Deanship of Graduate Studies
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Environmental and Genetic Risk Factors for Pediatric Asthma in East Jerusalem / Palestine

Kifaya Juma Hamed Abu Ghaith

Master Thesis

Jerusalem – Palestine

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Jerusalem – Palestine

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Dedication

I would like to dedicate this work to my family, who supported me in all phases of this thesis, particularly to my husband and my son who help will not be forgotten.
Special dedication to my lovely father, for his support, care and love.

Signature

……

Declaration

I certify that thesis submitted for the degree of master is the result of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed

Kifaya Juma' Abu Ghaith

Date: 10 / 06 / 2007

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Abstract

Pediatric asthma is a serious illness that poses tremendous stress on patients and their families alike. Unfortunately the disease's incidence is on a rise worldwide.

Pediatric asthma is a chronic disease affecting the small bronchi leading to inflammation with subsequent edema and hypersecretion resulting in narrowing of the lumen demonstrated in cough, dyspnea and wheezes. Pollution, cigarette smoke, dust mite, domestic animal and extreme weather conditions are considered causative and triggering factors. Genetic factors play critical role in respiratory hypersensitivity also identified to be an important risk factor in pediatric asthma.

Children are primary victims, being exposed, early on in life, to thousands of attacks of acute severe asthma and requiring hospital referral. The study aims was to identify the most prevalent environmental - genetic risk factors that affect pediatric asthma in east Jerusalem/ Palestine.

The sample size consists of 300 children from East Jerusalem between 5 and 16 years old. One hundred patients represent bronchial asthma ,case and 200 with other diseases.

The purposive sample is taken from four medical centers in East Jerusalem and two major medical institution ,Al- Makassed Islamic Charitable Hospital and Augusta Victoria Hospital (AVH). The study was approved by the scientific research committee at Al –Quds University, and a permission to conduct the study from the administration of Al- Makassed Islamic Charitable center, the Arab medical health center, the American medical center and from the Palestinian ministry of health center also along with permission from AVH and Makassed Islamic Charitable Hospital was obtained

The Alpha 1 Antitrypsin genotype was perform for 50% of the samples (50 case, 100 control) in addition 300 questionnaire was distributed for 300 families of children selected in the study area . Pearson chi square was used to check the association of environmental risk factors that affect pediatric asthma in east Jerusalem Palestine. Result of the study demonstrate that there is a strong association between pediatric asthma and the presence of domestic animal in home , second hand smoking, and family history of asthma is strongly related to asthma .on the other hand genetic risk factor is poorly associated with asthma among children in east Jerusalem /Palestine.

ملخص الدراسة

داء الربو القصبي مرض مزعج يقض مضاجع المصابين به والذين يعيشون معهم وهو آخذ في الانتشار سنة تلو الأخرى. فالربو هو مرض مزمن يصيب الرئة ويؤدي إلى التهاب الشعب الهوائية الصغيرة مما يتسبب في السعال وضيق التنفس والأزيز. ويعتبر والحيوانات الببيتية وطبيعة الطقس من العوامل التلوّث والتدخين والغبار والعث المنزلي التي تسبب الربو ، بالإضافة أن المرضى المصابين بالربو لديهم استعداد وراثي .

والأطفال هم ضحاياه الأوائل ويتعرض الآلاف منهم، وأكثرهم في عمر مبكر، لأزمات ربو لا يمكن تهدئتها إلا في المستشفيات. هدفت هذه الدراسة إلى التعرف على العوامل البيئية والجينات الوراثية المحفزة و المساعدة في تأزم نوبة الربو في منطقة شرقي القدس / فلسطين، وخصص من هذه الجينات نقص نوع من البروتينات ألا وهو: (Alpha -1- Antitrypsin deficiency among pediatric asthma)

اشتملت العيّنة على 300 طفل، (100 مصاب بالربو – 200 من أمراض أخرى)، حيث تم استثناء الأطفال المصابين (Chest infection) بالتهابات رئوية وقد كانت العيّنة مستهدفة من كل أطفال شرقي القدس الذين تتراوح أعمارهم ما بين 5 – 16 سنة، هذا وقد تم أخذ العيّنة من المراكز الصحيّة الموّزعة في شرقي القدس بالإضافة إلى مستشفى المقاصد ومستشفى المطّلع. وقد تمت الموافقة على هذه الدراسة من قبل لجنة البحث العلمي في جامعة القدس كما وأخذت موافقة مدراء المراكز التي تمت فيها الدراسة واشتملت على مراكز جمعيه المقاصد الخيرية، مركز الأمريكان، المرك ز الصحي العربي، مركز صحة القدس/ السلطة الوطنية ومستشفى المقاصد ومستشفى المطّلع. تم فحص 50% من العينة المستهدفة للبحث عن الجينات الوراثية **المساعدة** في حدوث نوبة الربو كما ووزع 300 استبيان على جميع العينة في منطقة القدس. تم اختبار العينة عن طريق استعمال Pearson chi square وقد أشارت الدراسة وجود علاقة إحصائية بين داء الربو القصبي والتدخين في بيئة الطفل المصاب، ووجد أيضا علاقة قوية مع الحيوانات المنزلية بلاضافة إلى أن العامل الوراثي يلعب دور هام. من ناحية أخرى لم يثبت وجود علاقة بين الجينات الوراثية (Alpha -1- Antitrypsin deficiency) وداء الربو .

إننا نوصي بدراسات أخرى بحيث تكون شاملة على عدد أكثر م ن المصابين بمرض الربو ومساحة اكبر.

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List of Abbreviations

ADAM33	Adisintegrin and metalloproteinase domain 33
AAAAI	American Academy of Allergy Asthma and Immunology
AAT	Alpha -1-Antitrypsin
AATD	Alpha -1-Antitrypsin deficiency
AVH	Augusta Victoria Hospital
COPD	Chronic Obstructive Pulmonary Disease
EIA	Exercise induced asthma
ETS	Environmental tobacco smoke
GERD	Gastro esophageal reflux disease
IgE	Immunoglobulin E
MICH	Makassed Islamic Charitable Hospital
PMOH	Palestinian Ministry of Health
NYSDOH	New York State Department of Health's
NIEHS	National Institution of Environmental Health Services
NSAID	Non-steroidal anti-inflammatory drug
PHC	Public health center
PSE	Passive smoking effects
SPSS	Statistical Package for the Social Science
SES	Socio-economic status

Chapter one

1. Introduction

1.1General background

Pediatric asthma is a chronic respiratory condition that affects the lung of a child and is characterized by narrowing of air channel and inflammation of bronchial wall and muscles, which result in extra mucus production (Mayo clinic, 2004) The mucus will accumulate and result in symptom of wheezing cough and tightening of chest (James, Robert 1999) "Asthma is most simply defined as a disorder characterized by narrowing of airways that is reversible with time , either spontaneously or as a result of treatment " (Fores and Jacson, 2003).
Asthma is classified into three stage: Acute, subacute and chronic. These stages will explain the pathophysiology of asthma as a complex disease which result in airway inflammation or intermittent airflow abstraction and bronchial Hyperresponsiveness (Morris, etal 2005) In 2002, it was show that the incidence, prevalence and mortality of Asthma have increased in children over the past three to four decades (Smyth .R, 2002).

1.2 Asthma occurrence and severity

Many factors play a role in asthma occurrence and severity including environmental , genetic and hygiene factors in addition to lifestyle differences which play potentially causative roles in USA (Smyth, 2002). The main causes of asthma are unknown but may be related to environmental factors such as indoor and outdoor pollution (Anderson, 1994). In 1999 approximately 25 children and more than 500 adult younger than 65 years died from asthma" (Smyth, 2002). These trends provide some reassurance that the increase in hospital admissions in children that has occurred over the past three decades has not been associated with as increase in the life threatening events in this age group (Smyth, 2002). Both inherent and environmental factors influence the development of asthma in childhood ; Sex ,genetic predisposition and lung size are regarded as inherent factors ,while diet, allergen, environmental pollution including tobacco smoke, infection, socioeconomic status and region of residence are considered external factors (Barnes,1998)

A major obstacle in the genetics studies of asthma is the clinical diagnosis because no single clinical parameter always delineates asthma from other pulmonary diseases or a healthy state (Barnes,1998). Certain well-defined genotypes such as S ,Z exits that are strongly associated with Asthma, also mutation in different genes may result in identical Genotypes; genetic heterogeneity. (Barnes, 1998)

alpha-1 Antitrypsin (AAT) deficiency have been interpreted as indicating that AAT deficiency is a rare disease that affects mainly Caucasians (whites) from northern Europe. (Frederick, 2003)

In a recent publication on worldwide racial and ethnic distribution of AAT deficiency, new data were presented demonstrating that it is also found in various populations including African blacks ; Arabs and Jews in the Middle East ; and Central, Far East, and Southeast Asians, as well as among whites in Australia, Europe, New Zealand, and North America (Frederick,2003)The new data on the incidence of AAT deficiency worldwide and the suggestion that it may be the most common single gene hereditary disease for humans mandate the development of better mechanisms for effective diagnosis and treatment. Alpha-1 Antitrypsin deficiency is an inherited disorder that can cause lung and liver disease in children. Alpha-1 Antitrypsin (AAT) is a protein that protects the lungs. The liver usually makes the protein, and releases it into the bloodstream. Because of a gene problem, some people have little or none of it (Frederick, 2003).

The large numbers of AAT deficiency carriers and those with deficiency allele combinations for the two most common alleles PiS and PiZ worldwide clearly indicate that most carriers and deficiency allele combinations for PiS and PiZ have not been diagnosed (Geogr,1994) The fact that this disease is not just a disease of white northern Europeans but affects essentially all racial subgroups worldwide impacts the commonly accepted standards for diagnosis of AAT deficiency by general practitioners and such specialists as allergists and pulmonary and hepatic physicians. Particularly important is the unique sensitivity of AAT-deficient individuals to exposure to chemical and particulate environmental agents. (Frederick, 2003).

1.3 Risk factors for asthma

Many factors appear to play a role in both the etiology of asthma and its exacerbation. It is not clear which factors are causative and which are promoters of the disease. Risk factors are determinants of the risk of developing childhood asthma and may increase or decrease the probability of an individual, and can be personal characteristics - inherited or acquired or environmental characteristics (Badash, 2001)

Asthma can develop at any age and has to be considered in every child presenting with wheezing although some studies suggest racial differences in the prevalence of asthma. Socio-economic and environmental differences must be taken into account when conclusions are made in this regard(Andrew ,etal,2000) Inhalation of cigarette smoke during pregnancy have linked with abnormal lung functions, airway hyper-reactivity and raised IgE levels in the newborn. (Kathleen, etal, 2003) Tobacco smoke is also an important trigger factor for asthma attacks (Kathleen,etal,2003) Viral infections are important triggers for asthma attacks .(Sigurs N,2000) There is no conclusive evidence to indicate that early infancy viral infection lower respiratory tract illnesses lead to subsequent long term increase in airway responsiveness and asthma. Viral infections are a major cause of wheezing in early infancy, but proof of induction of the asthma state with typical airway inflammation as found in the known asthmatic is still lacking. (Sigurs N, 2000)

A complex relationship exists between atopy and asthma. Umbilical cord blood IgE is a poor predictor of early infant wheezing, but if children with a raised cord blood IgE of >0,9 KU/l are followed to the age of 11 years, a five fold increase risk for asthma is found.(Johnson.etal,2002)

Many different foods and preservatives have been implicated in triggering asthma attacks. (Smit, 2001) Inducing the asthma state by certain food substances have not been proven. Food elimination diets have been shown to postpone the development of atopic eczema, urticaria and gastrointestinal tract allergic disease but not asthma (Smit, 2001)

There is increasing evidence that early exposure to inhaled allergens (house dust mites, moulds, cats, "cockroach, pollen") in the genetically predisposed infant may lead to increased airway responsiveness and asthma. The increase of the prevalence of atopy when born in a specific month of the year can also be attributed to early exposure to the prevailing allergen at that specific time (Richard, 2005)

Emotional factors play a major role in eliciting asthma attacks in the known asthmatic. (Weil.m,1999) No evidence exists that asthma can be induced by these factors. Certain psychological factors are seen as risk factors for eliciting severe and fatal asthma attacks .also behavioral and psychosocial factors affect asthma morbidity in children(Weil.m,1999) Patients with asthma who are at risk from an allergy trigger need to be identified. Other triggers include respiratory tract infections, certain drugs, and both indoor and outdoor pollutants.(Etzel,2003)

1.4 problem statement and study justification

Bronchial Asthma is a common chronic respiratory disease among children. Shortness of breath, wheezing, coughing are known to be the major symptoms. there are many provoking factors that lead to spasm or constriction of airways such as: cold air, construction dust, strong fumes, smoke, Inhaled irritants and emotional upset. In addition, children with genetic risk factors have a high risk for bronchial asthma.(Smyth , 2002)
Bronchial Asthma is a common disease among children worldwide and in Palestine as well .Nationally many studies were done about asthma, discussing: Pathophysiology of asthma (AAAAI,2006), structure of lung tissue during asthma attack(American Lung Association,2007) **,** environmental and genetic risk factors for asthma (NIEHS,2006) , morbidity and mortality of asthma

(American Lung Association, 2005), biological risk factors are discussed in American journal of respiratory care . (Stefania, etal**,** 2003) In Palestine bronchial asthma is one of a common disease in childhood. (Palestinian Central Bureau of Statistics ,2000) Few studies were done, investigate the prevalence and severity of asthma. (El Sharif N, etal, 2002).

Other researcher looked for domestic mite and pet allergens and endotoxin in Ramallah / Palestine, Geographical variations of asthma and asthma symptoms among schoolchildren were studied among familial diseases as significant predictors of childhood asthma in Ramallah and North Gaza in Palestine. (El Sharif N, etal, 2003) Moreover, indoor environment such as presence of cats and domestic moulds also appear to play a role. (El Sharif N, etal, 2003) .Attendance of asthma in emergency room was considered (Mohammad ,2006). And no previous study was held to discuss the role of environmental -genetic risk factors in pediatric asthma .

In this study we will try to identify the most environmental risk factors that contribute to the development of pediatric asthma in east Jerusalem. Our large interest is applied to detect the role of alpha- 1- Antitrypsin (Proteinase inhibitor PI*)* in serum and the most common mutation subtypes(PIZ -PIS)as a genetic disorder that increases asthma severity and occurrence. The different genotypes studies could give a clear idea about pathogenesis of asthma in east Jerusalem. Association between environmental –genetic risk factor in pediatric asthma could add new information about the role AAT deficiency in pediatric asthma severity in east Jerusalem Palestine and suggest new intervention.

1.5 Goal of the study

To identify the most environmental - genetic risk factors that affect pediatric asthma in east Jerusalem/ Palestine.

1.6 Objectives of the study

1.6.1 General objectives

1. A clear idea about asthma pathogenesis in east Jerusalem/ Palestine.
2. Assess the potential risk factors for childhood asthma
3. Recognize some common indoor environmental factors that plays a role in increasing asthma prevalence.
4. Investigate the role of alpha -1- Antitrypsin genotype in child hood asthma.
5. Evaluate the parent's knowledge about Asthma management.

1.6.2 Specific objectives:

1. To determine the relation between the presence of indoor Environmental risk factor and pediatric asthma.

2. To assess the relation between socio-demographic variables (including parents knowledge, etc) and frequency of pediatric asthma attack.

3. To determine the most common subtypes of PIM mutation that contributes to genetic asthma in childhood in east Jerusalem/ Palestine

4. To estimate the frequency of carriers and the number of those individuals who are homozygous and heterozygous for the Z, S defective alleles of AAT deficiency

1.7 Research questions

The investigation was initiated to answer the following questions

1. What is the most environmental risk factor for pediatric asthma in east Jerusalem/ Palestine

2. What is the percentage of Alpha -1- Antitrypsin deficiency among 50 case=50% of total number of asthmatic child?

3. What is the percentage of Alpha -1- Antitrypsin deficiency among 100 control=50% from anther diseases except upper and lower respiratory tract infection?

1.8 Study hypotheses

1. Alpha -1- Antitrypsin deficiency is correlated with the severity of asthma.
2. The genetic factor increases the frequency of asthma.
3. Children with family history of asthma are more susceptible to respiratory problem upon expose to environmental risk factor.
4. Environmental genetic interaction plays a role in the prevalence of asthma

1.9 Thesis chapter's description

This thesis consists of six chapters:

Chapter 1: give a view about background, significance, Asthma occurrence and severity, Problem statement and study justification, aim and objectives of the study, hypotheses and question. Further more, we described the demography of east Jerusalem area, and we focused on the villages around.

Chapter 2: Review for literature and previous studies, about asthma and genetic factors, especially alpha one Antitrypsin deficiency and focus on Pathophysiology and the risk factors of Pediatrics Asthma also mention Genetic transmission of AAT deficiency**.**

Chapter 3: Conceptual frame work, including asthma definition, its natural history, path physiology of alpha1 Antitrypsin deficiency, Epidemiology of Alpha one Antitrypsin , and Intervention studies.

Chapter 4: Describes the methodology followed, including study design, sample size, population, data collection and analysis, Sampling Approaches, Ethical Consideration, and Pilot testing.

Chapter 5: Presents the main results and finding.

Chapter 6: Discuses the main study results including socio-demographic, environmental and genetic risk factor effect. The study results with previous studies are discussed. At the end of the chapter, the main conclusions, recommendations, and suggestion.

Chapter 7: References

1.10 Demography of east Jerusalem

Jerusalem occupies a unique status in the life of Palestinians, not only because of its religious importance, but also because of the historic role the city has played in Palestinian economic, social and cultural life. Regarded as the most important Palestinian city, Jerusalem is held up as the future capital of an independent Palestinian state (Mustapha, 2000)

The current total population of the Jerusalem Governorate is (470103) residents with a distribution of 246651in J1 area and 223452 in J2 area (PCBS, 2003). The Health status of East Jerusalem population is generally good with health indicators resembling those of a middle-income country. Indicators of health status such as life expectancy are among the best in the region. Men have an average life expectancy of 69, while women are at 71. Infant mortality, another important indicator, is low, at 17/1000 as compared to the West Bank, Israel and other countries (PCBS, 2000)

1.10.1 Health care providers:

The Palestinian Ministry of Health has a big role as health care providers in east Jerusalem Governorate. Its activities are focus in the area outside the Jerusalem Municipality boundaries and provide PHC services to the Palestinians based on the Palestinian Governmental Health insurance. (PCBS, 2000).

The MOH runs 16 PHC clinics distributed in the villages around Jerusalem, the main Health center in Ezaria, which operates 6 days a week, as seen in (Appendix 1.1)

Makassed Charitable Society operates five health centers in Jerusalem area; two inside the municipal boundaries and three in the suburbs. The largest centers are located in the Old City and al-Ram. These clinics offer a variety of services that includes: general medicine, specialized clinics, and x-ray and laboratory basic facilities (Khamaisy, 1997), as seen in(Appendix 1.2) The remaining health care providers can seen in(Appendix 1.3 , 1.4 , 1.5, 1.6)

1.10.2 East Jerusalem governorates:

The administrative classification of the ministry of local Government that were used in the 1997 census , divided the Palestinian Territory into nine governorates one of them was Jerusalem governorate which includes 30 different zones *(see the map Appendices 4.8)*

These are AL-Ezaria(Bethany), Abu-Dees, AL-Sawahreh ash sharqiya, Asheikh Sa'd,Arab Al Jahlen, Anata, Qalandia, Qatanna, Al-Jeeb, Al-Qubieba, Al-Nabi Smawil, Al-Ram و Dahiyat al Bareed, Beit Ijza, Biddu, Beit Iksa, Beit surrik, Biet Duqqu, Biet Hanina Al-Balad, Biet Anan , Bir Nabala , Jaba, Hizma, Kharayib um al-lahim, Rafat, Kafar Aqab, Mikhmas,and Qalandia camp.

The population housing density in the Jerusalem Governorate is 1.79 and about 19.9% of all household live in housing units with three persons or more per room (PCBs, housing report, 2000).

Chapter 2. Literature review

2.1. Introduction

Asthma is a clinical syndrome characterized by airway Hyperresponsiveness and airway inflammation. Furthermore; pediatric asthma is considered one of the most common chronic diseases of childhood that causes inflammation and spasm or tightening in the bronchial tubes which are responsible of carrying air to the lung. (Hughes, 2004). Its clinical manifestation is not as typical as adult asthma. Recurrent episodes of cough and wheezing are the most frequent symptoms. However, numerous investigations of the occurrence of pediatric asthma have been conducted worldwide. In the United States, data from nationwide samples and survey populations indicate that asthma is a common disease in children, with an overall prevalence of 5% (James, 1999).

Asthma can start at any age, but the majority of all people with asthma had their first symptoms by the age of 10. On the other hand, a big proportion of children with asthma had their first asthma attack before the age of six. (Morres,2005).

The exact causes of asthma are not fully understood, and the disease is probably caused by interaction of hereditary and environmental factors, but how they interact together is still not fully investigated. However, many endogenous and exogenous risk factors have been identified for asthma. Studies of familial aggregation of asthma and twins show a strong familial influence on the prevalence of asthma without separation between genetics from common environmental effects. However, all individuals with asthma have a characteristic hyper reactivity of the airways to a variety of environmental factors, including irritants such as house dust mites and pollutants; strong odors; cold air; and rapid changes in temperature and humidity. Descriptive studies of pediatric asthma have consistently shown an increased prevalence in males, which may be explained by differences in airway geometry. (Masoli ,etal ,2004). Atopy, defined by positive skin tests to common aeroallergens, predicts increased risk of asthma if present in parents or child. Moreover, episodes of lower respiratory tract infection are associated with subsequent asthma and increased airway reactivity (Payne, etal 2004). Ambient air pollution may exacerbate asthma, but it has not been established as a risk factor for childhood asthma. Similarly, environmental tobacco smoke has been shown to exacerbate asthma, but its role in the development of asthma is uncertain. (Marittas, 2002)

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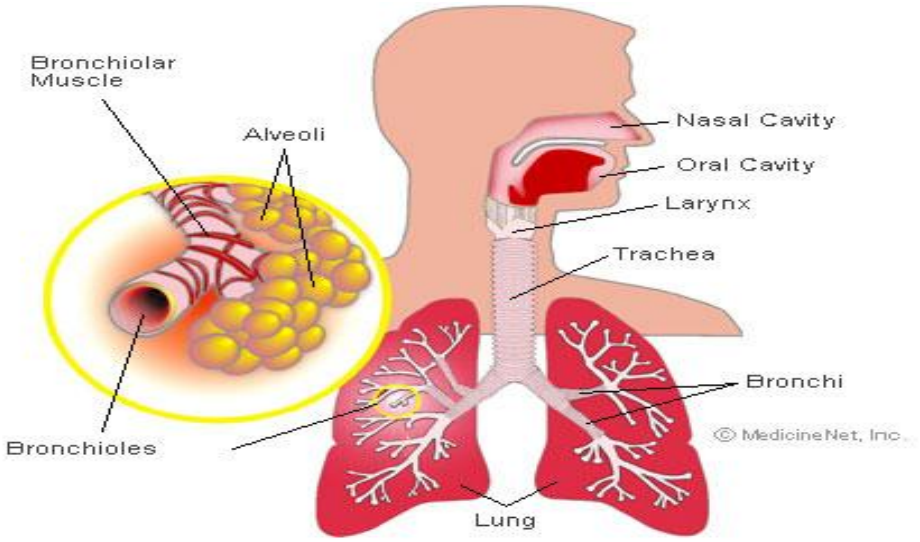
On the other hand; Alpha 1 – Antitrypsin deficiency is a hereditary autosomal disorder, resulting from a variety of mutations in alpha one Antitrypsin gene and associated with a high risk for the development of early onset of pulmonary emphysema. (Stockley, 2001).Also alpha one Antitrypsin deficiency phenotypes have been noted to contribute to highlight the risk of developing asthma and a topic diseases especially in children. (Wenzel, 2004).). However; many studies have proved an association between alpha one Antitrypsin deficiency and asthma. For example, information from the British Registry of alpha one Antitrypsin deficiency patients has reported the occurrence of asthma in 11% of the cases. (Luisetti, 2004).

In addition to that other researchers such as Seersholm and his colleagues found an increase in the prevalence of MS phenotype to 18% and MZ phenotype to 7% among Puerto Rican children attending the asthma clinic in New York city in the United States (Seersholm, etal, 2000)
On the other hand; Edward Eden from Columbia University reported that genetic testing of asthmatic people to investigate the deficiency of alpha one Antitrypsin phenotypes is very important as abnormal phenotypes are associated with an increased prevalence and severity of asthma, (Edward, 1997). Other researchers suggested that normally alpha one antitrypsin modulates the effect of inflammatory mediators involved in the pathogenesis of asthma. (Luisetti, 2004). Furthermore; the development of asthma in patients with deficiency phenotypes of alpha one antitrypsin will increase the rate of the development of irreversible airway obstruction and emphysema in a mechanism that asthma and alpha one antitrypsin deficiency are connected path physiologically. (Schluchter, etal. 2000) The present study is the first case –control study in Palestine to estimate the number of carriers and the number of those individuals who are homozygous or heterozygous for the Z, S defective alleles of AAT deficiency among 150 children in east Jerusalem .also environmental risk factor such as family history of asthma, domestic animal and second hand smoking and different Sociodemographic variables will be included.

2.2 Normal Lungs Function

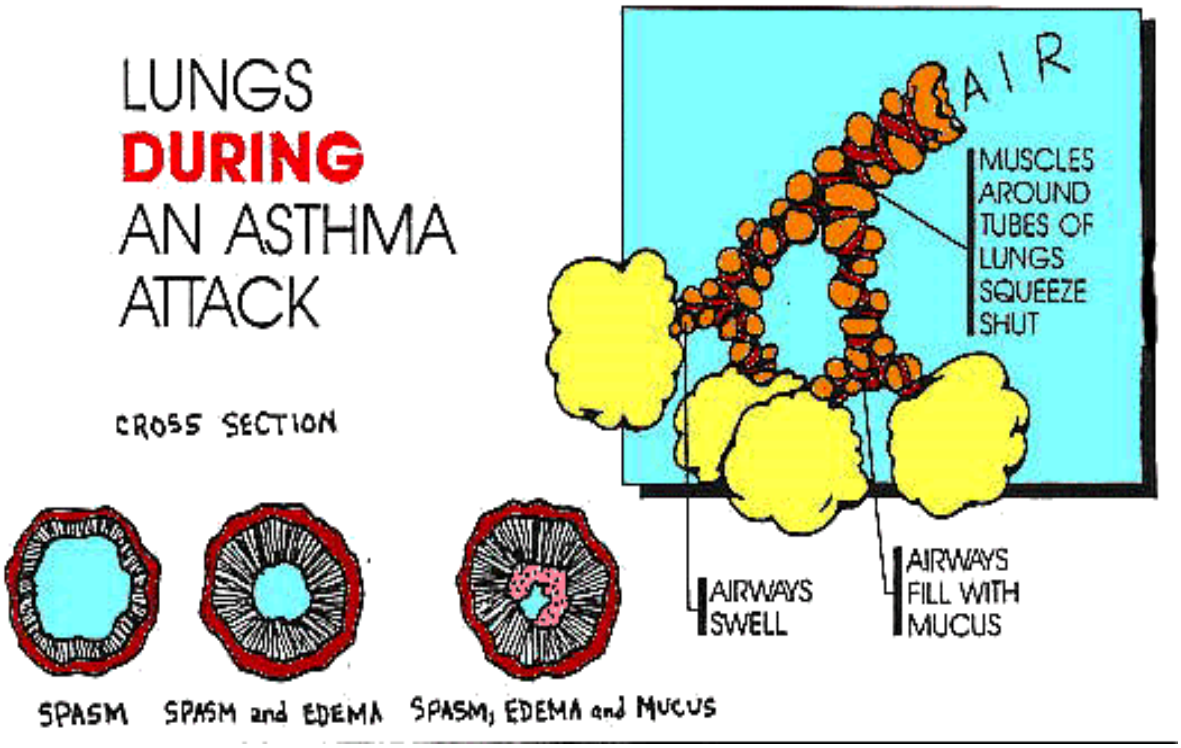
Air usually enters the nose and mouth and goes down the air tube (trachea) to two main air passages (bronchi). These passages allow air to go into the right and left lung. Each bronchus branches out into grape-like air sacs called alveoli. Through the alveoli, oxygen enters the bloodstream during breathing in (inspiration), and carbon dioxide, a waste product, leaves the body during breathing out (expiration).as seen in Figure 2.1

Figure 2.1: normal lungs



Source: - MedicineNet.com

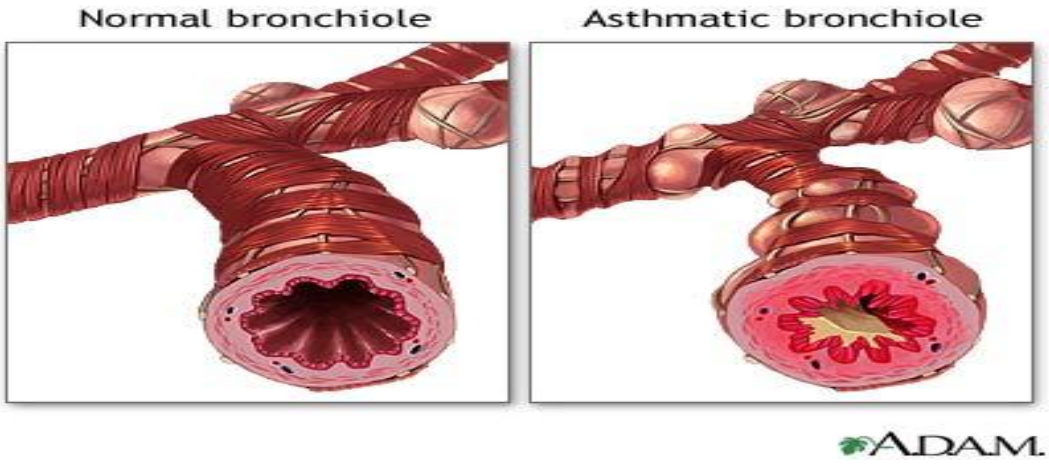
Figure 2.2: lungs during asthma attack



(Source : Mister seed's Health Centre, 1994).

Figure 2.3 Normal Asthmatic Bronchiole

During asthma attack smooth muscles located in the bronchioles of the lung constrict and decrease the flow of air in the airways. The amount of air flow can further be decreased by inflammation or excess mucus secretion. (Frederic, 2004).



(Source: Department of Allergy and Pulmonary/Critical Care Medicine, Boston University, 2004.)

2.3. Pathophysiology and contributing factors of Pediatrics Asthma

The exact cause of asthma is not yet understood, but through an asthma attack, the airways in the lungs react to some stimulus or trigger. In response to exposure to these triggers, the bronchi contract into spasm. Inflammation soon after follows, leading to a further narrowing of the air ways and increased mucus production which leads to wheezing, coughing and other breathing problems. (Lilly, 2006). In severe causes of asthma, damage to the lungs can accumulate over time, resulting in permanent narrowing of the airways. However; two factors contribute in provoking asthma; these are either triggers or inducers. Triggers irritate the airways and result in bronco constriction, and children with asthma when they encounter a trigger, an exacerbation can occur. Triggers are common, including, cold air; dust, strong fumes; exercise; emotional upsets; smoke; and inhaled irritants. On the other hand, inducers cause both airway inflammation and are defined to be causes of asthma. The most common known inducers are allergens and respiratory viral infections. (Brunekreef, 2002).
Prevalence and severity of childhood asthma were studied in 200 asthmatic children Remission of asthma was defined as a period of at least 2 years free of asthma while receiving no treatment. In their study univariate analysis showed significant associations between persistence of asthma and perennial symptoms with an odds ratio (OR) of 2.5 ; sensitization to house dust mites OR 3.5 ; sensitization to molds, OR 7.9 ; sensitization to pollen, OR 4.8; and sensitization to milk protein, OR 5.4. Researchers found that there was a positive association of remission of asthma with good treatment compliance, OR 12.1. (Anderson, etal .1994)

In 2001 cross-sectional national survey was done in Taiwan , 35 036 age selected from 6- to 15-year-old schoolchildren from 22 elementary and 22 middle schools located within 1-km in area of Taiwan Parental atopy and environmental exposures are recognized risk factors for childhood asthma. This study was undertaken to identify risk factors, estimate the population attributable risk of each exposure, and compare the data for boys versus girls for physician-diagnosed asthma in Taiwanese school children. Investigation hereditary and indoor and outdoor environmental factors for childhood asthma by questionnaire. Parental atopy contributed more to childhood asthma than did indoor or outdoor environmental factors. Exposure to indoor/outdoor environmental factors increased the risk of asthma in children regardless of the coexisting hereditary factors. (Ling, Y, 2003)

In general either triggers or inducers, the contributing factors in pediatric asthma can be summarized as follows:

2.3.1. Bronchial hyper reactivity

Bronchial hyper reactivity means that the intra thoracic airways of the asthmatic child narrow to a far greater degree in response to certain stimuli. The mechanisms of airway hyper responsiveness are numerous and complex.

The inflammatory process is very important, It is characterized by epithelial damage and sloughing, by cellular infiltration of the bronchial mucosa and sub mucosa and by anatomical modifications of the bronchial wall. The cellular infiltrate is characterized by the presence of eosinophil, lymphocytes, monocytes-macrophages and mast cells. These cells are activated and release bronchus constrictor and inflammatory mediators. (Forbes,2003) Eosinophil have toxic effects on the bronchial epithelium through the release of basic proteins, while lymphocytes play a central role through the release of cytokines, which can activate and recruit other cells. Mast cells have an important role in the stimulation of the reaction but may also maintain it. Allergen inhalation in the laboratory, when a late response occurs, is responsible for an inflammatory reaction comprising eosinophil influx and activation and T lymphocyte activation.(Morres;2005) The intensity of the reaction is related to the transient increase in airway hyper responsiveness confirming the important role of atopy and allergic reactions in airway hyper responsiveness.(Lissauer,2001) However the same kind of inflammatory reaction can be present without atopy and anti-inflammatory treatments, even if they reduce airway hyper responsiveness, they may not completely abolish it. This emphasizes the complex mechanisms involved in persistent airway hyper responsiveness. (Clark ; 2000).
In 2004 thirty six children with difficult asthma were studied. Asthmatic airways removed by bronchial biopsy show marked inflammatory changes, notably epithelial cell disruption and damage, and the presence of large numbers of eosinophil. The epithelial damage is seen in mild cases, the epithelium, thus, may actively participate in the inflammatory changes in asthma, where it may be a source as well as a target. The researchers found that drug therapy aimed at preventing inflammatory changes in the epithelium, such as cytokine and adhesion molecule expression, may be an important step forward in halting disease progression in asthma. (Payne, 2004).

2.3.2 Allergy

Respiratory allergic diseases appear to be increasing in most countries. In particular, asthma morbidity and mortality have been reported to be increasing despite the availability of effective asthma medications. It has been also observed that subjects living in urban and industrialized areas are more likely to have respiratory allergic symptoms than those living in rural areas. (Vonk, 2006). This increase has been linked to air pollution, rather than to a modification of the genome of the patient.(Etzael,1991) The interplay of genetic and environmental factors in the development of allergic disorders remains a subject of investigation.(Meyers,2004) In the outdoor environment, the most important air pollutants are sulphur dioxide, ozone and particulate matter, in particular diesel exhaust emissions. These pollutants, besides acting as irritants, increasing airways hyper-reactivity, are thought to be causal factors which act to modulate the immune response, with an adjuvant activity on immunoglobulin E (IgE) synthesis (Blumenthal,2005). In other words, a topic state can be regulated by environmental influences, and some subjects develop a topic disease in response to these environmental factors.

Since airborne allergens and air pollutants are often both increased in the same areas, potentiation, either in the degree of acquired sensitization or in the degree of the response to allergens, should be considered as an important factor which might help to explain the increasing frequency of allergic respiratory disease. (Vonk, 2006). In the light of our present knowledge, it is evident that further investigation in human subjects, aimed at evaluating specific agents, and their concentration in the atmosphere, which can influence pulmonary function, is needed. These studies may help to explain increasing problem of asthma morbidity and mortality.(Kaliner,1999) "Allergens can trigger episodes of asthma in atopic patients but asthma is more often aggravated by non –specific factors such as cold air, tobacco smoke, dust, and fumes also respiratory viral infection and emotional stress."(Haslett, 1999)

2.3.3. Infection

Viral infections are known to the commonest factors for asthma attacks in children. And have been estimated to account for more than 80% of acute exacerbations of asthma in children (Gelfand, 2000) .The mechanism of interaction between viral infections and asthma attacks is not known in spite of the fact that some viruses can induce immunological changes in the host. Viral respiratory infections in humans have been associated with exacerbations of late allergic responses and asthma, as well as with airway abnormalities that persist after resolution of the acute infection (Murry, 2000).

A viral respiratory infection in children increases the risk of developing asthma. A study in2004, show a link between respiratory syncytial virus (RSV), infection and asthma in mice. A related study, also in mice, suggests that a medication neutralizing the virus could decrease children's chances of developing asthma. (Mercola,2004) They hypothesized that augmented parasympathetic contractile mechanisms may contribute to post viral airway dysfunction. They studied airway physiology in anesthetized rats at one to eight weeks after inoculation with Para influenza 1 virus . The inoculate rat groups had airway obstruction (abnormal lung mechanics, gas exchange and residual volume), and increased sensitivity to intravenous methacholine at one to four weeks. Although methacholine hypersensitivity was minimal in non inoculated rats; these abnormalities were absent at seven to eight weeks after inoculation. The researchers concluded that respiratory virus infection in rats produces airway dysfunction that remains for weeks after resolution of the acute infection.(Murray,2004)On the other hand, microbes appear to be involved in the etiology of some cases of asthma. In addition to previous findings indicating that viral infection may exacerbate acute asthma, emerging evidence now implicates bacterial infection as a cause of chronic asthma. (Zucker, 2001) Richard Martin, and colleagues report detecting infection with Mycoplasma pneumonia or Chlamydia pneumonia in 31 of 55 asthma patients using a combination of polymerase chain reaction (PCR), serology, and culture.(Martin,2001)

2.3.4. Smoking and other environmental pollution

A child with asthma has sensitive airways inside their lungs. Certain triggers can make these airways narrow. If the child has asthma, smoking can lead to more asthma symptoms and more frequent asthma attacks. Secondhand smoke is a well-known asthma trigger. If the child has asthma. Secondhand smoke can damage the lungs by leading to long-term breathing problems or worsening existing breathing problems. (Joseph, 2004)The World Health Organisation (WHO) convened an International Consultation on Environmental Tobacco Smoke (ETS) and Child Health in 1999. The Consultation brought together experts from developed and developing countries to examine the health effects of ETS on child health and to recommend interventions to reduce these harmful effects and eliminate children's exposure. (WHO, 1999) "Both asthma and respiratory systems (wheeze, cough) are increased among children whose parents smoke, on the basis of over 60 studies of school-aged children. The relative risks for either parent smoking range from 1.2 to 1.4." (WHO, 1999) When a person inhales tobacco smoke, irritating substances settle in the moist lining of the airways. These substances can cause an attack in a person who has asthma. (Winzd, 2006)

Tobacco smoke irritates and damages the lungs, prompting the body to send more white blood cells to protect them. The more white blood cells there are, the more neutrophil elastase is made, causing even more lung damage. Also, the smoke itself changes alpha-1 antitrypsin so that it cannot do as good a job protecting the lungs from harm. Smokers with alpha-1 antitrypsin deficiency have a faster rate of lung damage (Medicine, 2006)

The harmful effects of passive smoking (PSE) start early in intrauterine life and comprise direct toxic effects of components of tobaccos smoke on the fetus as well as indirect effects by impeding the normal nutrition of the growing child over effects on the placenta. Consequences are diminished birth weight, and increased natal mortality. (Wearer, 2006) The sudden infant death syndrome is associated with PSE as are increased incidence of respiratory illnesses in early childhood. Increased bronchial responsiveness, increased asthma prevalence, delayed lung growth and increased incidence of chronic respiratory symptoms later in childhood may well put these children at increased risk for developing chronic obstructive pulmonary disease in their later life. However; even if it is difficult to obtain correct epidemiological evidence, there is a body of evidence which suggests that the frequency of allergic respiratory diseases is increasing. (Murry, 2000)

The majority of atopic patients, in particular in childhood and adolescence, develop immunoglobulin E (IgE) antibodies with clinical symptoms to aeroallergens, such as those derived from house dust mites, pollens and pets. Since, in the economically-developed countries individuals spend most of their time indoors (home, school and workplace), indoor pollutants (tobacco smoke etc.) and allergens (house dust mite, cats, etc.) are the most important source of exposure. (Marittas, etal, 2002)

Researchers find exposure of nonsmokers to environmental tobacco smoke (ETS) has become an important public health issue; it is generally agreed that increased exposure is related to morbidity and mortality. Precise prevalence estimates of exposure are not yet available, and measurement methodology for ETS exposure rates is still in its formative stage. (AAAAI, 2006) Recent interventions have attempted to reduce ETS exposure, particularly in children of smoking parents. Studies have relied primarily upon reduction of parents' smoking rates to indirectly reduce children's ETS exposure. In order to effectively design interventions to achieve reductions in ETS exposure, more attention must be given to smoking behaviors which lead to passive exposure. (Wolf, 2004); Researchers say that early exposure to smoke can speed the decline in lung function normally associated with age, increasing the risk of heart and lung problems or even death.(Winzd,2006). "Children breathing secondhand smoke are more likely to suffer from bronchitis and pneumonia, ear infections, coughing and wheezing, and more frequent and severe asthma attacks. " (AAAAI, 2006)

A study of ninety-one families with at least one smoking parent and an asthmatic child were recruited from four allergy clinics, and interviewed regarding their smoking history, current residential smoking patterns, and the children's exposure patterns. Descriptive data are presented showing that the asthmatic child symptoms were mostly triggered by passive smoking. It is recommended that interventions focus closely on these patterns rather than on reduction of smoking rates alone, in order to effect reduction in ETS exposure especially on children with asthma. (Wolf, 2004) On the other hand; the Institute of Medicine committee found that the exposure to certain environmental pollutants such as house dust mites cause the development of asthma in the susceptible children. The committee also determined tobacco smoke as a risk factor that triggers asthma and is directly associated with the development of asthma in younger children (Stern, 1994). Lichtenstein added that asthmatic children can be particularly sensitive to outdoor air pollution especially what is known of ambient air pollutants such as ozone and sulfur dioxide. (Lichtenstein, 1997). Other researchers emphasized that air pollution might act synergistically with other environmental pollutants to worsen asthma (Nazario, 2006) On the other hand Stern added that asthmatic children can be particularly sensitive to outdoor air pollution especially what is known as ambient air pollutants such as ozone and sulfur dioxide. Stern etal (1994); emphasized that air pollution might act synergistically with other environmental pollutants to worsen asthma. Examples are the diesel exhaust particulates that increase the capacity of producing IgE antibodies.(Forbes and Jackson,2003).

2.3.5 Exercise

Exercise induced asthma (or EIA) causes symptoms of coughing, wheezing, chest tightness to breathing, or shortness of breath. Children with EIA may experience breathing difficulty 5-20 minutes after exertion begins. EIA may occur more easily on cold, dry days than on warm, humid days. (AAAAI, 2006)

Exercise is considered one of the physical stimuli that can provoke attacks of asthma in the asthmatic child. Because children are naturally and physically more active than adults; the incidence of exercise induced asthma (EIA) increases especially if the exercise is hard and persists for a long period which considered enough for the asthmatic child to develop bronchospasm. In other words; given sufficient exercise intensity, exercise can trigger acute exacerbations in virtually all individuals with asthma. Heat loss, water loss, postexertional airway rewarming, and the role of several mediators have been proposed as possible mechanisms responsible for the airway obstruction induced by exercise.(Morres,etal,2005) Exercise-induced asthma can be easily diagnosed and treated in the majority of patients. Physical training should be part of the asthmatic patient's overall plan of management. When properly treated, asthmatic individuals should be able to participate or compete in the majority of sports. (Joseph, 2005)
When asthma is triggered only by physical activity, it is called exercise-induced asthma (EIA). Just as with other asthma triggers, a person who is triggered into an asthma attack by exercise has airways that narrow and tighten after they begin to exercise. In addition, the symptoms of EIA can be much worse with seasonal allergies. (Joseph, 2005)

2.3.6. Emotional factors

In the past it was thought that asthma was mainly an emotional disorder. Today The Asthma Center specialists know that the basis of bronchial asthma is a biochemical abnormality in the cells lining the bronchial tubes as well as hyper-irritability of the airways. However, a subgroup of individuals who are under or have undergone stressful situations may find themselves suddenly wheezing. Therefore it is apparent that while emotional stress can be a significant triggering factor in asthma (Kolbe, etal, 2002).

Researchers at National Jewish Medical and Research Center have now added another risk factor for the development of asthma -- the early psychological environment of the child. They agreed that emotional and psychological factors can act on the abnormally labile bronchi via the autonomic nervous system of the asthmatic child in a way that make the airway obstruction worse (UniSci Daily Java News, 2001)Emotional anxiety and nervous stress reactions from stress and anxiety are considered to be more of an effect than a cause. They can cause fatigue, which may affect the immune system, increase either asthma symptoms or bring on an attack. " (Allergy and Asthma, 2001)

2.3. 7 Gastro – esophageal reflux

Gastro esophageal reflux is a backward flow or reflux of stomach contents into the esophagus. Everybody has some reflux. Abnormal amounts of gastro esophageal reflux can cause gastro esophageal reflux disease (GERD).

This occurs when the valve of smooth muscle between the esophagus and the stomach does not function properly. This muscle band is called the lower esophageal sphincter. (National Jewish, 2006) "It has been recognized that gastro – esophageal reflux can produce an increase in bronchial reactivity, which may be responsible for the very severe attacks of nocturnal asthma which occur in some children."(Clark andCodfrey 2000)

In the same field several studies have shown the relationship between gastro-esophageal reflux, bronchial asthma and chronic nocturnal cough and this should not be neglected, particularly in patients who present an unfavorable development in spite of conventional treatment. For diagnosis of gastro esophageal reflux, amongst other investigations, esophageal gammagraphy of swallowing, that detects alterations in the mobility of the esophagus, secondary to a possible oesophagitis. (Clark and Codfrey 2000) The relationship between GER and asthma symptoms also led investigators to assume that anti reflux therapy would improve asthma. The results of studies on the effects of anti reflux therapy on asthma patients with GER are also conflicting. Some investigators, reported that anti reflux therapy was beneficial, whereas others were unable to identify its effect on asthma (Stephen, 2002)

2.4 Genetic background

The role of genetics in pediatric asthma has been studied worldwide. Researchers studied mostly the hyper reactivity of the bronchial airways and asked if this is acquired or is with the baby from birth (David, 2001).Another study in 2001 noticed that there was a relatively high incidence of atopy and bronchial hyper reactivity amongst healthy relatives of asthmatic children and wheezy infants. (Stockly, 2001).
In the same field; Daily Policy Digest Environmental Issues interviewed the parents of about 4000 identical and fraternal twins of four years old. They noticed that asthma rates were more similar among identical twins than others because in addition to their same home environment; they also share the same genes (Koeppen ,etal 2001). In general , genes account for 68% of the prevalence of asthma. They documented that even asthma is highly heritable , it is more likely to develop through an interaction via hereditary and environment (Koeppen ,etal 2001).

On the other hand; Genetic and Molecular Regulation of ADAM33: ADAM33 was the first asthma susceptibility gene identified as a result of a genome-wide positional cloning effort .Astudy conducted by researchers in Southampton University has identified a relationship between a gene located on chromosome 20 and asthma. This gene is ADAM33 which is responsible on the over respond and the process of airway passage constriction. (Maniatis, etal.2005).

On the other hand; alpha one Antitrypsine deficiency is an autosomal recessive disorder which results in pulmonary emphysema from the damage of the lower lobes of the lungs as well as liver disease. (Frederick J. 2002).

Alpha one Antitrypsine is a protein circulating normally in the blood and it in vitro assays inhibits trypsin activity. In families in which a patient with pulmonary emphysema has been shown to be homozygous for deficient Antitrypsin activity; there is an increased incidence of pulmonary disease in relatives heterozygous for the deficiency. Frederick (2002) suspected that the alpha one anti trypsin protein is a serine protease inhibitor which inhibits bacterial proteinase in a mechanism that will otherwise destroy the alveolar architecture. However; the AAT gene consists of seven exons spanning of 12 kilo bases and are located on the long arm of chromosome 14 PiM is the normal designation of the gene (Frederick, 2002). PiM is the normal designation of the gene. Information from genetic epidemiological surveys shows that there were at least 75 deficiency alleles which have been already described. Alleles such as PiZ and PiS are studied by gene – mapping techniques and information showed that combination of alleles of major genotyping classes of interest are: (PiMM; PiMS; PiMZ; PiSS; PiSZ; PiZZ). (Ehrenstein,2003). A study conducted by Frederick J. (2003); showed that in a total population of 4.4 billion from 58 countries recruited from different 11 geographical regions, there are at least 116 million carriers of Pi MS and PiMZ and 3.4 million deficiency allele combinations of (PiSS; PiSZ; PiZZ).

Asthma associated with alpha 1-antitrypsin deficiency can impose serious impairment. A study conducted by Stoller etal (1994) in order to gather information about the impact of severe alpha 1-antitrypsin deficiency. Authors sent a survey to 1730 subscribers to a national newsletter, 850 of who had previously stated they had alpha 1-antitrypsin deficiency. A total of 414 questionnaires were returned; 398 respondents said they had alpha 1-antitrypsin deficiency, and 300 said they had the PiZZ phenotype. Sixty-six respondents who said they had the disease did not know their phenotype. Among the 304 respondents with severe deficiency, the mean age at the time symptoms first appeared was 35.0 years, but the mean age when the disease was diagnosed was 41.3 years. Overall, 75.3% of respondents with severe deficiency reported at least one adverse effect: 44.4% retired early, and 19.1% changed to a physically easier job. The duration of diagnostic delay correlated with the degree of adverse psychosocial effects. This study concluded that Alpha 1-antitrypsin deficiency frequently escapes diagnosis despite many medical encounters; the affected individuals are often unaware of basic details of their disease, and many patients report adverse psychosocial effects. However; delay in diagnosing this disease is associated with adverse psychosocial effects.(Stoller etal; 1994).

2.4.1 Alpha-1 Antitrypsin

Alpha-1 Antitrypsin is a protein that is made in the liver. The liver releases this protein into the bloodstream. Alpha-1 antitrypsin protects the lungs so they can work normally. Without enough alpha-1 antitrypsin, the lungs can be damaged, and this damage may make breathing difficult. In addition, liver damage (hepatitis, cirrhosis) can occur in both children and adults. Alpha-1 antitrypsin deficiency is an inherited (passed down from parents) disorder that causes low levels of, or no alpha-1 antitrypsin in the blood. (Anonymous, 1994)

2.4.2 Alpha 1 Antitrypsin Deficiency

When the lungs do not have enough alpha-1 antitrypsin, neutrophil elastase is free to destroy lung tissue. As a result, the lungs lose some of their ability to expand and contract (elasticity)(Koeppen, etal, 2001) White blood cells normally found in our bodies help protect us from infection. But white blood cells also release an enzyme, called neutrophil elastase, that can damage the lungs. In normal lungs, alpha-1 antitrypsin protects the lungs from the harmful effects of neutrophil elastase. (Savransky, 1994)

Alpha-1 Antitrypsin (AAT) deficiency is a genetic, chronic and progressive disease that causes lung and/or liver problems. AAT is a protein that circulates in the blood throughout the body which protects the lung tissues from toxic agents, including an enzyme called elastase. When this AAT protein is deficient, the elastase level increases, destroying the elasticity of the lung tissue and thus causing a condition *known as* genetic emphysema. . (Schluchter, etal.2000)

Everyone receives one gene for alpha-1 antitrypsin from each parent. The M gene is the most common type of gene, and it is normal. The person who inherits an M gene from each parent has normal levels of alpha-1 antitrypsin. The Z gene is the most common defect that causes the disorder. If a person inherits one M gene and one Z gene, that person is a carrier of the disorder. While such a person may not have normal levels of alpha-1 antitrypsin, there should be enough to protect the lungs. The person who inherits the Z gene from each parent is called "type ZZ." This person has very low alpha-1 antitrypsin levels, allowing elastase to damage the lungs (Murry and Nadel, 2000).

2.4.3 Physiology of ALPHA 1 Antitrypsin deficiency

Alpha 1-antitrypsin is produced in the liver, and one of its functions is to protect the lungs from the neutrophil elastase enzyme." Normal blood levels of alpha-1 antitrypsin are 1.5-3.5 gm/l. In individuals with PiSS, PiMZ and PiSZ phenotypes, blood levels of Alpha 1-antitrypsin are reduced to between 40 -60% of normal levels.".(King , 1999).

Alpha one Antitrypsin deficiency is a genetic disorder that is characterized by an insufficient amount of serum AAT which predisposes to chronic obstructive lung disease, chronic liver disease and in some cases skin and vasculitis disorders. Alpha 1-Antitrypsin (AAT) deficiency is associated with predisposition to developing liver cirrhosis in early childhood, and chronic degenerative lung disease in early adult life. The probable molecular basis for the disease associations is known. One of the common variants, Z and S, has the propensity to form polymers, a phenomenon which is concentration- and temperature-dependent. This results in accumulation of the protein in hepatocytes, the predominant tissue source of AAT, and leads to cell damage. AAT deficiency results in loss of protection in the lung against neutrophil elastase (NE) the major target for AAT. NE is capable of destroying the architecture of the lung, leading to pulmonary lung disease especially emphysema.

The disease process is exacerbated by cigarette smoke, which is capable of oxidizing a critical methionine residue at the active site, rendering AAT an inefficient inhibitor of NE. The combination of deficiency and cigarette smoking are critical to the development of pulmonary emphysema. Researcher identified a mutation in an enhancer sequence which, in all probability, predisposes to disease by a novel mechanism related to diminished expression of AAT during inflammation.(Schuchter,etal.2000) Moreover; AAT deficiency is often misdiagnosed as asthma or smoking- related Chronic obstructive pulmonary disease, as many as about 3% of all people diagnosed with COPD have alpha one Antitrypsin deficiency However; AAT deficiency has been identified in all different populations with the fact that about 20 million people are carries of the defective gene worldwide with the ability to pass it to their offspring.(Anonymous,1994) However; information from the American Journal of Respiratory and critical care medicine shows that there is a serum threshold level of AAT above which the lung tissues appears to be protected. This threshold lies at about 35% of the average normal level. On the other hand; AAT is a polymorphic protein molecules which has an about of 100 different alleles combined in homozygous or heterozygous states and are assigned a letter code (A to Z). (American Journal, 2003). The most common allele is defined as M, and the normal individuals have a protein phenotype (PiMM). The deficient genotypes include Z and S variants. The most frequent deficient alleles is the Z variant and those with(PiZZ) homozygousity have AAT levels of about 15% of the normal and considered at the highest risk of developing AAT associated lung disease. However; there are about 200,000 Swedish infant screened of AAT deficiency in the early 1970s. (Sharp, etal, 2003).

On the other hand; the S variant homozygousity forms give plasma levels of the enzyme about 60% of the normal. Heterozygous forms include PiZS, PiMS; PiMZ and persons with such deficient alleles are at increased risk of developing AAT deficiency associated diseases. The most severe cases of AAT deficiency are associated with the null alleles designated as PiQQ were there is no or about 1%of the normal level of AAT. (American Journal; 2003).longitudinal lung function study in heterozygous PiMZ phenotype subjects found it is a matter of controversy whether subjects who are heterozygous (PiMZ) for alpha 1-antitrypsin deficiency are at risk of developing pulmonary emphysema. To assess the role of MZ phenotype in the development of abnormal lung function the authors performed a 10 year follow-up study of 28 PiMZ subjects, compared to 28 matched-paired normal PiMM subjects. Maximal expiratory flows and mechanical properties of the lungs were studied, in order to determine the changes of the lung function parameters characteristic of pulmonary emphysema. Total lung capacity and residual volume increased, whereas forced expiratory volume in one second, expiratory flows, diffusing capacity of the lungs for carbon monoxide, and static transpulmonary pressures decreased in the PiMZ patients. The majority of the controlled functional parameters were found to deteriorate significantly in PiMZ patients during the 10 year period. Trypsin inhibitory capacity in the PiMZ group (mean +/- SD) was 0.65 +/- 0.17 mg.ml-1 as compared to 1.52 +/- 0.3 mg.ml-1 in the PiMM group.

These changes exceeded the values expected as physiological changes due to ageing. The findings in the present longitudinal study--especially the decrease in elasticity, which is the primary path physiological damage in alpha 1-antitrypsin deficiency--support the concept that the PiMZ phenotype is a risk factor for the development of pulmonary emphysema at younger age than in those without the deficiency. (Tarjan, etal. 1994).

2.4.4 Epidemiology of Alpha one Antitrypsin deficiency

Alpha 1 antitrypsin deficiency is a widely distributed genetic disease. Data shows that there are 100,000 patients in the United States with the ZZ phenotype. Where the prevalence of MS and MZ phenotype in the United States is calculated to be (1/50). (Molucular,2005). However; the prevalence of the three major variants of AAT phenotypes is registered in many surveys throughout the world with the highest prevalence of the PIZ variant in the northern and western European countries compared to North America. On the other hand; the frequency distribution of PIS differs significantly from that in PIZ as it is also more homogenous. The mean gene frequency of PiS in the southern Europe was the highest .peaking in Iberian peninsula (Luisetti and Seersholm, 2004) However; the gene frequencies of PiZ and PiS variants in Australia and New Zealand are closely similar to those reported in north America . (Luisetti and Seersholm, 2004) In South America, however; no reported data on the epidemiology of AAT variants. , Serres has proved in a global research study evidence that there is a significant prevalence of both PiZ And PiS alleles in populations from the middle east, Africa; central and southern Asia, highlighting the fact that AAT deficiency is prevalent over racial and ethnic boundaries, a thing that increases the need for further researches in this field . According to areas in the fast East Asia; the gene frequency of Piz is more in Japan than in South Korea and zero in china. (Luisetti and Seersholm, 2004)

In united stat 2002; Browne conducted a research study in which 26,866,600 death certificates reports were analyzed in the multiple cause mortality files compiled by the National center for health statistics. The deaths choose are those which were occurred during the 13 year period (1979-1991). Results show that among all deaths there were 1930 had alpha 1 antitrypsin deficiency listed as the major cause of death. Moreover; the age adjusted mortality rate with AAT deficiency listed increased 86% from 4.3 per 10 million in 1979 to 8 per 10 million in 1991. (Browme, 2002)Also Browme found that alpha one antitrypsin deficiency was reported in 2.7% of all deaths with obstructive lung disease among adults, where AAT deficiency was 1.2% of all deaths listing hepatic disease among children less than 14 years old. On the other hand; Browne noticed that deaths from alpha one antitrypsin deficiency were higher among whites than among blacks or persons of other races. The researchers emphasized the fact that alpha antitrypsin deficiency is an important risk factor for obstructive lung disease in the United States Globally; the distribution of the alpha 1-antitrypsin (Pi) phenotypes and subtypes was investigated in a population sample of 1060 unrelated individuals from Serbia (Yugoslavia).

The allele frequencies estimates were: Pi*M1: 0.702; Pi*M2: 0.183; Pi*M3: 0.088; Pi*Z: 0.013, Pi*S: 0.007; Pi*P: 0.004; Pi*F: 0.003. (Geoge.G, 1994).

A study was conducted by Lieberman and colleagues on a sample of 965 patients with chronic obstructive pulmonary disease in order to investigate the prevalence of AAT deficiency alleles especially the PiZZ phenotypes. Results of this study show that 1.9% of the study population show severe deficiency phenotype of PiZZ while 8% are of intermediate PiMZ phenotype. (WHO; 2001). On the other hand; a study conducted by the AAT deficiency detection center in Sant Lake City on 16,748 individuals with different lung diseases including asthma shows AAT deficiency in about 3.1% of the total sample, of these, only one individual had the PiSZ phenotype while the others are of the PiZZ phenotypes. (Stockley ,etal ; 2001).

Edward E. (1997) describes the asthma features in a cohort of 1129 subjects with serum AAT levels < 11 micro mole/liter and with PIZZ genotyping DNA probe analysis. In order to determine if asthma is associated with AAT deficiency. Results of this study show that asthma was present in 21% of the cohort and that features of asthma are common in those with AAT deficiency. However; in a small percentage of the study population 17%, an elevated IgE is associated with signs and symptoms of asthma and allergy history, which in turn is associated with an increased rate of Forced Expiratory Volume in the first second (FEV1) decline but is not an independent risk factor. (Edward etal,1997). Also, several previous studies showed and investigated that clinical features of asthma are present in some persons with severe AAT deficiency. Information from the British Thoracic Society Survey shows that among 166 patients with PIZ AAT deficiency alleles; 11% were diagnosed as asthma. (Roberts, and William, 2004). However; Silverman (1989); found that among 52 subject of AAT deficiency; asthma was present in 25% of those with an FEV1<65% predicted. (Edward etal, 1997).

In Thailand alpha one phenotypes was determined in 423 individuals from the northeast area of Thailand and 429 individuals from Bangkok, using the isoelectric focusing polyacrylamide gel. In the rural northeast areas of Thailand the M; S; Z, Pi alleles were detected. When measuring the serum concentration of alpha one Antitrypsin using the electro immunoassay; it was noticed that the concentrations were slightly higher among Thailand than those from the European countries. (Pongpaew, 1980)

2.5 Summary

Alpha-1 Antitripsine deficiency is an inherited disorder that can cause lung or liver disease. Alpha-1 is the name of a protein. Deficiency means there is not enough of it. This protein protects the body from being damaged by a powerful enzyme called neutrophil elastase. Neutrophil elastase is released from white blood cells to fight infection, but it can attack normal tissues (such as the lungs) if not carefully controlled by alpha-1 Antitripsine. A mutation in the SERPINA1 gene can lead to a shortage (deficiency) of alpha-1 Antitripsine protein or an abnormal form of the protein that cannot control neutrophil elastase.

Uncontrolled, neutrophil elastase destroys tiny air sacs in the lungs and will lead sever asthma symptoms.

Subsequent prevention of lung inflammation due to cigarette smoking, infection, and airborne irritants form the most rational approach to slow the progression of the lung destruction associated with alpha 1 Antitrypsin deficiency. Currently, less commonly, many inflammatory and/or immune-mediated diseases have been described in association with alpha 1 Antitrypsin deficiency. These observations are probably related to the role that alpha 1 Antitrypsin plays in the immune response both as a target for modulation by cytokines and as a modulator of the immune response

Chapter 3 Conceptual Framework

3.1 At the global level

3.1.1 Definition of asthma

"Asthma is a disease of the respiratory system that causes breathing difficulty and expressed by repeated but reversible episodes of constriction and inflammation of the airways and lungs. Typical symptoms include wheezing, coughing, and shortness of breath. Technically, asthma is described as a chronic inflammatory disorder of the respiratory system. Asthma has both a genetic and environmental basis. The symptoms of asthma are caused by allergic-like reactions of the body's immune system to environmental and behavioral stimuli."(Marshal, etal, 2002)

3.1.2International statistics

According to Global Initiative for Asthma (GINA), a world-wide asthma research and education program, there are over 150 million asthmatic individuals worldwide. Some studies have revealed a 75% increase in asthma cases between 1980 and 1994 globally. Children accounted for the greatest increase in numbers.(GINA,1995) Health statistic for US in 2002 find nine million under 18 have been diagnosed with asthma(health survey, 2002).While about 2% of children in China display symptoms of asthma, approximately 30% of young people in Britain have indications of this disease. In Australia, the incidence of asthma is very high in Caucasian children, but much lower in Aboriginal children. Overall death rate from asthma has increased by 40% from 1982-1992 (Beers and Berkow, 1999) asthma incidence and mortality have sharply increased in the past two decades, particularly among children. The study cites statistics showing a doubling of asthma cases from 6.8 million in 1980 to 14.6 million in 1996, and a further increase to 17.3 million in 1999. (AAAAI, 2006)

In the meddle East the prevalence of asthma increased over recent decades (Khalid ,etal ,2001)increase rate recorded in Israel, kingdom of Saudi Arabia ,Lebanon and AL-Kuwait (AL-Frayh, etal 2001) .the prevalence also increases in Morocco and in Iran ,it was 3.5%-5.5% respectively (Beasley,1998)

IN Palestine asthma considered one of the majored respiratory disease that effect the mortality and morbidity rate(MOH,1999).Studies done in Palestine between 2000-2003 shows high risk of asthma in camps in comparing to villages .(Mohammad,2006)

3.2 Classification of asthma

The widely accepted classification of asthma in the United States is that recommended by the National Heart, Lung, and Blood Institute's (NHLBI) These guidelines place major emphasis on diagnosis, classification of asthma and management (NHLBI, 1997)

The guidelines divide asthma severity into four classes that range from mild intermittent asthma to severe persistent asthma. This classification is based on history of asthma symptoms and measurements of lung function. Specifically, history of asthma symptoms includes the frequency of daytime and night-time symptoms and the effect of the exacerbations on daily activities also FEV1 (percentage predicted). (GINA, 2002)

NHLBI, NAEPP, GINA, and AAAAI Guidelines Classification is based on history of asthma symptoms and lung function before therapy begins and is described as mild intermittent, mild persistent, moderate persistent, and severe persistent Classification of a patient into any of these levels can be accomplished by assessing the frequency of symptoms or by pulmonary function testing.(NHLBI,1991)

3.3 Risk factor for childhood asthma

Risk factors are determinants of the risk of developing childhood asthma and may increase or decrease the probability of an individual developing the disease (Vonk, J 2006).Both genetic and environmental factors can increase your child's chances of having asthma. Children with a family history of asthma are at greater risk of developing the disease. (David, 1998)

Other environmental factors that may increase your child's chances of developing asthma include: Previous allergic reactions to environmental allergens, Exposure to tobacco smoke, living in a large urban area with increased exposure to environmental air pollutants, Family history of asthma, allergic rhinitis, Obesity (Andrew, etal, 2000)

Recent international studies have suggested a relatively strong causal relationship between increased risk of childhood asthma and exposure to antibiotics during childhood. The increased asthma risk was seen whether antibiotics were used to treat respiratory or non-respiratory infections The study was also able to evaluate any relationships between antibiotic exposure and asthma for confounding by other risk factors such as bedroom allergen levels, pet ownership, cigarette smoke exposure, and parental history of asthma or allergy. The result was the child is over four times more likely to develop asthma symptoms than the child who has never taken antibiotics. (Wichens, 2007)

Costa Rica, one of the most prosperous Latin American nations, has a very high asthma prevalence. A Cross-sectional study was done to examine potential risk factors and childhood asthma the result Sensitization to house dust mites, low parental education, and parental history of asthma are associated with asthma in Costa Rica. (Celedon, 2001)

A case-control study was conducted by Dr. Frank Gilliland and colleagues from the University of Southern California for children who developed asthma by age 5 and compared these children to asthma-free children. Parents were asked to provide information on early life exposures through interviews.

Result was: children had an increased risk of asthma if they were exposed within the first year of life, but not at older ages, to cockroaches, herbicides, pesticides, farms crops, dust or animals. Exposure to wood smoke, soot or exhaust anytime between birth and age 5 was also associated with a higher risk of asthma.(Schultz.L,2003)

Characteristics of parental atopy as factors in childhood asthma was tested in a cohort study of children of 476 families from birth until ages 6-7 years. They found that development of asthma in a child was more closely associated with the paternal history of atopy asthma than the maternal atopy asthma history. Asthma history in the father (past or present) was significantly associated with asthma occurring in the children. (Alford et al, 2004)

3.3.1 Environmental risk factors in childhood asthma.

Genetic factors are important in determining the risk of developing asthma, environmental factors are believed to be the primary determinants of the expression of the disease (Sears, 1997) Indoor allergens and irritants play a significant role in level of asthma morbidity experience by children living in urban centers The New York State Department of Health's Center for Environmental Health conducted a study ,notice that a potentially increased ambient air level of ammonia from industrial facilities might be associated with an increased risk of childhood asthma. Also environmental residential factors (such as frequent truck traffic in the neighborhood, chemical odors indoors, parental smoking, and humidifier or vaporizer use), several socioeconomic factors, having a family member with asthma, and having limited access to medical care. The results demonstrated that indoor and outdoor environmental factors play important roles in increasing the risk of having asthma. (Gomez,m,2005)

National Cooperative Inner-City Asthma Study actually indoor as well as outdoor air quality. They found that a quarter of the children had relatively high levels of nitrogen dioxide exposure and these had more
symptoms and lower peak flows. And once again, those children who were not allergic were at particularly high risk from the respiratory pollutants. (Pamela R.2002) Allergens in house dust have been controversially implicated in the development and severity of asthma in children. House dust include mite, cat, dog , cockroach, and fungi (Platts ,2005) allergens are among the most important because of their suspected role in the development and exacerbation of asthma. Recent cohort studies that measured allergen exposure in infancy and followed children for recurrent wheeze and asthma have failed to find a strong association with dust mite or cat allergen (Lau, 2000)

3.3.2 Genetic risk factors in childhood asthma

The mechanisms underlying the inflammatory response in asthma are still not fully understood, it has become clear that both genetic predisposition and subsequent environmental exposure to allergen are integral to the development of the disease , studies have revealed that asthma has a strong genetic component but does not follow monogenic patterns of inheritance (Michael B.2002) Genes and environment play a role in the development of asthma. When asthma runs in families, genetic factors play a relatively large role. When asthma does not run in families, the genetic influence is not as significant as the environmental exposures. (David.L, 1998)

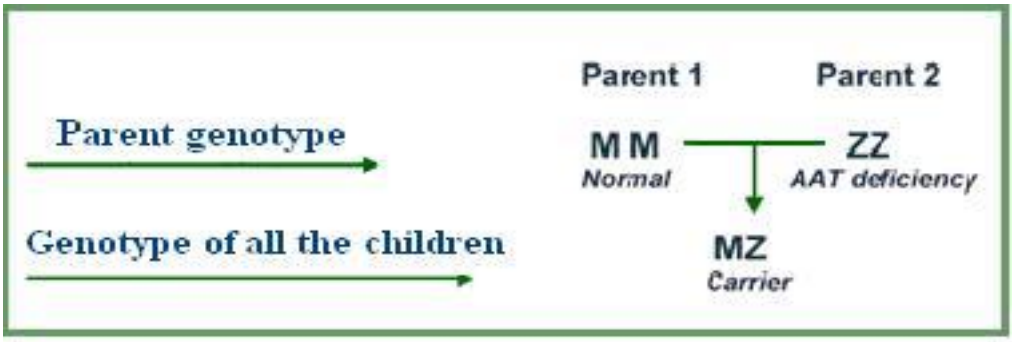
Researchers define Asthma as complex genetic disorder that is highly prevalent in the population when compared with other genetic pulmonary disorders, such as cystic fibrosis, in which the genetic characteristics are more easily understood. Children with asthma are more likely to have a parent, who has a positive history of asthma and atopy (Sears, 1997). Genetic markers within and around chromosome 5q31-33 have been linked to total serum IgE concentration in the United States and Holland (postma, 1995). These markers provide strong evidence of one or more loci in *5q31-33* closely involved in serum IgE levels and bronchial hyperresponsiveness. The gene encoding IL-4 is within this region and is a possible candidate for the reported genetic linkage. (Michael, 2002)

In this study we point to the risk of genetic factor by alpha 1 Antitrypsin deficiency. Seersholm N. Conducted a research cohort study on 1551 PIMZ patients in Denmark in order to study the risk of the deficiency alleles of alpha one Antitrypsin and increasing the incidence and the prevalence of obstructive pulmonary diseases. (Seersholm, etal.2000) Results showed that 47 patients identified with a discharge diagnosis of obstructive pulmonary disease in comparison with 206 patients with the same diagnosis in the control group giving a relative risk RR = of 2.2. However; 36% of the cohort were first degree relatives of the Piz index cases which give a notice that this group was at increased risk of hospitalization admission of obstructive pulmonary disease with a relative risk of 3.4. The researchers concluded that the PIMZ phenotype considered a risk for hospital admission for obstructive pulmonary disease only if they are first degree relatives of (PIZ) index cases. (Seersholm, etal.2000)

3.3.2.1 Genetic transmission of AAT deficiency

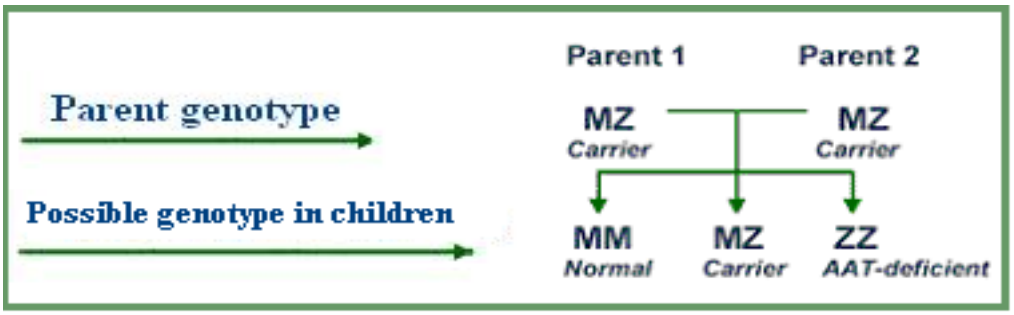
AAT Deficiency is hereditary, transmission occurs when defective genes are inherited from both parents. Our conceptual frame work depend on table(3.1 ,3.2 ,3.3) A person who inherits a normal gene, called genotype (**MM**), from one parent and an AAT deficient gene, genotype (**ZZ**) from the other parent becomes a carrier of the AAT-deficient gene, i.e. genotype (**MZ**). Few if any symptoms will appear in a person said to be a carrier of the gene. (Canada Lung Association,.2005)and the following table clarify :

Table 3.1



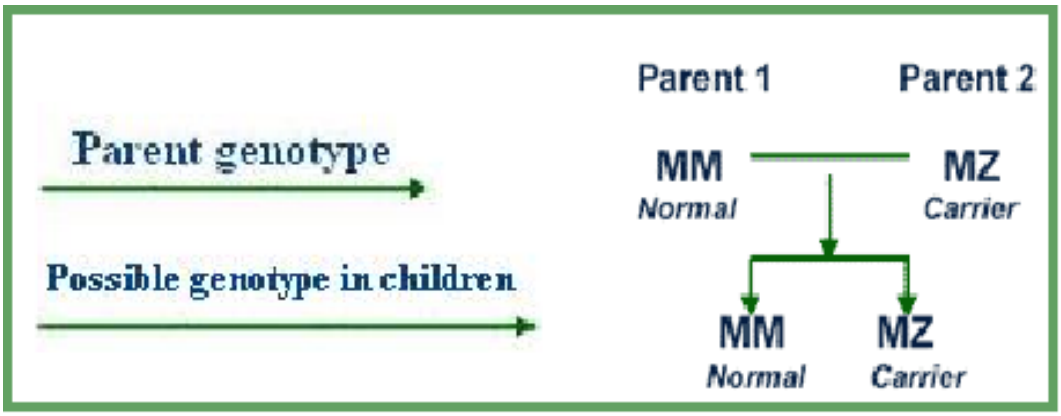
However, if both parents are genotype (**MZ**) or carriers, they can pass down normal, carrier or AAT-deficient genes to their children.

Table 3.2



If one parent is a carrier, g*enotype* (**MZ**), and the other is *normal*, *genotype* (**MM**), they have a 50/50 chance of having a carrier child.

Table3.3



Source :**(** Canada Lung Association, .2005)

3.4 At the regional level

To compare the trends of asthma mortality and place of death in young patients between the years 1980 and 1997 retrospective study for different major population groups in Israel was done the result was absence of a difference in the mortality rates outside of hospitals between Jews and Arabs suggests similar quality and accessibility of health care and no genetic predisposition for death from asthma.(Picard E, 2002).Anther study was done in Ben-Gurion University of the Negev, Beer-Sheva, Israel The aim of this study was to examine a possible association between birth season (date of birth) and future development of asthma in children. They conclude that Asthmatic children were more likely to be born between March and June and least likely to be born between October and December, compared to controls ($P < 0.05$).Farther study was done at al-Iraq about risk factors for asthma among primary school children in Baghdad the result were : significant risk factors for asthma development: crowding rate of > or = 5 (odds ratio [OR]=1.65, 95% confidence interval [CI]=1.1 - 2.4), lower educational level of parents, prematurity (OR=1.61, 95% CI=1.003-2.59), low birth weight (OR=2.41, 95% CI=1.87-3.09), family history of asthma whether father (OR=3.86, 95% CI=2.54-5.87), or mother (OR=8.27, 95% CI=5.21-13.15) or sibling (OR=4.33, 95% CI=3.24-5.8) CONCLUSION: Crowding, low parental education, prematurity, low birth weight, family history of asthma and smoking are significant risk factors for asthma development among primary school children. Efforts must be concentrated for hygienic environment, good antenatal care and quitting smoking habits in order to overcome this health problem.(Kubaisy W,2005)

3.5 Asthma study in Palestinian

Study was conducted in autumn of 2000, with a sample size (3,382) schoolchildren ,aged 6-12 yrs from 12 schools in Ramallah District /Palestine, the researcher were investigate the prevalence and severity of asthma and asthma symptoms in schoolchildren. They fined; children from refugee camps at higher risk of asthma than children from neighboring villages or cities. Prevalence of asthma and asthma symptoms in Palestine appears like of Jordan, and lower than Israel, Kuwait and Saudi Arabia, and more than developed countries. (El-Sharif N, etal,2002)

Nested case-control study was done in Ramallah in 2001; the researcher looked for domestic mite and pet allergens and endotoxin in Palestine. Results were higher level of Endotoxin compared to developed countries. Also the researcher fined that indoor environmental factors such as dampness seemed to be important determinants for allergen and endotoxin, but living habits such as lack of mattress cover appeared unimportant. (El Sharif N, etal, 2006)

Geographical variations of asthma and asthma symptoms among schoolchildren aged 5 to 8 years and 12 to 15 years was study in two districts (Ramallah and North Gaza in Palestine, the results shows that Younger children living in North Gaza district have slightly higher prevalence rates for asthma and asthma symptoms .

Older children had higher rates in Ramallah district the prevalence of asthma symptoms in Palestinian children are similar to several countries in the Mediterranean region such as Spain and Turkey, but lower than other Middle East countries such as Saudi Arabia and Israel. Reasons for such differences were related to different environmental and lifestyle factors. (El Sharif N, etal, 2003) A study publish in 2003 looked for Familial and environmental determinants for wheezing and asthma in a case-control study of school children in Ramallah- Palestine. Showed that familial diseases are significant predictors of childhood asthma in Palestinian children. Moreover, indoor environment such as presence of cats and domestic moulds also appear to play a role. (El Sharif N, etal, 2003)

3.6 Intervention studies

According to the experience of many practitioners, the lack of adherence to prescribed treatment for pediatric asthma is the single most important explanation for occurrences of uncontrolled asthma that necessitate care in the hospitalization (Goodkin, 2000). A research study emphasize that Barriers to effective asthma care that currently exist include the persistence of environmental risk factors, disparities in care that stem from poverty and cultural differences ,also parental adherence to asthma treatment plans was affected by their own health beliefs about medication usage and safety.(Martha K,2005)
A new experimental procedure involves injecting "anti-IgE" substances that combine with IgE in the blood. This prevents IgE from stimulating the release of histamine from mast cells. It is hoped that anti-IgE treatments would reduce the amount of corticosteroid use by asthmatic patients. So far, this form of treatment provides only temporary relief and scientists are actively searching for more effective anti-IgE medications.(AAAAI,2006) children could then be placed in early intervention programs that would be designed to help them avoid specific situations that could set off their immune systems and produce typical asthma symptoms. (Hall, I 1997)

Future research may lead to the development of genetic screening tests that can identify children who may be at risk for developing asthma. A number of major gene therapy research projects are now focusing on developing new techniques for controlling the activity of genes involved in producing symptoms of asthma. Researchers want to figure out how to shut off or reduce the intensity of typical symptoms of asthma without impairing normal body function. (Hall, I 1997)

Approximately 1% of people in North America carry the PiZ defect in the gene encoding the serum protein alpha 1-antitrypsin (AAT). Homozygote is subject to early onset emphysema and liver disease. (Savransky, 1994); conducted a study through which he demonstrated a means of correcting this gene defect and a point mutation in chromosome 14. Results of this study show that when exercised on human PiZZ GM2522 fibroblasts, targeting replaces exon V of the endogenous gene, containing the PiZ mutation, with the exon V counterpart of a normal complementary DNA.

Simultaneously displacing the mutated exon V away from its promoter. This study concluded that targeted homologous recombination offers advantages in potential gene therapy to correct AAT defects. (Savransky , 1994).

King, and other researchers examined the roteinase-antiproteinase balance in the bronchoalveolar lavage (BAL) fluid from alpha-1-proteinase inhibitor (alpha 1PI)-deficient lung transplant recipients to determine whether they would derive benefit from intravenous augmentation therapy with alpha 1PI. BAL fluid from eleven alpha 1PI-deficient lung transplant recipients and eight control subjects was assayed for free neutrophil elastase activity, immunoreactive alpha 1PI, and elastase inhibitory capacity. However, three of seven alpha 1PI-deficient lung transplant recipients had measurable free elastase activity, which was inhibited ex vivo by addition of alpha 1PI. The researchers concluded that alpha 1PI-deficient lung transplant recipients demonstrate free elastase activity in BAL fluid during severe lower respiratory tract inflammation, which is not present during health. Intravenous supplementation of alpha 1PI-deficient lung transplant recipients with exogenous alpha 1PI during respiratory tract inflammation may be indicated to inhibit elastase-mediated injury to the transplanted lung. (Schluchter, etal, 2000)

Also; related to the augmentation therapy; Weccker M. found in his study; that in patients with severe alpha-1-protease inhibitor (alpha 1-Pi) deficiency forced expiratory volume in first second (FEV1) is an accepted parameter to monitor the progression of emphysema. In a patient with severe alpha 1-Pi deficiency (PiZZ) more than 1,000 FEV1 measurements were performed over a period of 12 years. FEV1 dramatically decreased initially (delta FEV1 > 500 ml/year), but stabilized after augmentation therapy was instituted. Three years later, the FEV1 decreased again abruptly; the deterioration was paralleled by an increasing number of severe bronco pulmonary infections. This nonlinear decline implies a positive influence of augmentation therapy and a deleterious effect of bronchopulmonary infections in the disease ($p < 0.0005$). Daily variation of FEV1 in infection-free intervals exceeded 30% and was thus higher than the mean decrease in FEV1 per year (Weccker, etal, 2001)

Assessments of alpha 1-antitrypsin replacement therapy (AAT) for effected Patient characteristics were analyzed along with the possible side effects of the treatment and its efficacy in maintaining appropriate AAT blood levels the treatment protocol began with 4 weekly intravenous doses of 60 mg/kg AAT (Prolastin) and continued with monthly doses of 240 mg/kg. AAT serum levels were measured before each dose. Every 6 months pulmonary function tests were performed. No side effects of treatment was observed. (Misaritlles, 1994)

Chapter 4 Methodology

4.1 Introduction

This chapter describes the methodology used in the present study. The design, setting sample, instrumentation, data collection and data analysis procedures are discussed.

4.2 Study design

This study is case control study. Cases were defined as children, aged (5-16) diagnosed with Asthma (cases) and controls were defined as children within the same age group who were diagnosed with other diseases

4.3 Target population

The target populations for this study were Palestinian children whom live in east Jerusalem and their age rang between (5- 16 years) old.

4.4 Sampling

According to the study aim and objectives a case- control study and non - random purposive sample were used to collect data from all asthmatic child (5-16) years old ,whom attending the chosen five health center (Ministry of health centers, Arab health center ,Spafford clinic ,Makassed Islamic charitable society, , and klalit pediatrician clinic) also we include tow major hospital in east Jerusalem(Augusta Victoria Hospital ,AL- Makassed Hospital). The sample size was 300 child, 100 was asthmatic case and 200 child was a control according to appendices (4.5)

4.5 child inclusion and exclusion criteria

4.5.1 Selection criteria for cases:

1. Children whom (Age group between 5-16 at study period).
2. Children who were diagnosis with asthma by a pediatrician.
3. Place of the child's residence is east Jerusalem.
4. Family consent for the participation of their child in the study

4.5.2 The selection criteria for control

1. Children whom (Age group between 5-16 at study period).
2. All children attending the clinic for treatment except children with upper and lower respiratory tract infections.
3. Place of the child's residence is east Jerusalem.
4. Family consent for the participation of their child in the study.

4.6 The study setting

The study was carried out in east Jerusalem center s ,mainly in the following sites , Ministry of health centers, Arab health center ,Spafford clinic ,Makassed Islamic charitable society, klalit pediatrician clinic) two major hospitals in east Jerusalem(Augusta Victoria Hospital ,AL- Makassed Hospital) .All of case and control were interviewed in health setting . Blood aspiration was carried out in above mention area .

4.7 Data Collection

The author approach all hospitals and health centers administration and permission and obtained (consent form) prior to data collection and prior to blood aspiration as per the University policy.
Data was collected through a questionnaire and blood tests. The questionnaire was filled by the researcher during the clinical interview.
The questionnaire composed of thirty questions divided into six domains:-
Demographic data, History of child health (familial), current child health, Illness attack (Asthma), Environment risk factors, and knowledge about Asthma Management.
Blood samples, we collected 2-3cc of whole blood in EDTA tube after obtaining consent of agreement for each child parents

4.7.1 Blood samples

In EDTA tubes from each child or from children who met the criteria and his/her family agreed to participate a total of 150 blood samples (50 case ,100 control)were collected. Which equal 50٪ of the total sample(50٪ =50case, and 50٪=100control) total(n=150 case and control)have blood test for alpha 1 Antitripsine deficiency.
EDTA blood samples were collected (2-3cc) from each child and centrifuged for 10 minutes at 3000 rpm. Hemolysed samples were representing by new .sample .
All sample was analyzed by expert genetic lab technician and under vision of the researcher in Al-Quds university (research lab)and after permission of the Laboratory mangier.

4.7.2 DNA Extraction

4.7.2.1 DNA Purification Protocols :

EDTA-anticoagulant blood sample was obtained by vein puncture from each participant child by the researcher himself and analysis at Al-Quds research laboratory. Then DNA was extracted from leukocytes by expert genetic lab technician using Master Pure ^{TM} Genomic DNA Purification Kit for Blood (Epicenter Technologies Co., USA) according to the following procedure:
1-After draw 3ml of blood into an EDTA Vacutainer tube; separate fractions by centrifugation at 14,000 **x g** for 15 minutes.

2- Carefully transfer 600 □ l of Buffy coat (the white interface between the plasma and the red blood

3- Vortex mix the Buffy coat sample. Transfer 300 □ l of the sample to two 1.5 ml micro centrifuge tubes and add 1.2 ml of Lysis Buffer. Invert 3 times to mix and then flick the bottom of the tube to suspend any remaining material.

4-Incubate at room temperature for 5 minutes; invert 3 times to mix and then flick the tubes as outlined above. Continue incubating at room temperature for an additional 5 minutes; invert 3 times to mix and then flick the tubes

5- Pellet the white blood cells by centrifugation for 25 seconds in a micro centrifuge.

6. Pull off most of the supernatant, leaving 25 □ l of liquid. Vortex mix to suspend the pellet.

7. Resuspend the white blood cells in 600□ l of Lysis Buffer 2 by pipetting the cells up and down 5- 7 times. The samples may be stored for several months at room temperature.

8. Than add 250 □ l of the Precipitation Solution and vortex mix vigorously for at least 30 seconds.

9. Pellet the debris by centrifugation for 10 minutes at ≥ 10,000 x g in a microcentrifuge.

10. Pour the supernatant into a clean microcentrifuge tube and add 700 □ l of isopropanol. Invert the tube several (30-40) times; a stringy precipitate should be visible.

11. Pellet the DNA by centrifugation at 4°C for 10 minutes in a microcentrifuge.

12. Carefully pour off the supernatant without dislodging the pellet. Rinse twice with 75% ethanol, being careful to not dislodge the pellet. Centrifuge briefly if the pellet is dislodged. Remove all of the residual ethanol with a pipet.

13. Resuspend the DNA in 100□ l of TE Buffer; incubate overnight at room temperature. Alternatively, resuspend the DNA by pipetting repeatedly followed by vortex mixing for 10 seconds. Store the purified DNA at -20°C.

14. Quantify the DNA by using electrophoresis, spectrophotometry or fluorimetry. The concentration should be approximately 300 □ g/ml.

4.7.2.2 Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP)

This method is one approach that is used for mutation detection. It consists of two steps: (1) specific DNA fragment amplification and (2) restriction enzyme digestion of the PCR product (Zuntar et al., 2003).

The fragments were amplified in a reaction volume of 25 µl containing 0.2 µg of genomic DNA, 0.2 mM dNTPs mix, 1X PCR buffer (50 mM KCl, 1.5 mM $MgCl_2$, 10mM Tris-HCl), 0.625 U of SAWADY Taq DNA polymerase (Peq lab ,Erlangen), and 0.15 µg of each primer (Primers for PCR amplification)(Sandford etal, 1999) .The mixture was subjected to 40 cycles of 30 sec at 94ºC, and 30 sec at 59ºC, and 10 sec at 72ºC. Initial denaturation for 5 min, final extension for 5 min at 72ºC. An aliquot (7µl) of the specific PCR product was digested with 10U TaqI(T↓CGA) (Biolabs, NEW ENGLAND), 1µl of 10X NE buffer (50 mM NaCl, 10 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM DTT pH 7.9) in a final volume of 10µl reaction mixture, and incubated at 65 ºC for 1 hr. Than subjected to heat inactivation step at 80 ºC for 20 min . inactivation step at 80 ºC for 20 min .For PCR amplification of the region of exon V containing the Z mutation the following oligonucleotide primers were used:5'TAAGGCTGTGCTGACCATCGTC3'and5'CAAAGGGTTTGTTGAA CTTGACC3'. Analysis of the S allele in exon III was performed by a similar method. Primers were designed so that the up stream primer introduced an artificial TaqI restriction siteysis were5'GAGGGGAAACTACAGCACCTCG3' and 5'ACCCTCAGGTTGGGGAATCACC3' The mutational status of the subjects were revealed by subsequent electrophoresis in 3% agarose gels containing ethidium bromide.

4.7.2.3 Spectrophotometry

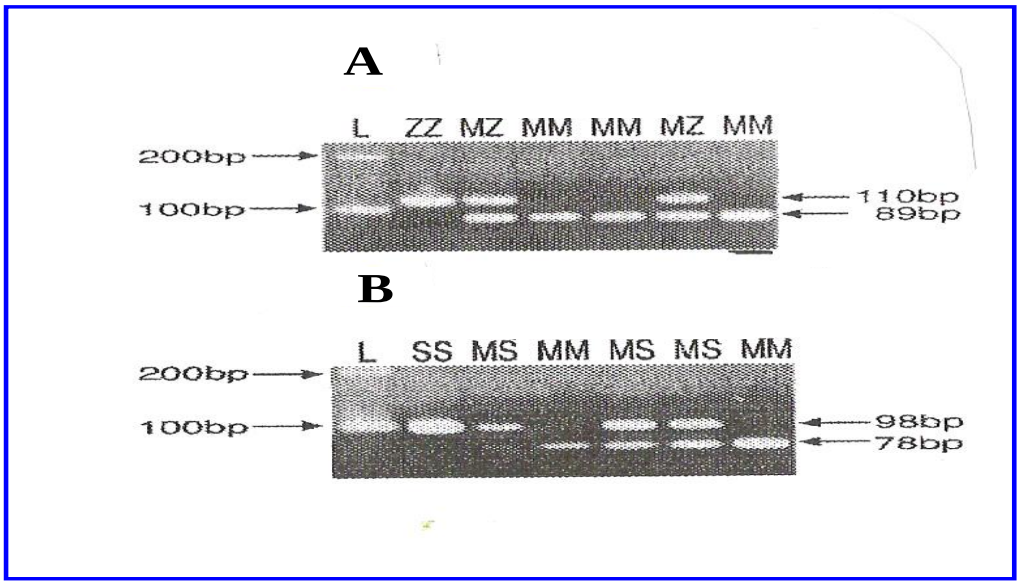
A spectrophotometer is employed to measure the amount of light that a sample absorbs. The instrument operates by passing a beam of light through a sample and measuring the intensity of light reaching a detector.

The beam of light consists of a stream of photons, represented by the purple balls in the simulation. When a photon encounters an analyte molecule (the analyte is the molecule being studied), there is a chance the analyte will absorb the photon. This absorption reduces the number of photons in the beam of light, thereby reducing the intensity of the light beam.

The light source is set to emit 10 photons per second. Watch the motion of the photons and observe how some of the photons are absorbed (removed) as the beam of light passes through the cell containing the sample solution. The intensity of the light reaching the detector is less than the intensity emitted by the light source

For Z- mutation ,child with the ZZ genotype show a single band of 110 base pair (bp),those with the MM genotype show two bands of 89 bp and 21 bp and those with the MZ (heterozygous) genotype show three bands of 110bp, 89bp , 21bp as seen in (**figure 4 .1 - A**)

Figure 4.1



For **S** mutation ,individual with the SS genotype show a single band of 98bp,those with the MM genotype show two bands of 78bp ,and 20bp ,and those with the MS (heterozygous) genotype show three bands of 98bp ,78bp, 20bp as seen above in (figure **4 .1 -B**)

4.8 Data Analyses:

SPSS was used to analyze the collected data. Diagrams and tables are included to describe the trends and frequencies in the variables, and we will try to correlate some variables with each others to understand and determine the risk factors of Asthma in east Jerusalem district.

4.9 Ethical consideration:

Approval and permission for conducting the study at the hospital settings were obtained from the hospitals and health centers administrations after formal written request for that from the university (see appendixes **4.2)**. Full disclosure about the study was given to Parents who were informed about the purpose and objectives of the study as well as blood withdrawal procedures. In addition, they were informed when they except to get the result of the blood tests.

Mother were assured of anonymity and confidentiality. Furthermore, they were told that they might experience some pain and re-withdrawal.

Also, every child family was interviewed separately and was given the opportunity with to talk about Asthma with out critiquing the information provided.

4.10 Instrumentation:

The research instrument was a quantitative method which includes assessment of demographic variables, socio-economic status of the family and complete medical history. The measurement tool was piloted and initially pre-tested by filling it out from randomly selected mothers at some health centers. In addition to that, two consultants (Dr.Ghassan Balousha Dr. Lina El-Khairy) were consulted to catch the desired validity and trust the measurement reliability, at this pilot, the observations of the researcher were taken into consideration and the questionnaire was modified consequently to ensure the clarity of the questions. Face to face validity of our measurement was brought to light after consulting expert's consultants. Our operationalization of case was (every child who has dyspnea ,wheezing and difficulty of breathing and diagnosis by pediatrician as asthma) which mostly reflects the conceptual definition of our dependent variable. Socio-economic status of the family was constructed by creating a SES index which includes the educational level of the women and her husband, employment status, average of the family income and the place of residency.

The data was then entered into the computer, coded, recoded and analyzed using the statistical package for the social sciences (SPSS).

4.11 Pilot testing

Pilot testing was done for 10% of total sample. Accordingly few simple modification were simple incorporated in the questionnaires. Two-stage pilot testing of ٪validity was carried out to test the clarity, consistency and relevance of the questions to the parents, who would be surveyed.

4.12 Definition of variables:

1-Gender:

***Theoretical definition*:** It is divided into male and female. (PCBS, 1997*)*

Operational definition: sex of the person.

2-Age:

Theoretical definition: Is defined as the temporal span extending from the birth date expressed by years (PCBS, 1997)

Operational definition: Refers to date in which the person was born and the age categorized into two group from (5-10) and from (>10-16).

3-Urban:

***Theoretical definition*:** Any locality whose population amounts to 10,000 person or more (PCBS, 1997)

***Operational definition*:** It refers to old city /Jerusalem.

4-Rural:

Theoretical definition: Any locality whose population is less than 4,000 persons or whose population varies from 4000 to 9,999 persons but lacking four of the aforementioned elements (PCBS, 1997)

***Operational definition*:** It referred to villages in east Jerusalem

5-Camp:

***Theoretical definition*:** It refer to any locality referred to as a refugee camp and administered by the nations refugees and work agency in the near east U.N.R.W.A (PCBS, 1997)

***Operational definition*:** It referred to place for sitting of Palestinian refugee in east Jerusalem

6-Illiterate:

***Theoretical definition*: it** applies to persons unable to read or write in any language and who were never awarded certificate from any formal education system (PCBS, 1997)

***Operational definition*:** Any person haven't chance or skills to write and to read

7- School education

Theoretical definition: Is education level for persons who successfully complete the sixth elementary grade, preparatory level, and secondary level (PCBS, 1997)

***Operational definition*:** The same as Theoretical definition

8-Graduate education

***Theoretical definition*:** The highest successfully complete educational attainment ,associate diploma ,bachelor degree (BA/BS) higher diploma ,master degree (MA/MS),doctorate (PhD) (PCBS, 1997)

***Operational definition*:** The same as Theoretical definition

9- Employee

Theoretical definition: It refer to person engaged in certain productive activity or work

***Operational definition*:** The same as Theoretical definition

10- Labor work

Theoretical definition: Hard careers in the course of their working lives **(**Bureau of Labor Statistics, 1986)

Operational definition: person who works in public and private and receives wage

11- Civil jobs

Theoretical definition relating to citizens and their interrelations with one another or with the state: the civil branches of government job (Bureau of Labor Statistics**,** 1986)

Operational definition: person who employee in any job and have monthly income.

12-Private work:

Theoretical definition: It refers to individual activity or personal work (Bureau of Labor Statistics, 1986)
Operational definition: any person who work and he is responsible for his work income.

13-wheezing
Theoretical definition: a whistling sound when breathing (Johnson, 2002)
Operational definition: abnormal sound heard during breathing.

14- **Gene:**
Theoretical definition: The basic biological unit of heredity. (Frederick, 2003**)**
Operational definition **:** The same as Theoretical definition

15- Alpha-1 Antitrypsin deficiency:
Theoretical definition: An inherited disorder that results in low or no production of a protein called alpha-1 Antitrypsin **(**Hegab, 2004**)**
Operational definition: The same as Theoretical definition

4.13 Constrains and limitation of the study

1-Sample size was (300 child) 1/3 of the total number have asthma and 2/3 from other disease therefore the sample size dose not represent all asthma in east Jerusalem.

2- Genetic marker was expensive therefore the alpha 1-antitrypsin deficiency test was done to 50٪ of the sample

3-The child with asthma mostly came tired to the health center therefore few families refuse to share.

4. This is a family reported study, and a recall bias might be present so; this will effect the result

Chapter five (Results)

5.1. Socio-demographic data

A total of 300 children (200 controls, 100 cases) were the target group of this study, they were recruited from different health centers, mostly from Al-Makassed charitable society clinics 30.3%, among the 300 children, 176 were males in a percent of 58.7%, and on the other hand, 124 children were females. The majority of the participants had governmental insurance in a percent of 56.3%, while 29.3% of them had private one. Other while, 14.3% had no insurance.
Figure 5.1. Show the distribution of the participants according to the recruitment health center. However; all the demographic data of the 300 participants are presented in (table 5.1) below.

Table 5.1.Distribution of the study population by socio demographic variables

Sociodemographic variables	Total respondents			
	case		control	
	number	%	number	%
sex				
female	40	13.3	84	28
male	60	20	116	38.7
Age of the child				
5-10	37	12.4	76	25.3
>10-16	63	21	124	41.3
Season of child birth				
Summer	34	11.3	65	21.7
Winter	40	13.3	84	28
Autumn	19	6.3	28	9.3
spring	7	2.3	23	7.7
Place of residence				
Urban	10	3.3	26	8.7
Ruler	85	28.3	167	55.7
Refugee camp	5	1.7	7	2.3
Marital status of the mother				
Married	80	26.7	189	63
Divorced	8	2.7	6	2
Widow	12	4	5	1.7
Educational level of the mother				
Illiterate	10	3.3	4	1.3
School education	74	24.7	179	59.7
Graduate education	16	5.3	17	5.7

Educational level of the father				
Illiterate	3	1	5	1.7
School education	85	28.3	170	56.7
Graduate education	12	4	25	8.3
Monthly family income				
2500 NIS and less	0	0	1	0.3
>2500-5000 NIS	94	31.3	187	62.3
5000 NIS and more	6	2	12	4
Mothers occupation				
Without	90	30	193	64.3
Employee	10	3.3	7	2.3
Father's occupation				
Labor work	51	17	113	37.7
Civil jobs	17	5.7	28	9.3
Private work	20	6.7	54	18
Note: n=17 of the participants father sample were died (12 for the cases, 5 for the controls).				

As shown in table 5.1, the majority of the mother's participants were unemployed. 5.6% of them were employees in different jobs as different clerical works, teacher, nurse, cleaners.

5.2 Medical history of studied population

As mentioned before the 300 studied individuals were divided into 100 asthmatic cases and 200 controls. Asthmatic children were chosen specifically not suffering from the upper chest respiratory tract infections. However, as data show (n=31) children were newly diagnosed, while about half the cases (n=57) were diagnosed for a period more than three years.

On the other hand, 74 of the cases were suffering from chest wheezing that diagnosed asthma, and 97 of the case children were suffering from chest discomfort and / or difficulties in breathing at different times. Data showed that 97 of cases were suffering from interrupted sleep at night as a result of continuous cough, which are characteristics for asthma. Table 5.2

Table 5.2. Characteristics of medical history variables among cases.

Children medical history variables	total respondents	
	Number/cases	Percent (%)
Type of the target asthmatic child	100	100
Duration of having asthma Recently diagnosed ≤3 years >3 years	 31 57 12	 10.3 19 4
Complaining of chest wheezing Yes no	 74 26	 24.7 8.6
Children with morning chest discomfort/breath difficulty episodes Yes No	 97 3	 32.3 1
Lasting of Asthmatic attack ≤30 minutes 30-60 minutes more than one hour Indeterminate Not complain	 44 30 3 20 3	 14.7 10 1 6.6 1
Suffering from night coughs Yes No	 97 03	 32.3 1
Suffering from breathing difficulties Yes No	 97 03	 32.3 1
Time frequencies of Asthmatic attacks Night Day time Both day & night No suffering	 62 14 21 3	 20.7 4.6 7 1

Frequency of Asthmatic attacks last month		
Twice a week	33	11
3-5 times a week	21	7
Almost every day	43	14.3
Not at all	3	1
Frequency of hospitalization with Asthma in the past 3 years.		
Not at all	40	13.3
Once	29	9.7
Twice	19	6.3
Three	9	3
Four	1	0.3
Five and more	2	0.7

5.3 asthma management& treatment

Several questions were asked about the medical history of the children, such as if the children were treated for any medical conditions at the time of data collecting, questions about the nebulizer usage for the asthmatic child.
All these data are presented in table. (Table 5.3)

Table 5.3.Distribution of asthmatic medications variables

Treatment and management plane	Total case	
	number	Percent
Having treatment during the time of the study		
Yes	94	31.3
No	6	2
Present prescribed medications		
Bronchial dilator	67	22.3
Antibiotics	21	7
Ferritine	1	0.3
Coronary therapeutic drugs	2	0.7
NSAID	3	1
Antihistamine	1	0.3
Prednisone	1	0.3
Bronchodilator &anti allergic	4	1.4
Frequency of using bronchodilators		
Seldom	24	8
Every day	18	6
More than once/day	24	8
Five times and more\ day	5	1.7
Once a month	0	0
Not using	29	9.6

5.4. Hereditary disease

Table5.4. Distribution of the hereditary disease variables among the study population

did any of the family members suffer from:	Total respondents	
	number	Percent
Asthma		
Yes	77	25.7
no	223	74.3
Presence of asthma in family		
Brother	23	7.7
Grandfather	15	5
Father	18	6
Mother	13	4.3
ante	2	0.7
Uncle	2	0.7
Grandmother	4	1.3
No diagnosed relatives	223	74.3
Family history of hypertension		
Yes	96	32
no	204	68
Family history Heart problems		
Yes	57	19
no	243	81
Family history Diabetes		
Yes	86	28.7
no	214	71.3
Family history Kidney diseases		
Yes	12	4
no	288	96
Family history Cancer		
Yes	21	7
no	279	93
Family history Rheumatism		
Yes	52	17.3
no	248	82.7

As it is clear from the above table that there were different health problems among the families of the target children, but specifically 25.7% of them have asthma as demonstrated from the 77 family members who had asthma. From this 77; the majority are first class relatives.

5.5. Home environmental data

Literature gives us different environmental risk factors for asthma. Such as domestic animals. Here 29% of the participants had domestic animals mostly birds. Smoking is another risk factor and here about half of the targets had smokers in their houses. Data of the home environment are presented in the table 4.5

Table 5.5 Distribution of home environmental risk factors

Home environment risk factor:	Total respondents	
	Number	Percent
Presence of domestic animals in the house		
Yes	87	29
no	213	71
Type of animal		
Cats	34	11.3
Dogs	7	2.3
Birds	43	14.3
Others	3	1
No animals	213	71
Presence of smokers in the house		
Yes	154	51.3
No	146	48.7
Season in which usually symptoms appear		
Winter	45	15
Spring	16	5.3
Summer	1	0.3
Autumn	2	0.7
All seasons	28	9.3
Non specific	8	2.7
No asthma	200	66.7

5.6. Mother's Knowledge about asthma

During the interviews; mothers were asked about their knowledge on asthma. 40% of the mothers said that they had certain knowledge on asthma but there were only 25.7% said that they had a lot of information about this subject. (Table5.6) to evaluate this: mothers were asked different questions and they were answered by either yes or no. all the data related to this are presented in (table 5.7)

Table5.6 Evaluation of the mother's knowledge about asthma

knowledge evaluation variables	Total respondents	
	Number	Percent
Having knowledge about asthma Yes No	 120 180	 40 60
Classification of knowledge Having a lot of information Having no information Having little information	 77 180 43	 25.7 60 14.3

Table 5.7 Distribution knowledge variables about asthma among the mother of the targets

knowledge variables:	Total respondents	
	Number	Percent
Does sport motivate asthma Yes No	 63 237	 21 79
Does cold motivate asthma Yes No	 61 239	 20.3 79.7
Does odors motivate asthma Yes No	 14 286	 4.7 95.3
Does psychological problems motivate asthma Yes No	 35 265	 11.7 88.3
Does climate changes motivate asthma Yes No	 72 228	 24 76
Does parfan motivate asthma Yes No	 49 251	 16.3 83.7
Does chalk motivate asthma Yes No	 36 264	 12 88
Does molds motivate asthma Yes	 39	 13

No	261	87
Does smoke motivate asthma		
Yes	104	34.7
No	196	65.3
Does dust motivate asthma		
Yes	78	26
No	222	74
Does flowers motivate asthma		
Yes	23	7.7
No	277	92.3
Does animals motivate asthma		
Yes	16	5.3
No	284	94.7
Does the exposure to animals initiate nasal discharge		
Yes	13	4.3
No	287	95.7
Does the exposure to animals initiate itching		
Yes	21	7
No	279	93
Does the exposure initiate chest wheezing		
Yes	13	4.3
No	287	95.7
Does the exposure to animals initiate difficulty in breathing		
Yes	11	3.7
No	299	96.3

5.7. Statistical relationship

5.7.1. Domestic animals

Literature gives us many different examples about domestic animals and its relationship with the prevalence and incidence of asthma. On the other hand; domestic animals are tested with the expression of asthmatic symptoms among the children suffering from the disease in meanings of cough; chest discomfort and difficult in breath. This study show strong statistical relations which proves domestic animals as a risk factors for pediatric asthma. As p value gives different readings less than 0.05 under the curve of Pearson chi square.
Table 5.8.Distribution of children according to the presence of domestic animals in their home and with the different diagnostic criteria's for the cases.

Variable	**Presence of domestic animal in the home environment**					P value
	yes		no		Pearson Chi square	
	n	%	n	%		
Type of target Case control	 39 48	 13 16	 61 152	 20.3 50.7	7.285	0.007
Domestic animals make the child: Cough Chest wheezing Chest discomfort Breath Difficult More than one nothing	 6 2 3 6 22 48	 2 0.7 1 2 7.3 16	 15 0 1 5 40 152	 5 0 0.3 1.7 13.3 50.7	16.190	0.006
complaining of chest wheezing: yes no	 34 53	 11.3 17.7	 40 173	 13.3 57.7	13.7	0.000
Complaining of chest discomfort or breath difficult Yes no	 42 45	 14 15	 55 158	 18.3 52.7	14.235	0.000
Awaking from cough at night Yes no	 38 49	 12.7 16.3	 59 154	 19.7 51.3	7.208	0.007

5.9. **Statistical relationship of domestic animals variables among cases and controls**

Variable	**Distribution of the respondents by cases & controls**					P value
	cases		controls		Pearson Chi square	
	n	%	n	%		
Presence of domestic animal in the house						
Yes	39	13	48	16	7.285	0.007
no	61	20.3	152	50.7		
Type of the animals						
Cats	19	6.3	15	5	12.422	0.014
Dogs	3	1	4	1.3		
Birds	17	5.7	26	8.7		
others	0	0	3	1		

5.7.2 Presence of smoker among family members

Table 5.10 Distribution of children according to the presence of smoker in their home environment with the prevalence of asthma and with the different diagnostic criteria's for the asthmatic children

Variable	**Presence of smoker among family members**					P value
	yes		no		Pearson Chi square	
	n	%	n	%		
Type of target						
Case	65	21.7	35	11.7	11.215	0.001
Control	89	29.7	111	37		
Hospitalization in the last three years						
Not at all	115	38.3	125	41.7	10.091	0.073
Once	21	7	8	2.7		
Twice	9	3	10	3.3		
Three	6	2	3	1.0		
Four	1	0.3	0	0		
five	2	0.7	0	0		

complaining of chest wheezing:						
yes	48	16	26	8.7	7.2	0.007
no	106	35.3	120	40		
Using bronchial dilator						
Seldom	32	10.7	16	3.3	24.8111	0.000
Daily	17	5.7	1	0.3		
>once/daily	9	3	15	5		
five times/month	4	1.3	1	0.3		
not using	92	30.7	113	37.7		
Duration of being asthmatic						
Newly	21	7	10	3.3	12.365	0.006
Less /3years	38	12.7	19	6.3		
More/3 years	5	1.7	7	2.3		
No asthma	90	30	110	36.7		
Awaking with difficult in breath						0.000
Yes	66	22	31	10.3	16.018	
No	88	29.3	115	38.3		
frequency of chest discomfort (among Smokers family members)						
Twice	19	6.3	14	4.7	23.705	0.000
Every night	9	3	7	2.3		
> twice/week	17	5.7	4	1.3		
Always	22	7.3	5	1.7		
Not at all	87	29	116	38.7		

As noticed from the statistical relationships in the previous table; the effect of having a smoker among family members has a great effect on being asthmatic or not.

5.11 Statistical relationship of family history for asthma among cases and controls.

Variable	Distribution of the respondents by cases & controls					P value
	cases		controls		Pearson Chi square	
	n	%	n	%		
Family history of asthma						
Yes	56	18.7	21	7	72.34	0.000
no	44	14.7	179	59.7		
Relationship of asthmatic family member to the						
child	15	5	8	2.7	80.65	0.000
Brother	12	4	3	1		
Grandfather	15	5	3	1		
Father	10	3.3	3	1		
Mother	2	0.7	0	0		
Untie	0	0	2	0.7		
Uncle	2	0.7	2	0.7		
grandmother						

As shown from the above table there is a strong positive relationship for asthma among family members and the children as being cases and controls.

5.8 Genetic risk factor

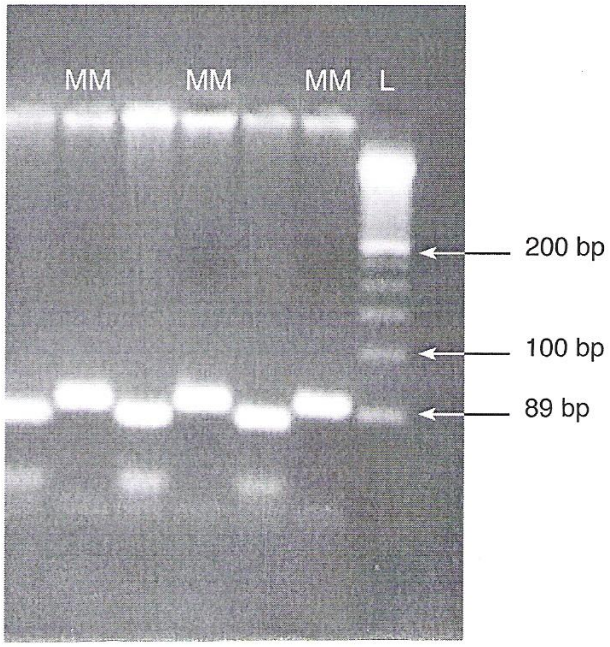
As shows in next figure we used the genetic testing, looks for most common gene changes associated with alpha -1- Antitrypsine deficiency known as S and Z, the DNA was gathered from blood sample.

M is considered the normal version of the gene people with MZ or MS are called carriers people with two copies of Z are likely to have the most severs complication people with two copies of s or a combination of S and Z are at slightly less risk for developing complications.

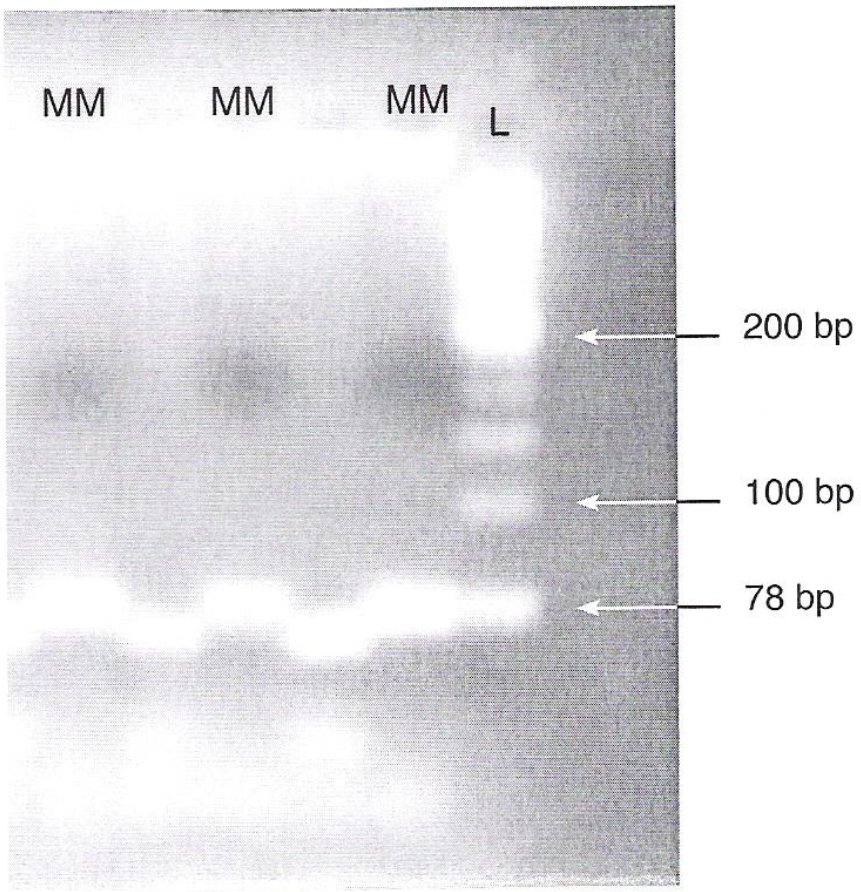
Analysis of the alpha -1- antitrypsin Z and S mutations using restricting endonuclease digestion figure (5.2) Taq I digestion of PCR products amplified from exon V yields and 89 – bp fragment from the M allele and a 110 – bp fragment from Z allele.

Figure (5.3) TaqI digestion of PCR products amplified from exon III yields a 98 – bP fragment from M allele and 78 – bp fragment from S allele L = 100bp DNA ladder both figure (5.2 ,5.3) shows no mutation.

Figure5.2 *Taq I digestion of PCR products amplified from exon V yields and 89 – bp fragment from the M allele and a 110 – bp fragment from Z allele*



Figur 5.3 TaqI digestions of PCR products amplified from exon III yields a 98 – bP fragment from M allele and 78 – bp fragment from S allele



Chapter (6) Interpretation and Discussion.

6.1 Introduction

The present study is one of many study that focus on asthma in Palestine, but the first study that concerned with environmental and genetic risk factor for pediatric asthma in east Jerusalem. The purpose of this study was to identify the most environmental genetic risk factors that effect pediatric asthma in east Jerusalem. To fulfill the purpose of our study, a case control design was conducted and 300 pediatric participant were our target population n=100 child selected from different health center diagnosed with asthma by pediatrician and n=200 was the control whom selected from other disease from the same study area. The distribution of participants in related to health center is clarify in (Figure 5.1)

Non random purposive sample was used to collect the data from participant child family and the respondent group range between (5-16) years old.

A locally designed questionnaire that included both close and open ended question was used to fulfill the purpose of our study. Mainly we concentrate about the most environmental risk factor that induces the attack ,on the other hand we investigate the phenotype (Z) and (S) mutations of alpha -1- antitripsine genotype as genetic risk factor or as a marker for pediatric Asthma .

We found that second hand smoking, domestic animal and family history are positive association with asthma but Alpha -1- Antitripsine deficiency was negatively associated with asthma.

6.2 Main Result

Demographic data was obtained from 300 participant family child. 33.3% of total respondents were cases (n = 100) and 66.7 of total respondents were control

(n =200). The majority of respondents were males 58.7% (n = 176) on the other hand 41.3% of the children were female (n = 124) , this is similar to study published on 2002 at Allergy Journals in which the writer emphasis that boys are at greater risk of asthma in childhood (Vermeulen, 2002) . Explanation for this shift in asthma predominance from boys to girls through aging have been discussed in several reviews on sex differences (vonk,2006), on the other hand when we look for population size and structure in Palestine, we can see that the males constituted 50.7% and females 49.3% out of total population in Palestine ,this may give another explanation .Other researcher concluded that asthma predominantly occurred in boys in child hood, with male to female ratio of 2:1 until puberty when the male to female ratio become 1:1 (Morris,2005).

Age group was chosen from (5-16) years old, as e medicine article mention that Two thirds of all asthma cases are diagnosed before the patient is aged 18 years, Approximately half of all children diagnosed with asthma have a decrease or disappearance of symptoms by early adulthood(Morris, 2005).

Anther finding that 41.3% of total participant child was born in winter (n = 124), 33% born in Summer 15.7% borne on Autumn and 10% of all sample borne on Spring department of epidemiology in Ben-Gurion University of Negev / Israel find an association between birth season and future development of childhood asthma farther more, asthmatic children were more likely to be born between march and June and birth season during late winter and spring associated with asthma during childhood (Gazala,2006) and this match our result for season of child birth in summer and winter equal (33%,41.3) respectively.

On the other hand ruler of east Jerusalem occupied the large area in related to place of residence, approximately 84% of total sample was from villages and 12% related to urban and 4% related to camp as seen in table (5.1) and this result may reflect the nature of east Jerusalem villages, mostly villages in this area like city, a lot of pollution, a lot of manufactory in addition to car‘s pollution, and agricultural land very small.
Education level of mother‘s and father is important in dealing with asthma child ,study was done about the risk factors for asthma among primary school children and one of main result was lower education level of parents consider one of significant risk factors (Kubaisy,2005)

In our study the education level between asthmatic mother and father is not differ, Illiterate 3.3% for mother and 1% for father, School education (24.7%,28.3%)for mother and father respectively ,Graduate education (16% for mother and 12% for father)
31.3% from cases family and
62.3% from control family was the monthly income range between 2500-5000 NIS and just 6%of total population exceed 5000 NIS monthly .

6.3 Health status for the study population:

The data shows that (n = 31) child from total (n = 100) was newly diagnosed with asthma – while about half of the cases were diagnosed for period more than three years, and in related to sings and symptom 24.3% (n = 74) complain of chest wheezing, 32.3% (n = 97) of case children were suffering from chest discomfort and 32.3% (n = 97) awaking at night as result of cough. 20% (n = 60) of total study population reported that they admitted to hospital from once to five and more due to asthma.

6.4 Hereditary disease

Asthma have been recognized to have a familial basis the exact mechanisms that that underlie this familial basis unknown but there is strong association between family history and having asthma in our study specifically 25.7% of total population had history of asthma in first class relatives, our findings are consistent with other similar studies (Cloutier, 2005) .

7.4 Environmental risk factor

7.4.1 Domestic animals and asthma.

Anther findings in our study that domestic animals (cats, dogs, birds) trigger asthma attacks, however the dander which consists of small scales or flakes of dead skin cells that are continually shed by all animals and these dander is sticky and easily airborne and our result is consistent with other studies that identified the proteins in dander can trigger asthma attacks in people with allergic asthma (AAAI,2006).

7.4.2 Secondhand smoke and childhood Asthma.

Secondhand smoke is consider one of asthma trigger; a kids health article mention that smoking causes the airways to become swollen, narrow and filled with sticky mucus; the same problems that cause breathing trouble in child with asthma(joseph,2004) .
One of the main findings of this study that the effect of having smoker among family members has a great effect on being asthmatic or not from all population have a smokers in their home (n = 154), the case(n=65) and control (n=89). Frequency of chest discomfort between asthma case and second hand smoking is strongly related
(p 0.000).

Our results are consistent with other studies that identified second smoke a significant risk factor for asthma and also increased respiratory symptoms, such as wheezing and difficulty of breathing (Swartz,2005; AAAI,2006) also WHO mention ETS is real and substantial threat to child health and causes adverse health effects, worsening of asthma ,also coughing and wheezing (WHO ,1999). From our study results we conclude that other hereditary disease such as(hypertension heart problems, diabetes, kidney disease, cancer and rheumatism) were reported in the child family but not significant related to child asthma.

7.4.3 Asthma and house dust.

Studies showed significant relation between pediatric asthma frequency to house dust (p = 0.001). 20.7% from all cases gets more than on symptom if they exposed to house dust , our finding are similar to other study (cloutier, 2005) that indicate asthma frequency and other risk factor such as smoke, dust, cockroaches are strongly related.
Exercise is anther risk faction that we take care about but we find it not significantly related to asthma symptom.

7.5 Genetic risk factor.

7.5.1 Alpha -1- antitrypsin deficiency and asthma .

The first 150 sample collected (case n = 50) and (control n = 100) were checked for alpha -1- antitrypsin deficiency genotypes Z,S in Al- Quds university research lab, we demonstrated that our sample (n = 150) were of M genotype, and S,Z genotypes were detected .

Our finding result was no consistent association between alpha -1- Antitripsine genotypes S and Z and pediatric asthma.
Explanation for this result; that there is no one asthma gene, several genes interact and cause susceptibility to asthma, anther explanation our sample was small (n = 150) and requires farther confirmation also many study emphasize that genes need environmental stimuli to be expressed. (Akawi, etal, 2006)

7.6 Conclusions

Environmental genetic risk factor for pediatric asthma in east Jerusalem / Palestine is our case control study, sample was consist of 300 participants child (n = 100 asthma case) (n = 200 control), the purposive sample was chooses from different health center, and hospital distributed in east Jerusalem area, the aim of the study was to identify the environmental genetic risk factors for pediatric asthma in children aged between 5 – 16 years old.
We prepared 300 questionnaires according to the international study of asthma in childhood criteria 50% of total sample was checked for genetic risk factor (n = 50 case, n = 100 control) and alpha -1- antitripsine genotype was preformed by expert genetic lab technician in Al-Quds research laboratory.
Result was : A family history of asthma, presence of domestic animal in home, and second hand smoking was strongly associated with environmental risk factor for pediatric asthma – anther finding in our study that their was no association between alpha -1- Antitripsine genotypes S and Z and pediatric asthma in east Jerusalem.
We can conclude that environmental risk factor such as family history of asthma; domestic animal and second hand smoking seemed to be important effect pediatric asthma attack but alpha -1- Antitrypsine
deficiency shows no mutation.

6.8 Recommendation

1-Designing of health education programs about environmental risk factor of asthma to increase awareness of people

2-Education and training program for health team in east Jerusalem centers to improve the outcome for management of asthmatic patient.

3-Establish screening program for AAT deficiency in east Jerusalem centers.

4-Repeat this study on a larger random sample on same community (east Jerusalem).

5-We suggest comparative study using three communities such as (city, village and camp) or to be more generalize

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Appendix

Appendix 1.1

الوضع الصحي في مديرية صحة القدس

اوجز لكم من خلال الارقام المدونة ادناه : عدد المستفيدين من الخدمات التي تقدمها مديرية الصحة

ومن خلال المراكز الصحية التابعة لها في المديرية ..

اولا: معلومات عامة

عدد التجمعات	50
عدد السكان	470103
عدد العيادات	16
العيادات العامة	1
عيادات الاختصاص	6
عدد مدارس المحافظة	91

ثانيا: عدد المستفيدين من الخدمات المقدمة في المديرية	المعدل
عدد مراجعي العيادات العامة والاختصاص / شهريا	10000
عدد المختبرات	7
عدد العينات المسحوبة	4500
عدد التلفونات في المحافظة	46000
عدد التحويلات /شهريا (المقاصد + المطلع + الاميرة بسمة)	600
مؤسسة طبية / شهريا	50
عدد اللجان / شهريا	90

Appendix 1.2

فحص النظر /شهريا	40
تطعيمات حج وعمرة واطفال / شهريا	1500
فحص طلاب المدارس / شهريا	450
خدمات البينة / شهريا	
خدمات تنظيم الاسرة	
خدمات التثقيف الصحي	
خدمات الامومة والطفولة	

حملات تطعيم ،،، تشمل المحافظة بالكامل حسب الحملة المعدة والفئة العمرية

عدد المستفيدين من الخدمات المقدمة بالمعدل الشهري ما يقارب(١٨٠٠٠) مستفيد ...

المراكز التي تقدم خدمات صحية غير حكومية

مستوصف المقاصد	البلدة القديمة
العيادة النمساوية	البلدة القديمة
مستوصف المقاصد / الرام	الرام
مركز الامل الطبي / الرام	الرام
سباقورد	البلدة القديمة
المركز الصحي العربي	باب العامود
المركز الصحي العربي	العيزرية

Appendix 1.3

الامريكان	البلدة القديمة
اتحاد لجان الاغاثة الطبية الفلسطينية	بيت عنان
اتحاد لجان الاغاثة الطبية الفلسطينية	بيت دقو
الطريق الصحيح للمعاقين	جبل المكبر
تنظيم وحماية الاسرة	القدس
الجمعية العربية للمعاقين جسديا	ابو ديس
مركز مارتن بوش للعناية بكبار السن	البلدة القديمة
الملجا الخيري الاثوذكسي	الجزرية
الملجا الخيري الاثوذكسي	القدس

لجان العمل	قلنديا
الاغاثة الطبية	بدو
الاغاثة الطبية	بيت دقو
وكالة الغوث	البلدة القديمة
	شعفاط
	قلنديا

Appendix 1.4

الوضع الصحي في محافظة القدس الشريف ،،

اوجز لكم من خلال الارقام المدونة ادناه الوضع الصحي في المستشفيات العاملة في مدينة القدس :

اولا : مستشفى المقاصد ،،،

عدد الاسرة	215
الطاقة الاستيعابية في حالات الذروة	250
المعدل العام لنسبة الاشغال	100%
غرف الانعاش / عدد الوحدات	6
عدد الاسرة في غرف الانعاش	66
عدد الاسرة في وحدة الخداج	30
المعدل العام لنسبة الاشغال في وحدة الخداج	100%
النقص في وحدة الخداج / سرير	20
عدد المحولين للعلاج من قبل مديرية صحة القدس للعام ٢٠٠٦	8282

الوضع العام : نقص في الكادر التوظيفي التخصصي ، وعجز مالي ، ونقص في الوحدات التشخيصية .

Appendix 1.5

مستشفى المطلع ،،مستشفى تخصصي،

161	عدد الاسرة
75%	المعدل العام لنسبة الاشغال
5	عدد وحدات ICU/ - سرير
	وحدة العلاج الكيماوي
	وحدة غسيل الكلى
3549	عدد المحولين الى المستشفى من قبل مديرية صحة القدس

مستشفى الهمون ،،،مستشفى تخصصي

71	عدد الاسرة المرخصة
46	عدد الاسرة العاملة
90%	نسبة الاشغال للاسرة العاملة
3	وحدة طوارئ/ اسرة

الاسرة غير العاملة تنقصها التجهيزات ولا يوجد في المنظور القريب خطة لتفعيلها

Appendix 1.6

ثانيا : مستشفى الهلال للولادة ،،،

عدد الاسرة	30
الطاقة الاستيعابية / ولادة	300
المعدل العام لنسبة الاشغال	138%
عدد الوحدات / ICU	3
النقص في وحدات / ICU	3

الخطة المستقبلية / مضاعفة الطاقة الاستيعابية من خلال التعاون مع البنك الاسلامي ، وقد بدا الشروع في دراسة الجدوى للمشروع .

ثالثا : مستشفى اقرنساوي ،،، : مستشفى عام .

عدد الاسرة	73
المعدل العام لنسبة الاشغال	80%
وحدة طوارئ / سرير	6

الوضع العام : لا يوجد أي نقص في الكادر الوظيفي ، وليس هناك من ازومة مالية ، ولا يوجد في المنظور القريب خطط تطويرية من اجل رفع مستوى الاداء

Appendix: 4.1

MAKASSED ISLAMIC
CHARITABLE HOSPITAL
MOUNT OF OLIVES
Jerusalem
P.O.Box: 19482
Tel.: 02-6270222
Fax:02-6288392

مستشفى
جمعية المقاصد الخيرية الاسلامية
القـــدس
ص.ب. ١٩٤٨٢
تلفون: ٠٢-٦٢٧٠٢٢٢
فاكس: ٠٢-٦٢٨٨٣٩٢

Ref.No. .....
Date: .....

رقم الشارد: ٦٠٨/٢/٣
التاريخ: ١٢ تشرين ثاني ٢٠٠٦

حضرة الدكتور غسان بعلوشة المحترم
منسق دائرة التشريح / جامعة القدس
أبو ديس
فاكس : ٢٧٩٩٢٣٤

من بعد التحية والسلام ،

بالإشارة إلى كتابكم المؤرخ ٢٠٠٦/١٠/٢٨ بخصوص مساعدة الطالبة كفاية جمعة أبو غيث في بحث حول مرض الربو لدى الأطفال .

فإنه لا مانع لدينا من مساعدتها بتعبئة نموذج إستبيان وكذلك أخذ عينات دم لإتمام البحث .

مع جزيل الشكر والاحترام ،،،

الدكتور هيثم الحسن
مديـــر المستشفـــى

نسخة : الدكتور بسام أبو لبدة

أريل الفاسي
٢٠٠٦/١١/١٤

نموذج رقم ٧٢-٢١٩٠

Appendix: 4.2

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2006/10/28

حضرة السيد/ مدير مستشفى المقاصد الخيرية المحترم
بواسطة: الدكتور محمد شاهين/ عميد كلية الصحة العامة

الموضوع: المساعدة في بحث

تحية طيبة وبعد،،
يرجى السماح للطالبة كفاية جمعة ابو غيث ماجستير/ صحة عامة بتعبئة نموذج استبيان وكذلك اخذ عينات دم لضرورة إتمام بحث حول مرض الربو لدى الأطفال في منطقة القدس.

شاكرين لكم حسن تعاونكم،،

مرفق/ نسخة أطروحة البحث

المشرف
د.غسان يعقوشة
منسق دائرة التشويح/ جامعة القدس

2791556
627246
0542279292

مستشفى جمعية المقاصد الخيرية الإسلامية
MAKASSED ISLAMIC HOSPITAL
Received
Reg No.
Signature

نسخة: الملف

Jerusalem Branch/Telefax 02-2799234
Gaza Branch/Telefax 08-2878166,2878177
P.O. box 51000 Jerusalem

فرع القدس / تلفاكس 02-2799234
فرع غزة / تلفاكس 08-2878166-2878177
ص.ب. 51000 القدس

Appendix: 4.3

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2006/10/20

إلى عناية د. طارق بركات المحترم،
مدير المراكز الطبية/جمعية المقاصد الخيرية

تحية طيبة وبعد،
الموضوع: موافقة على إجراء دراسة لبرنامج الصحة العام

نرجو من حضرتكم تسهيل مهمة السيدة كفاية أبو غيث الطالبة في برنامج الماجستير في الصحة العامة تخصص بيئة وذلك لإتمام الجانب الميداني من رسالة الماجستير والتي تعمل على إعدادها وموضوعها " دراسة العوامل الوراثية المساهمة في ازدياد حدة الربو عند الأطفال من سن 5-16 سنة في شرقي القدس " حيث تهدف هذه الدراسة لمعرفة علاقة Alpha-1- Antitrypsin deficiency مع مرض الربو، كما وينظر بعيدا إلى طرح بعض الاقتراحات للمساعدة في علاج مرض الربو.

نثمن عاليا دعمكم للبحث العلمي بشكل خاص ولجامعة القدس بشكل عام.

مع فائق الشكر والتقدير،

أوافق مع تمنياتي لها بالتوفيق والنجاح

جمعية المقاصد الخيرية الإسلامية العربية
AUSTRIAN ARAB COMMUNITY CLINIC

مشرفة الطالبة
د. لينا الخيري

Jerusalem Branch/Telefax 02-2799234
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P.O. box 51000 Jerusalem

فرع القدس / تلفاكس 02-2799234
فرع غزة / تلفاكس 08-2878166-2878177
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Appendix: 4.4

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2006/10/20

إلى عناية د. سامي نابلسي المحترم،
مدير مركز سبافورد للأطفال

تحية طيبة وبعد،

الموضوع: موافقة على إجراء دراسة لبرنامج الصحة العام

نرجو من حضرتكم تسهيل مهمة السيدة كفاية أبو غيث الطالبة في برنامج الماجستير في الصحة العامة تخصص بيئة وذلك لإتمام الجانب الميداني من رسالة الماجستير والتي تعمل على إعدادها وموضوعها " دراسة العوامل الوراثية المساهمة في ازدياد حدة الربو عند الأطفال من سن 5-16 سنة في شرقي القدس " حيث تهدف هذه الدراسة لمعرفة علاقة Alpha-1- Antitrypsin deficiency مع مرض الربو، كما وينظر بعيدا إلى طرح بعض الاقتراحات للمساعدة في علاج مرض الربو.

نثمن عاليا دعمكم للبحث العلمي بشكل خاص ولجامعة القدس بشكل عام.

مع فائق الشكر والتقدير،

Spafford
Dr. Sami Nabulsi
Pediatrician

مشرفة الطالبة
د. لبنا الخيري

Jerusalem Branch/Telefax 02-2799234
Gaza Branch/Telefax 08-2878166,2878177
P.O. box 51000 Jerusalem

فرع القدس / تلفاكس 02-2799234
فرع غزة / تلفاكس 08-2878166-2878177
ص.ب 51000 القدس

Appendix: 4.5

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

Dear Sir

I am kifaya Abu Ghaith Master student in Public Health , Al-Quds university , I am interest to study childhood Asthma and I choose the Environmental and genetic factor that effect the severity of asthma , we chose two tools to measure the effect first Questioner to represent the environmental effect and blood test to check genetic effect so; every child diagnosis as asthma in your hospital will receive Questioner and if the parent agree we will draw a CBC Tube for him to check Alpha -1- Antitripsine deficiency level . Alpha-1 Antitrypsin deficiency is an inherited disorder that can cause lung or liver disease. Alpha-1 is the name of a protein. Deficiency means there is not enough of it. This protein protects the body from being damaged by a powerful enzyme called neutrophil elastase. Neutrophil elastase is released from white blood cells to fight infection, but it can attack normal tissues (such as the lungs) if not carefully controlled by alpha-1 antitrypsin. A mutation in the SERPINA1 gene can lead to a shortage (deficiency) of alpha-1 antitrypsin protein or an abnormal form of the protein that cannot control neutrophil elastase. Uncontrolled, neutrophil elastase destroys tiny air sacs in the lungs and will lead sever asthma symptoms.

sample will be (300) child distributed between medical center and hospital in east Jerusalem every case (Asthma case) will have tow control from other disease until reach the target size , and the period will be eight weeks . Pediatric ward, out patient clinic, and emergency ward suspected to be the interest area for collection of the sample

Thank you
Fax: 6273243
Tel: 6273246

Jerusalem Branch/Telefax 02-2799234
Gaza Branch/Telefax 08-2878166,2878177.
P.O. box 51000 Jerusalem

فرع القدس / تلفاكس 02-2799234
فرع غزة / تلفاكس 08-2878166-2878177
ص.ب. 51000 القدس

Appendix: 4.6

بسم الله الرحمن الرحيم

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2006/10/28

حضرة السيد/ مدير مستشفى المطلع المحترم
بواسطة: الدكتور محمد شاهين/ عميد كلية الصحة العامة

الموضوع: المساعدة في بحث

تحية طيبة وبعد،،
يرجى السماح للطالبة كفاية جمعة ابو غيث ماجستير/ صحة عامة بتعبئة نموذج استبيان وكذلك اخذ عينات دم لضرورة إتمام بحث حول مرض الربو لدى الأطفال في منطقة القدس.

شاكرين لكم حسن تعاونكم،،

مرفق/ نسخة أطروحة البحث

المشرف
د.غسان بعلوشة
منسق دائرة التشريح/ جامعة القدس

يسمح للسيدة كفاية ابو غيث
باجراء دراستها واخذ العينات
ضمن الاشراف والقواعد المتبعة
في المستشفى

ATIF AL-RIMAWI
Director of Human Resources
Augusta Victoria Hospital
Lutheran World Federation

١١/١١/٠٦

نسخة: الملف

Jerusalem Branch/Telefax 02-2799234
Gaza Branch/Telefax 08-2878166,2878177
P.O. box 51000 Jerusalem

فرع القدس / تلفاكس 02-2799234
فرع غزة / تلفاكس 08-2878166-2878177
ص.ب. 51000 القدس

APPENDICES 4.7

الموافقة على إجراء فحص دم

التاريخ: / / ٢٠٠٦

أنا الموقع اسمي أدناه والد/ه الطفل.....

أوافق على أن يكون أبنى / ابنتي ضمن المجموعة المطلوبة لهدف دراسة مرض الربو عند الأطفال / من قبل جامعه القدس كما و أوافق على إجراء فحص دم لابني/ ابنتي لهدف البحث العلمي فقط .

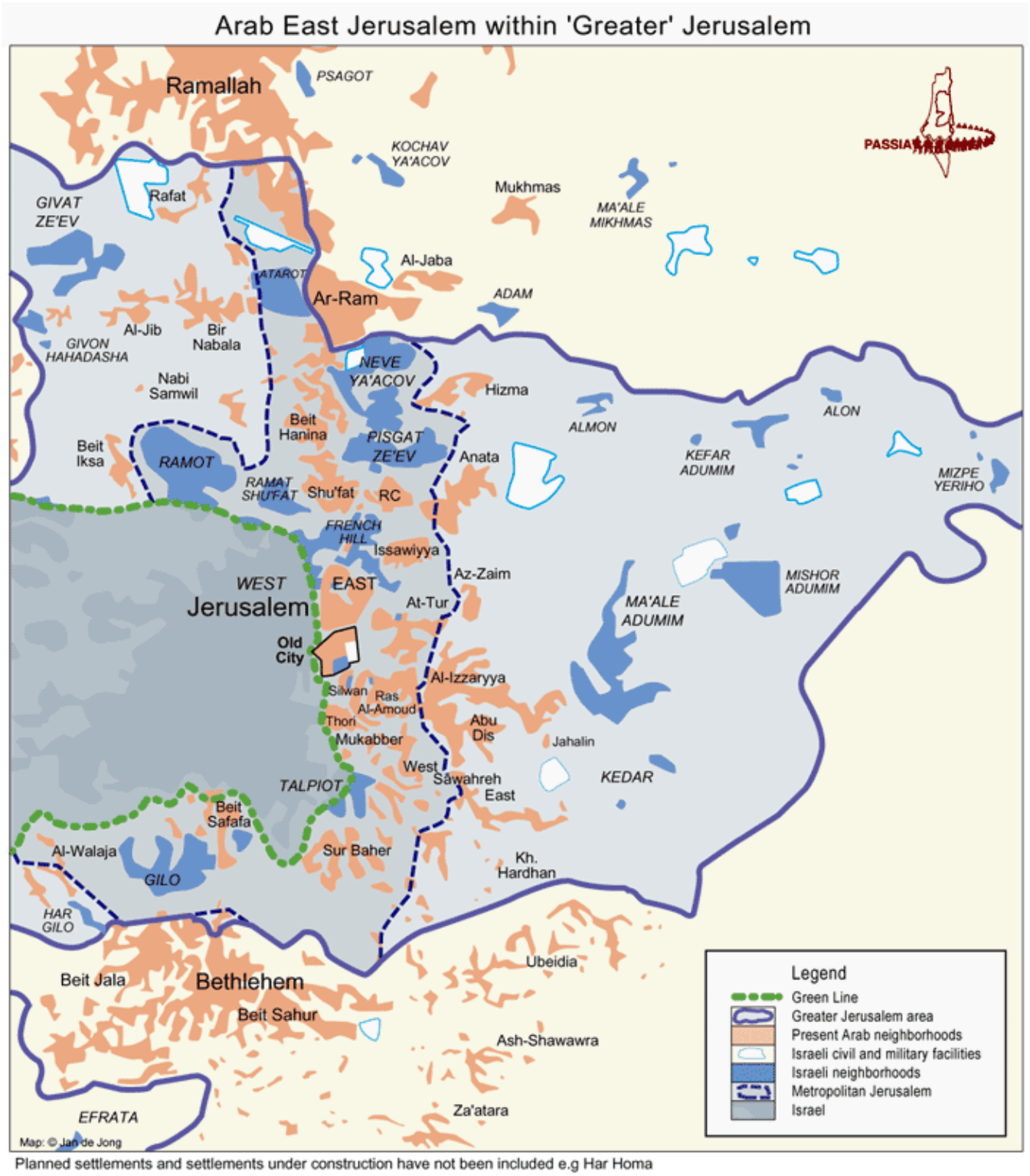
هوية رقم .....

شاهد..... شاهد.....

توقيع ولي الأمر

.....

Appendices 4.8 East Jerusalem map



Source: The Palestinian Academic Society for the Study of International Affairs (PASSIA)

4.9The study questionnaire (English)

Child Asthma Questionnaire

Demographic Data:

1-Childs Name _____

2-Gender M ____ F_____

3-Age

1- (5-10) 2- >10-16

4-Home Phone Number _____

5-Type Insurance

a- Government *b*- Privet ***c***- No Insurance

7-Name of the health center

-------- 1-Al- Makassed Islamic Charitable Hospital

--------2- Augusta Victoria Hospital

--------3- Makassed Islamic Charitable center

--------4- Arab medical health center

--------5- American medical center

--------6-Palestinian ministry of health center

8-Place of residence:

1-urban 2- Ruler 3-refugee camp

9-laboratory code (----------)

Family Status:

1-Educational level of the mother:

a-Illiterate b-School education c-Graduate education

2- Educational level of the father:

a-Illiterate b-School education c-Graduate education

2-Mother's occupation:

a-Without b-Employee

3-Father's occupation:

a-Labor work b-Civil jobs c-Private work

4- Basic salary

a-2500 NIS and less b->2500-5000 NIS c-5000 NIS and more

Medical History

1. Has your child had wheezing at any time in the last month?

Yes_____ No_____

2. Did your child wake up at the morning with a feeling of chest tightness?

Yes_____ No_____

3. How long does your child feel chest tightness?

- Less than 30 min _____
- 30 min to 1 hour _____
- More than 1 hour _____
- Unknown _____

4. In the last month, has your child been awakened by cough at night.

Yes_____ No_____

5. Has your child had an attack of shortness of breath (difficulty to breath) at last month?

Yes_____ No_____

6. Do these attacks of shortness of breath come on _____

Night _____ Day _____

Past History:-

1. Has your child been treated for any other medical condition at the present time?

   Yes _____ No_____

3. Has anyone in your family been diagnosed with asthma?

   Yes _____ No_____

   - If yes please describe relation

   _____

4. How long has your child been having asthma?

   _____ Newly
   _____ Less than 3 years
   _____ More than 3 years

5. In the past 30 days and during the night how often did your child wake up or had hard time breathing

   _____ 2 times a week
   _____ Every night
   _____ more than 2 times a week
   _____ Constantly

6. In the past 3 years, how many times was the patient hospitalized for asthma?

   ___ 0 ___ 1 ___ 2 ____ 3 ____ 4 ____ 5 ____> 5

7. Which of the following heredity problems tend to run in your family?

   _____ Heart
   _____ Diabetes
   _____ Kidney
   _____ Cancer
   _____ Arthritis
   _____ Hypertension
   _____ Others

Home environment:

1. Do you have domestic animal at home?

Yes _____ No_____

2. If yes it is
_____ Cat
_____ Dog
_____ Bird
_____ Others

3. If your child is exposed to domestic animal dose he / she

_____ Start to cough	yes / No
_____ Start to wheeze	yes / No
_____ Get difficulty in breathing	yes /No
_____ Get runny nose / eyes	yes / No

4. Does any person in the house smoke yes / No

- If yes please describe relation
- ……

5. Which season of the year does your child usually have asthma symptoms

_____Winter
_____ Summer
_____ Spring
_____ Autumn

Knowledge and management of asthma:

1. Did you have enough knowledge to manage your child during asthma?
Yes / no

2. How would you classify your level of understanding regarding your child's asthma or breathing problem

_____ Very knowledgeable

_____ Somewhat knowledgeable

_____ lacking knowledge on the topic

3. What triggers your child asthma attacks?

_____ Smoke
_____ Animals
_____ Dust
_____ Flowers
_____ Mold
_____ Chalk dust
_____ Changes in weather
_____ Strong smells / Perfume
_____ Food
_____ Emotional upsets
_____ Sports
_____ Others

Treatment:

1. How often do you use an inhaler or nebulizer to treat your child's problem?

_____ Rarely
_____ Daily use
_____ More than once daily
_____ 5 or more times a month

2. Does your child take any other medication? If yes, lest them

_____
_____
_____
_____

4.10 study questionnaire(Arabic)

بسم الله الرحمن الرحيم

جامعة القدس
كلية الصحة العامة

حضرة المشارك / ة المحترم / ة :

أنا طالبة ماجستير في كلية الصحة العامة / جامعة القدس / أبو ديس أعمل على إعداد رسالة ماجستير بعنوان مدى تأثير الجينات الوراثية و العوامل البيئية على مرض الربو عند الأطـفال من سن 5 – 16 سنة في شرقي مدينة القدس .

الهدف من هذه الدراسة هو مساعدة الأطفال المصابين بمرض الربو للحد و التخفيف من شدة أعراض أزمة الربو في حال وقوعها مع العلم أن مشاركتكم في هذه الدراسة اختياري (تطوعي) و برغبتك الشخصية و يمكن الانسـحاب من المشـاركة في أي لحظة شـئتم ، أريد أن أؤكد أن المعلومات و فحوصـات الدم سـتسـتعمل للغاية الدراسية فقط و سـتكون في غاية السـرية .

شاكرين لكم حسن تعاونكم و مشاركتكم

طالبة الماجستير :

كفاية ابو غيث

استبيان حول مرض الربو في أطفال فلسطين

معلومات عن الطفل :

التاريخ:..../..../.....م

اسم الطفل.....

الجنس ذكر..... أنثى.....

العمر بالسنوات : 1- (5-10) 2- اكبر من(10-16)

هاتف البيت..... بلفون.....

التأمين الصحي: 1-حكومي 2-خاص 3- لا يوجد تأمين

العنوان: 1- مدينة 2- قرية 3- مخيم

الرقم المتسلسل..... (خاص بالمختبر)

الوضع العائلي للأسرة:

1- المؤهل العلمي للزوجة:

1- أمية 2- تعليم مدرسي 3- تعليم جامعي/دراسات عليا

2- المؤهل العلمي للزوج:

1- أمي 2- تعليم مدرسي 3- تعليم جامعي/دراسات عليا

3- عمل الأم:

1- تعمل 2- لا تعمل

4- عمل الأب:

1- عامل 2- موظف 3- أعمال حرة

5- معدل دخل الأسرة :

1- أقل من (2500) 2- من (2500-5000) 3- أكثر من (5000)

تاريخ صحة الطفل

١ - هل عانى طفلك من صفير في الصدر خلال الشهر الحالي؟
نعم \ لا

٢ - هل يصحو الطفل وعنده شعور بضيق بالصدر أو صعوبة في اخذ النفس؟
نعم \ لا

٣ - إذا كان الجواب نعم كم يستغرق هذا الشعور (الشعور بتضيق في النفس):

1- اقل من 30 دقيقة
2- من 30 دقيقة إلى ساعة
3- أكثر من ساعة
4- لا ادري

٤ - في الشهر الحالي هل كان الطفل يصحو خلال الليل نتيجة سعال مستمر:
نعم \ لا

5- هل عانى طفلك من صعوبة في اخذ النفس خلال الشهر الحالي:
نعم \ لا

6- هل كانت هذه الصعوبة في التنفس غالبا في :
1- الليل
2- النهار

التاريخ المرضي للطفل

1- هل تعالج الطفل من إي مرض خلال الفترة الحالية نعم \ لا
إذا كان الجواب نعم اذكر/ي اسم المرض.....

2- هل تم تشخيص أي فرد من إفراد الأسرة بمرض الربو نعم \ لا

- إذا كان الجواب نعم صف\ي العلاقة العائلية من فضلك\ي

3- هل هناك مشاكل صحية وراثية في العائلة :
..... القلب
..... السكري
..... الكلى
..... السرطان
..... التهاب المفاصل
..... الضغط؟
..... غير ذلك حدد\ي.....

البيت \ سكن الطفل

1- هل عندكم حيوانات أليفة في المنزل؟
نعم \ لا

2- إذا كان الجواب نعم فهل هو :
..... قط
..... كلب
..... عصافير \ طيور
..... غير ذلك

3- إذا تعرض الطفل لأي من هذه الحيوانات الأليفة:
..... يبدأ بالسعال
..... يبدأ بالصفير في التنفس
..... يرافقه الشعور بالتضيق في الصدر أو التنفس
..... يبدأ بالدموع ومخاط في الأنف

٥ - هل يوجد مدخنين ضمن إفراد المنزل؟
نعم \ لا
إذا كان الجواب نعم صف\ي العلاقة العائلية من فضلك\ي

5- أي من الفصول الأربعة تكون عادة محفزة لنوبة الربو عند الطفل
1-الشتاء
2-الربيع
3-الصيف
4-الخريف

6- خلال الشهر الماضي وخلال فترة الليل كم مرة استيقظ الطفل وعنده صعوبة في التنفس

1- مرتين في الأسبوع
2- كل ليلة
3- أكثر من مرتين في الأسبوع
4- باستمرار

7- كم المدة التي عانى فيها طفلك من مرض الربو

1- جديد
2- أكثر من 3 سنوات
3- اقل من 3 سنوات

9- خلال الثلاث سنوات الأخيرة كم مرة ادخل الطفل للمستشفى بسبب مرض الربو

0..... 1.... 2.... 3.... 4..... 5..... أكثر من 5.....

معلومات عن المرض

1-هل تجدين عندك المقدرة العلمية والمعلومات الكافية للتعامل مع مشكلة طفلك (الربو)
نعم \ لا

2- كيف تصنفين نفسك من ناحية المعلومات العلمية عن مرض الربو والتعامل مع مشكلة طفلك

1- عندي معلومات كثيرة
2- عندي معلومات قليلة
3- عندي نقص شديد في المعلومات عن مرض الربو

3- ما هو المحفز لنوبة الربو عند طفلك غالبا :

.....الدخان
.....الحيوانات
.....الغبار
.....المزروعات المنزلية
.....العفن
.....الطباشير
.....التقلب في الطقس
.....الروائح القوية مثل العطور
.....الأكل (أصناف معينة)
.....مشاكل نفسية وعاطفية
.....الرياضة
.....غير ذلك

العلاج الذي يعطى للطفل

1- متى تستعملين البخاخ المرطب وموسع مجرى التنفس
1- نادرا
2- كل يوم
3- أكثر من مرة في اليوم
4- خمس مرات أو أكثر في الشهر

2- الرجاء تسمية الأدوية التي تعطى للطفل حاليا :
1- ..... 2- .....
3-.....