies
   □ Si
   □ No
   (Si la resposta és si diga numero i localització d'aquestes fractures __/_____)
8. Dades de l´exploració física

□ Pes: ____ kg

□ Altura: _____ cm

□ Estadi puberal mesurat a l´escala de Tanner: nº ____

9. Activitat de la malaltia: **(Apartat només per a pacientes AIJ)**

   □ Inactiva

   □ Baixa activitat

   □ Alta activitat

15.2. ANNEX 2: INFORMATION DOCUMENT FOR THE PATIENT

FULL D'INFORMACIÓ PER AL PACIENT

Nom de l'estudi: Centre assistencial: Investigador/a principal:

Benvolgut/da, Ens dirigim a vostè per proposar-li participar, de forma totalment voluntària, en un estudi d'investigació dut a terme als serveis de reumatología pediàtrica de diferents hospitals de referència de Catalunya. Aquest estudi ha sigut aprovat per el Comitè d'Ètica i Investigació clínica dels hospitals corresponents i per l'Agència Espanyola del Medicament i Producte sanitari. La nostra intenció és que vostè entengui el motiu pel qual es realitza aquest estudi i què significa formar-ne part, per tal de poder decidir si desitja participar-hi. Li preguem que llegeixi aquest document atentament i qualsevol consulta o aclariment no dubti a consultar-nos-ho.

DESCRIPCIÓ I OBJECTIU DE L'ESTUDI

L'artritis idiopàtica juvenil és la malaltia reumatica més comuna de la infància, que es caracteritza per un procés d'inflamació de les articulacions afectades i altres símptomes acompanyants.

A dia d'avui gràcies a la seva detecció primerenca ia les opcions terapèutiques disponibles les comorbiditats han disminuït, però encara no coneixem bé les dades d'algunes comorbiditats de la malaltia, sobretot aquelles que no són detectables a simple vista, com la baixa densitat mineral òssia per a l'edat cronològica o fins i tot l'osteoporosi, que poden passar desapercebudes.

Aquestes comorbiditats podrien ser limitants a la vida adulta, augmentant el risc de fractures i deteriorament de la qualitat de vida si no són detectades i previngudes en la infància, ja que és en aquest període en què podem actuar fomentant la correcta formació de l'os.

L'objectiu de l'estudi és conèixer la salut òssia dels nens amb artritis idiopàtica juvenil ja que estan en risc de presentar baixa densitat mineral òssia per a l'edat cronològica o fins i tot osteoporosi per poder proporcionar un control i unes mesures terapèutiques adequades per evitar les possibles conseqüències a l'edat adulta.

L'estudi es realitzarà al seu centre de salut durant un període de 3 setmanas. Durant la següent consulta recollirem unes dades a través d'un formulari i farem una exploració física, a més es programarà una analítica i una densitometria per a l'estudi de la salut òssia. La densitometria és una prova diagnòstica que mesura el grau de mineralització de l'os i que s'aplica tant al diagnòstic precoç de l'osteoporosi com al control de la seva evolució i valoració terapèutica; és una prova no invasiva, realitzada de manera simple i de poca durada de temps; La quantitat de radiació necessària és realment petita. 0,001 mSv, equivalent a 2-3 hores dexposició solar.

BENEFICIS I RISCOS DE L'ESTUDI

Com a benefici podrà conèixer la salut òssia del pacient i aportar en el coneixement de la salut òssia dels nens amb AIJ, quant als riscos, no presenta cap risc la seva participació a l'estudi.

CONFIDENCIALITAT I PROTECCIÓ DE DADES

Des de l'inici de l'estudi, totes les dades personals recollides es gestionaran i emmagatzemaran amb total confidencialitat, tenint en compte la legislació actual Llei Orgànica 3/2018, de 5 de desembre, de Protecció de Dades Personals i Garantia dels drets digitals" i als reglaments 2016/679 del Parlament i Consell Europeu. Per garantir la màxima confidencialitat, a l'inici de l'estudi se li assignarà un codi numèric mitjançant el qual s'identificaran les seves dades i informació personal. L'accés a les dades de caràcter personal quedarà restringit a l'equip investigador. No es publicarà informació personal, i les dades sempre seran utilitzades amb finalitats d'investigació. D'acord a el que s'estableix en la legislació vigent, vostè pot exercir els drets a l'accés rectificació, oposició i cancel·lació de les dades; en cas de desitjar-ho haurà de posar-se en contacte amb l'equip investigador.

PARTICIPACIÓ I COMPENSACIÓ ECONÒMICA

L'equip d'investigació responsable d'aquest assaig clínic no obté cap benefici econòmic. Com a pacient, la seva participació es totalment voluntària i no obtindrà cap compensació econòmica. En cas de no voler participar a l'estudi, podrà tractar-se amb l'equip d'especialistes sense cap canvi en la seva atenció mèdica. Per participar, haurà de firmar

el consentiment informat que li facilitarem conforme ha llegit la fulla d'informació per al pacient i vol participar a l'estudi. Vostè està en el seu dret de sortir de l'estudi durant el transcurs d'aquest si així ho desitja. Preguem que si és el cas, informi a l'equip investigador. Abans de decidir si vol formar part de l'estudi, està en el seu dret de demanar segones opinions a altres professionals si ho desitja.

CONTACTE

En cas de qualsevol dubte o si necessita més informació, pot posar-se en contacte amb l'equip investigador de l'hospital corresponent mitjançant:_____

Gràcies per la seva atenció.

15.3. ANNEX 3: INFORMED CONSENT CONSENTIMENT INFORMAT

Jo, _____, amb document d'identificació personal (DNI/NIE) _____, declaro que:

- He rebut una copia de la fulla de informació per al pacient.
- He llegit i comprès tota la informació facilitada en la fulla de informació per al pacient. He pogut platejar qualsevol dubte que m'ha sorgit, i aquest ha sigut resolt adequadament.
- Estic conforme amb la quantitat d'informació facilitada.
- Comprenc que la meva participació en aquest estudi és voluntària i no remunerada.
- Comprenc els beneficis i riscos que comporta participar en aquest estudi.
- Comprenc que les meves dades personals seran confidencials i que puc sol·licitar la retirada i eliminació d'aquestes en qualsevol moment de l'estudi.
- Autoritzo que les meves dades i la meva història clínica pugui ser utilitzada per l'equip investigador per a fins relacionats amb l'estudi.
- He entès que puc revocar el meu consentiment informat sobre la participació a l'estudi, sense necessitat d'especificar el motiu i sense que aquest fet afecti a la meva assistència.

En conseqüència,

- Dono lliurament la meva conformitat a participar en l'estudi

□ Si

□ No

Signatura del pacient Signatura de l'investigador

15.4.ANNEX 4. PAQ-C QUESTIONNAIRE FOR CHILDRENS PHYSICAL ACTIVITY

Cuestionario de actividad física (escuela primaria)

Nombre:_____ Edad:_____

Sexo: M_____ F_____ Grado:_____

Profesor:_____

Se trata de conocer tu nivel de actividad física de los ***últimos 7 días*** (en la última semana). Esto incluye deportes o bailes que te hagan sudar o te cansen las piernas, o juegos que te hagan respirar con dificultad, como pillar, saltar, correr, escalar y otros.

Acuérdate:

1. No hay respuestas correctas ni incorrectas: esto no es un examen.
2. Le rogamos que responda a todas las preguntas con la mayor sinceridad y precisión posibles, ya que esto es muy importante.

---

1. Actividad física en su tiempo libre ¿Ha realizado alguna de las siguientes actividades en los últimos 7 días (la última semana)? En caso afirmativo, ¿cuántas veces? (Marque sólo un círculo por fila).

	No	1-2	3-4	5-6	7 veces o más
Saltar	○	○	○	○	○
Remo/canotaje	○	○	○	○	○
Patinaje en línea	○	○	○	○	○
Etiqueta	○	○	○	○	○
Caminar para hacer ejercicio	○	○	○	○	○
En bicicleta	○	○	○	○	○
Jogging o correr	○	○	○	○	○
Aerobic	○	○	○	○	○
Natación	○	○	○	○	○
Béisbol, softbol	○	○	○	○	○
Danza	○	○	○	○	○
Fútbol	○	○	○	○	○
Bádminton	○	○	○	○	○
Monopatín	○	○	○	○	○
Fútbol	○	○	○	○	○
Hockey callejero	○	○	○	○	○
Voleibol	○	○	○	○	○
Hockey sobre suelo	○	○	○	○	○
Baloncesto	○	○	○	○	○
Patinaje sobre hielo	○	○	○	○	○
Esquí de fondo	○	○	○	○	○
Hockey sobre hielo	○	○	○	○	○
Otros: _____	○	○	○	○	○

2. En los últimos 7 días, durante tus clases de educación física (EF), ¿con qué frecuencia estuviste muy activo (jugando duro, corriendo, saltando, lanzando)? (Marca sólo una).

Yo no hago PE.....O
Casi nunca.....O
A veces .....O
Muy a menudo .....O
Siempre.....O

3. En los últimos 7 días, ¿qué hiciste la mayor parte del tiempo *durante el recreo*? (Marca sólo una).

Sentado (hablando, leyendo, haciendo deberes.....O
De pie o paseando.....O
Corrió o jugó un poco.....O
Corrió y jugó bastante.....O
Corrió y jugó duro la mayor parte del tiempo .....O

4. En los últimos 7 días, ¿qué hizo normalmente *a la hora de comer* (además de almorzar)? (Marque sólo una).

Sentado (hablando, leyendo, haciendo tareas escolares). O
Se paró alrededor o caminó alrededor .....O
Corrió o jugó un poco.....O
Corrió y jugó bastante.....O
Corrió y jugó duro la mayor parte del tiempo .....O

5. En los últimos 7 días, ¿cuántos días *después del colegio* hiciste deporte, bailaste o jugaste a algo en lo que estuviste muy activo? (Marca sólo una).

Ninguno.....O
1 tiempo la semana pasada.....O
2 o 3 veces la semana pasada .....O
4 veces la semana pasada .....O
5 veces la semana pasada .....O

6. En los últimos 7 días, ¿en cuántas *tardes* hiciste deporte, bailaste o jugaste a juegos en los que estuviste muy activo? (Marque sólo una).

Ninguno .....O
1 tiempo la semana pasada.....O
2 o 3 veces la semana pasada .....O
4 o 5 la semana pasada .....O
6 o 7 veces la semana pasada .....O

7. *En el último fin de semana*, ¿cuántas veces hiciste deporte, bailaste o jugaste a juegos en los que estuviste muy activo? (Marca sólo una).

Ninguno .....○
1 tiempo .....○
2 - 3 veces.....○
4 - 5 veces.....○
6 o más veces.....○

8. ¿Cuál de las siguientes afirmaciones le describe mejor en los últimos 7 días? Lee *las cinco* afirmaciones antes de decidir cuál es *la* respuesta que mejor te describe.

A. Todo o casi todo mi tiempo libre lo pasaba haciendo cosas que implican poco esfuerzo físico .....○

B. A veces (1 - 2 veces la semana pasada) hice cosas físicas en mi tiempo libre (p. ej. practicaba deporte, salía a correr, nadaba, montaba en bici, hacía aeróbic).....○

C. A menudo (3 - 4 veces la semana pasada) hacía cosas físicas en mi tiempo libre .....○

D. Con bastante frecuencia (5 - 6 veces la semana pasada) hice cosas físicas en mi tiempo libre .....○

E. Muy a menudo (7 o más veces la semana pasada) hice cosas físicas en mi tiempo libre ○

9. Marca la frecuencia con la que realizaste actividad física (como hacer deporte, jugar, bailar o cualquier otra actividad física) cada día de la semana pasada.

	Ninguno	Pequeño bit	Medio	A menudo	Muy a menudo
Lunes	○	○	○	○	○
Martes	○	○	○	○	○
Miércoles	○	○	○	○	○
Jueves	○	○	○	○	○
Viernes	○	○	○	○	○
Sábado	○	○	○	○	○
Domingo	○	○	○	○	○

10. ¿Estuvo enfermo la semana pasada o algo le impidió realizar sus actividades físicas normales? (Marque una.)

Sí.....○
No.....○

En caso afirmativo, ¿qué se lo impidió? _____

15.5. ANNEX 5. PAQ-A QUESTIONNAIRE FOR ADOLESCENTS PHYSICAL ACTIVITY

Cuestionario de actividad física (secundaria)

Nombre:_____ Edad:_____

Sexo: M_____ F_____ Grado:_____

Profesor:_____

Se trata de conocer tu nivel de actividad física de los ***últimos 7 días*** (en la última semana). Esto incluye deportes o bailes que te hagan sudar o te cansen las piernas, o juegos que te hagan respirar con dificultad, como pillar, saltar, correr, escalar y otros.

Acuérdate:

3. No hay respuestas correctas ni incorrectas: esto no es un examen.
4. Le rogamos que responda a todas las preguntas con la mayor sinceridad y precisión posibles, ya que esto es muy importante.

---

1. Actividad física en su tiempo libre ¿Ha realizado alguna de las siguientes actividades en los últimos 7 días (la última semana)? En caso afirmativo, ¿cuántas veces? (Marque sólo un círculo por fila).

	No	1-2	3-4	5-6	7 veces o más
Saltar	○	○	○	○	○
Remo/canotaje	○	○	○	○	○
Patinaje en línea	○	○	○	○	○
Etiqueta	○	○	○	○	○
Caminar para hacer ejercicio	○	○	○	○	○
En bicicleta	○	○	○	○	○
Jogging o correr	○	○	○	○	○
Aerobic	○	○	○	○	○
Natación	○	○	○	○	○
Béisbol, softbol	○	○	○	○	○
Danza	○	○	○	○	○
Fútbol	○	○	○	○	○
Bádminton	○	○	○	○	○
Monopatín	○	○	○	○	○
Fútbol	○	○	○	○	○
Hockey callejero	○	○	○	○	○
Voleibol	○	○	○	○	○
Hockey sobre suelo	○	○	○	○	○
Baloncesto	○	○	○	○	○
Patinaje sobre hielo	○	○	○	○	○
Esquí de fondo	○	○	○	○	○
Hockey sobre hielo	○	○	○	○	○
Otros:					
_____	○	○	○	○	○
_____	○	○	○	○	○

2. En los últimos 7 días, durante tus clases de educación física (EF), ¿con qué frecuencia estuviste muy activo (jugando duro, corriendo, saltando, lanzando)? (Marca sólo una).

Yo no hago PE ○
Casi nunca ○
A veces ○
Muy a menudo ○
Siempre ○

3. En los últimos 7 días, ¿qué hizo normalmente *a la hora de comer* (además de almorzar)? (Marque sólo una).

Sentado (hablando, leyendo, haciendo tareas escolares). ○
Se paró alrededor o caminó alrededor ○
Corrió o jugó un poco ○
Corrió y jugó bastante ○
Corrió y jugó duro la mayor parte del tiempo ○

4. En los últimos 7 días, ¿cuántos días *después del colegio* hiciste deporte, bailaste o jugaste a algo en lo que estuviste muy activo? (Marca sólo una).

Ninguno ○
1 tiempo la semana pasada ○
2 o 3 veces la semana pasada ○
4 veces la semana pasada ○
5 veces la semana pasada ○

5. En los últimos 7 días, ¿en cuántas *tardes* hiciste deporte, bailaste o jugaste a juegos en los que estuviste muy activo? (Marque sólo una).

Ninguno ○
1 tiempo la semana pasada ○
2 o 3 veces la semana pasada ○
4 o 5 la semana pasada ○
6 o 7 veces la semana pasada ○

6. *En el último fin de semana*, ¿cuántas veces hiciste deporte, bailaste o jugaste a juegos en los que estuviste muy activo? (Marca sólo una).

Ninguno ○
1 tiempo ○
2 - 3 veces ○
4 - 5 veces ○
6 o más veces ○

7. ¿Cuál de las siguientes *opciones* le describe mejor en los últimos 7 días ? antes de decidir cuál es *la* respuesta que mejor te describe.

F. Todo o casi todo mi tiempo libre lo pasaba haciendo cosas que implican poco esfuerzo físico.....○

G. A veces (1 - 2 veces la semana pasada) hice cosas físicas en mi tiempo libre (p. ej. practicaba deporte, salía a correr, nadaba, montaba en bici, hacía aeróbic).....○

H. A menudo (3 - 4 veces la semana pasada) hacía cosas físicas en mi tiempo libre.○

I. Con bastante frecuencia (5 - 6 veces la semana pasada) hice cosas físicas en mi tiempo libre .....○

J. Muy a menudo (7 o más veces la semana pasada) hice cosas físicas en mi tiempo libre .....○

8. Marca la frecuencia con la que realizaste actividad física (como hacer deporte, jugar, bailar o cualquier otra actividad física) cada día de la semana pasada.

	Ninguno	Pequeño bit	Medio	A menudo	Muy a menudo
Lunes	○	○	○	○	○
Martes	○	○	○	○	○
Miércoles	○	○	○	○	○
Jueves	○	○	○	○	○
Viernes	○	○	○	○	○
Sábado	○	○	○	○	○
Domingo	○	○	○	○	○

9. ¿Estuvo enfermo la semana pasada o algo le impidió realizar sus actividades físicas normales? (Marque una.)

Sí.....○
No.....○

En caso afirmativo, ¿qué se lo impidió? _____