

Epidemiology of Autoimmune Liver Disorders

A Proposal to Study Concurrent
Autoimmune Diseases

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ABSTRACT

Background. Approximately 38 percent of people with an autoimmune liver disease have at least one other concurrent autoimmune disease, and research shows that the most prevalent concurrent autoimmune diseases are IBD, Sjögren's syndrome, thyroiditis, rheumatoid arthritis, Celiac disease, and ulcerative colitis, and diabetes type 1.

Objectives. Researchers of autoimmune liver disease epidemiology call for more rigorous studies to determine the prevalence of concurrent autoimmune diseases. Although narrowing down prevalence rates will help health care providers in the long run, patients still need education on the chances of developing a concurrent autoimmune disease, including possible warning signs of symptoms, to lessen the severity of the AD by receiving treatment as soon as possible. And helping patients to recognize symptoms of concurrent ADs may help determine prevalence rates.

Methods. Through a five-year three-phase epidemiological and anthropological study, the cross-disciplinary project team plans to develop the study protocol for the collaborative studies, implement the retrospective and prospective prevalence, incidence, risk factor and patient education studies, analyze the data and report the findings. Data collection instruments will include a modified version of the US National Health and Nutrition Examination Study (NHANES IV) questionnaire, study participant interview guides, and quantitative and qualitative data analysis software includes SAS and Atlas.ti.

Key words: concurrent autoimmune diseases, autoimmune hepatitis, chronic liver diseases, primary biliary cirrhosis, primary sclerosing cholangitis.

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Epidemiology of Autoimmune Liver Disorders

A PROPOSAL TO RESEARCH ASSOCIATED AUTOIMMUNE DISORDERS

I. INTRODUCTION

Approximately 38 percent of people with an autoimmune liver disease (ALD), including primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC), have one or more concurrent autoimmune diseases (ADs). The most prevalent ADs are autoimmune thyroiditis, ulcerative colitis (UC), type 1 diabetes, rheumatoid arthritis (RA), and Celiac disease (CD). Although the possibility of developing a concurrent AD is relatively high, I found in an informal survey of ALD support group members that 65.1 percent were not informed by their health care provider about the chances of developing one or more concurrent ADs, and of these patients, 86 percent would have wanted their provider to inform them so that they could seek treatment at disease onset, or at least as soon as symptoms present.

Although I conducted an extensive literature review, I have not found a study on ALDs that proposes patient education to help patients and providers look for warning signs of concurrent ADs. Instead the focus is on calling for more rigorous studies to determine the prevalence of concurrent autoimmune diseases. Narrowing down prevalence rates will help health care providers in the long run, but patients still need education on the chances of developing a concurrent autoimmune disease, including possible warning signs of symptoms, to lessen the severity of the AD by receiving treatment as soon as possible.

II. BACKGROUND

In the U.S., autoimmune diseases are among the leading causes of death among young and middle-aged women.¹ Incidence rates vary among the autoimmune diseases, with estimates ranging from less than one case of Goodpasture's syndrome to more than 20 cases of rheumatoid arthritis per 100,000 persons per year.^{1,2} Prevalence rates range from less than 5 per 100,000 (e.g. autoimmune hepatitis) to more than 500 per 100,000 (e.g. RA, autoimmune thyroiditis).¹⁻³

Among patients diagnosed with ADs, at least 85 percent are female.^{1,2} Age of disease onset depends on the disease characteristics. Some diseases primarily occur in childhood and adolescence (Type 1 diabetes), in the mid-adult years (multiple sclerosis), or among older adults (RA).^{1,2} Ethnic and geographic differences in incidence of specific autoimmune diseases have been documented, but specific groups may be at higher risk for some diseases and lower risk for other diseases.^{1,4-13}

A. Autoimmune Liver Diseases

Researchers have detected three autoimmune liver diseases: primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC). These diseases can occur individually or overlap with each other.¹⁴ Although much research on autoimmune liver diseases has focused on PBC and AIH,⁷ little is known about the etiology, prevalence, and incidence of PSC. The following provides an overview of these three ALDs.

1. Primary Biliary Cirrhosis

Chronic biliary duct destruction characterizes PBC, which mainly affects women aged between 35 and 60 years.¹⁵⁻¹⁷ⁱ PBC can cause prolonged liver inflammation which in turn causes scarring, eventually leading to cirrhosis and ultimately liver failure.^{16,17} The most common symptoms are pruritus (itching), asthenia (muscle weakness), or jaundice, although many patients do not present with symptoms.^{16,17} Health care providers may confirm diagnosis through medical tests, including lab tests (e.g. liver function tests, antimitochondrial antibodies), liver biopsy, and ultrasound (to detect biliary duct obstruction).^{16,18}

a. Prevalence and Incidence Rates

Researchers find that the highest annual incidence and point prevalence rates for PBC have are in the UK (incidence 3.1 per 100,000 population per year; prevalence 25.1 per 100,000 population),⁷ the US (incidence 2.7 per 100,000 population per year; prevalence 40.2 per 100,000),^{7,19} and among Alaskan natives (prevalence 16 per 100,000).⁹ Incidence and prevalence rate estimates from Sweden and Norway (incidence 1.4–1.6 per 100,000 per year and prevalence 9.2–15.1 per 100,000)⁷ are also

relatively high when compared with those reported in Japan (incidence 0.34–0.42 per 100,000 population and a prevalence estimated at 2.0 per 100,000),⁷ Canada and Australia (incidence 0.33 per 100,000 per year and prevalence 1.9–2.2 per 100,000, respectively).^{7,20ii}

In the UK, Feld and Heathcote⁷ find rates of PBC may be increasing over time. They report, “Between 1987–1994, prevalence rates in the UK have increased significantly from 14.9 to 25.1 cases per 100,000 population ($P < 0.00001$).” Though, as they point out, “these figures may represent true increases in disease, other explanations must also be considered. More exhaustive case-finding strategies and generally increased awareness of PBC likely account for some of the rise in incidence, and earlier diagnosis could increase prevalence without altering incidence. It will be important to examine PBC rates over time in other populations to see if this is an isolated finding in the UK or a more generalized phenomenon.” In fact, one study²¹ found that the prevalence of PBC increased in Finland by 5.1 percent during 1988–1999, which the research attribute to both the increased incidence (3.5 percent) and patients’ prolonged survival.

b. Risk Factors

Researchers^{7,15,22,23} report that in addition to gender and age, heredity is a major risk factor for PBC. Feld and Heathcote⁷ find the majority of familial cases of PBC in mother–daughter pairs and interestingly, in all cases, daughters presented with PBC at a younger age than their mothers, which is not attributed to screenings because their mother were diagnosed but rather, as Feld and Heathcote explain, “may suggest genetic anticipation within families in PBC.”

Environmental factors may induce PBC in genetically susceptible individuals.²²⁻²⁴ According to Metcalf et al.,²³ “These [associations] have included an unknown factor associated with the water supply, urinary tract infections caused by *Escherichia coli*, drugs (particularly phenothiazines), a history of obstetric complications or gynecological interventions, disease onset after childbirth or anaesthetic, and, an atypical mycobacterial infection (a response possibly associated with immune mimicry).” Past smoking history²² and use or hormone replacement therapies²² were also significantly associated with increased risk of PBC. Gershwin et al.²² found that the frequent use of nail polish slightly increased the risk of having PBC. However, as Metcalf et al.,²³ write, “none of these has been confirmed as having a direct or indirect causal relation.”

c. Autoimmune Cholangitis

Researchers have not identified whether autoimmune cholangitis (AIC) is a separate entity from PBC or not. Most likely, according to Washington,²⁵ “the two represent one disease differing only in its autoantibody pattern. Depending on the cohort of patients, AIC may comprise a diverse group of disorders including atypical PBC, small duct PSC, idiopathic adulthood ductopenia, and transitional stages of autoimmune hepatopathies.” Washington states that the AIC “has generally been applied to cases that are clinically, histologically, and biochemically compatible with PBC except for the lack of identifiable antimitochondrial antibodies; serum ANA and anti-SMA may be present in high titers.

Because this entity closely resembles PBC except in its autoantibody profile, it has been termed an 'outlier syndrome' rather than an overlap syndrome."

2. Autoimmune Hepatitis

Like PBC and the majority of ADs, women than men are more likely to develop AIH. AIH usually develops subtly with unspecific symptoms, such as lethargy, arthralgias (joint pain), jaundice, anorexia (loss of appetite), nausea, dark urine, and an enlarged liver typically with pain in the right upper quadrant.^{7,14,26,27} Zachou et al.²⁶ report that some patients may have no obvious symptoms of liver disease, while occasionally some patients may present with severe and nearly identical symptoms and signs of acute viral hepatitis. Diagnosis usually is by serological tests, (used to rule out viral hepatitis, as patients with AIH typically present with antinuclear antibodies, smooth muscle antibodies, and antibodies to liver and kidney microsomes), and liver biopsy.^{7,14,26,27} Three known types of AIH exist,ⁱⁱⁱ which are classified by which antibodies are found in the patient.^{7,26} Adults are more likely to present with the more common AIH type 1, while children aged 2 to 14 are more likely to present with the less common but more severe AIH type 2.^{7,26} Type 3, also called cryptogenic hepatitis, is exceedingly rare, and at least one study²⁸ calls for it to be considered a variant of type 1.

a. Prevalence and Incidence Rates

The incidence and prevalence of AIH differ depending on geographic region. The incidence of type 1 AIH among White populations of Northern Europe and North America ranges from 0.1–1.9 per 100,000 annually.^{7iv} Although a specific US prevalence rate was not found in this literature review, reports⁷ estimate that approximately 100,000–200,000 people in the US have AIH. In Northern European countries, including the UK, Sweden, and Norway, the estimated prevalence of AIH is 1.6–1.9 per 100,000.^{7,26,29} In Singapore, the prevalence of AIH was 4 per 100,000, with no significant difference between Chinese, Malay and Indian patients.¹¹ In Brazil, Cançado and Porta find that AIH is "more prevalent in White populations (mainly descendants from the Iberian Peninsular) (53.7 percent), although it is present in 33.5 percent of mulattos [African and White mixed populations], 11.4 percent in Afro-Brazilians, and 1.3 percent of those with Japanese ethnicity."⁵ Type 2 AIH is more frequent in southern Europe than in northern Europe, the United States, and Japan.^{7,30} And AIH accounts for 2.6 percent of the liver transplants in the European Liver Transplant Registry⁷ and 5.9 percent of liver transplants in the US.²⁹

b. Risk Factors

Like PBC, nonmodifiable risk factors for AIH include gender, typically affecting females more than males; age, type 1 most commonly affects women between the ages of 15 and 40 with peaks between 10–30 years and then older than 40 years of age,^v while Type 2 primarily affects young girls; and heredity. Certain genetic defects^{vi} increase the risk of autoimmune hepatitis,^{7,32} although, according to Feld and Heathcote,⁷ researchers have not studied familial risk of AIH rigorously. They

write, "There are few reports of AIH occurring in family members and no twin studies. While AIH itself does not appear to be common in relatives of patients, autoimmune disease per se is quite prevalent."

Researchers^{14,27,32} have also linked AIH to environmental factors, including a history of certain viral infections (hepatitis A or B,^{14,32} measles,^{14,32} and the Epstein-Barr virus^{14,32}). Use of certain medications (the high blood pressure drugs methyldopa,³² dihydralazine,²⁷ and tienilic acid,²⁷ the anti-inflammatory diclofenac,²⁷ the antibiotics minocycline³² and nitrofurantoin,³² the anesthetic halothane,²⁷ and perhaps certain statins such as atorvastatin, i.e. Lipitor)³² and herbs such as black cohosh and dai-saiko-to, may trigger autoimmune hepatitis.¹⁴ Yet, according to Krawitt,¹⁴ "whether drugs and herbs unmask or induce autoimmune hepatitis, or simply cause a drug-induced hepatitis with accompanying autoimmune features, is unclear."

Ethnicity may influence AIH's clinical presentation and outcome. Czaja³³ writes, "African American patients have a higher frequency of cirrhosis and poorer hepatic synthetic function at presentation than white North Americans. Alaskan natives have a higher occurrence of acute icteric [jaundice] disease and advanced fibrosis than non-native counterparts; nonwhite, non-European patients frequently have cholestatic features [condition where bile cannot flow from the liver to the duodenum]; Asians tend to have late-onset, mild disease; and South American patients are commonly young children with severe disease. These observations emphasize the clinical diversity of autoimmune hepatitis and the need to include it in the differential diagnosis of all individuals with acute and chronic hepatitis."

3. Primary Sclerosis Cholangitis

Compared to AIH and PBC, less is known about the incidence, prevalence, and etiology of PSC. Primarily, like PBC, PSC is a disease of the biliary ducts, although some cases may also involve the gallbladder and pancreas ducts. The walls of the bile ducts become inflamed, i.e. cholangitis. The inflammation causes scarring and hardening, i.e. fibrosis, that narrows the bile ducts. Because bile cannot drain properly through the ducts, it accumulates in the liver causing damage to liver cells. Eventually, so much bile is accumulated, it seeps into the bloodstream. Finally, with long term cell damage, the liver develops cirrhosis and ultimately liver failure.^{34,35}

Bile ducts can become infected, causing chills, fever and upper abdominal tenderness. Itching may occur when bile seeps into the bloodstream. As the disease progresses, chronic fatigue, loss of appetite, weight loss and jaundice may occur. A history of inflammatory bowel disease and abnormal blood tests are typical indicators for PSC. Diagnosis is usually made by cholangiography, an X-ray called ERCP that involves injecting dye into the bile ducts. Liver biopsy may also be needed for diagnosis.^{34,35}

a. Prevalence and Incidence Rates

As of 2008, very few epidemiological studies have been conducted. In one U.S. population-based study,³⁶ (part of the Rochester Epidemiology Project), the incidence rate in men was 1.25 per 100,000 person per year compared with 0.54 per 100,000 person per year in women. The prevalence is 20.9 cases per 100,000 men, and only 6.3 cases per 100,000 women. In another population-based study from Calgary, Alberta, Canada, the annual incidence rate adjusted for age was 1.01 per 100,000 person per year in men, and 0.84 per 100,000 person per year in women.³⁵ In Norway, researchers⁷ found the PSC incidence rate to be 1.31 per 100,000 per year and prevalence to be 8.5 per 100,000. And in Spain, researchers³⁷ demonstrated an increasing annual incidence and prevalence of PSC from 1985 to 1988. In 1988, they found the incidence of PSC to be 0.068 per 100,000 with a point prevalence of 0.22 per 100,000 population.

Feld and Heathcote⁷ report, "Other estimates of incidence and prevalence of PSC are extrapolated from ulcerative colitis (UC) data. Assuming that 3–5 percent of patients with UC have concomitant PSC, the prevalence of PSC in the US has been estimated to be 1–4 per 100,000. This compares with a similarly generated estimated value of 6 per 100,000 prevalence in Sweden."

b. Risk Factors

Unlike AIH and PBC, PSC is more common in men.⁷ Onset in patients usually occurs between 20–40 years of age; however, researchers have increasingly recognized as a cause of chronic liver disease in children.⁷ Researchers have not yet rigorously studied PSC, although, a number of individual cases of familial PSC have been reported.^{7,38} The prevalence of PSC appears to be increased among first-degree relatives of patients with PSC; the prevalence of PSC among first-degree relatives is estimated to be 0.7 percent; among siblings, the prevalence was 1.5 percent.³⁵

Feld and Heathcote⁷ write, "The largest series included just three cases of siblings with PSC, all of whom also had UC. Familial clustering of IBD [irritable bowel disease] has long been recognized and the recent identification of the NOD2 gene increasing susceptibility to Crohn's disease strongly supports a genetic component to IBD. The strong association between PSC and IBD, particularly UC, makes genetic susceptibility an attractive hypothesis for PSC; however, to date there is little pedigree data to support this notion."

B. Autoimmune Disease Associations

Worldwide, approximately 38 percent of patients with ALDs may develop one or more concurrent ADs.^{7,39vii} Feld and Heathcote⁷ find that "the most striking association [between ALDs and associated ADs] is between PSC and IBD. Approximately 70 percent of adult patients with PSC have concomitant IBD at some stage in their lives, while only about 5 percent of patients with IBD develop PSC." Researchers have also found ulcerative colitis to be prevalent in 25 to 90 percent of patients with PSC.³⁵

Gossard and Lindor⁴⁰ report that up to 10 percent of patients with PBC develop AIH, although Silveria et al.⁴¹ argue that this overlap in “diagnosis is challenging and the natural history of this syndrome has not been demonstrated.” McFarlane⁴² writes, “Overlaps with PBC are the most commonly reported, and the consensus now appears to be that such cases should be regarded as part of the spectrum of PBC and not as variants of AIH.”

Caramella et al.¹⁷ state, “PBC is often associated with other non-hepatic autoimmune diseases, especially primary Sjögren’s syndrome. PBC and RA have been suggested to coexist in 1.8 to 5.6 percent of patients with PBC, but data supporting this association are scarce,” and Parikh-Patel et al.,¹⁵ using standardized NHANES questions, find higher reports of concurrent Sjögren’s syndrome (17.4 percent) and Raynaud's syndrome (12.5 percent).

Regardless of geographic region or ethnicity, in patients with AIH, one clue to diagnosis may be the presence of other autoimmune diseases. The most common ADs concurrent in patients with AIH are thyroiditis,^{14,43} ulcerative colitis,^{1,14,43} type 1 diabetes,^{14,43} rheumatoid arthritis,¹⁴ and Celiac disease (CD).^{14,39,44} CD is epidemiologically associated with autoimmune liver diseases,^{33,45,46} and the prevalence of celiac disease concurrent in patients with ALD may be as high as 10 percent.^{33,39} Researchers^{33,45,46} recommend, due to the high prevalence, that serological screening testing for CD should be routinely performed in such patients.^{viii}

Table 1, developed by Feld and Healthcote,⁷ outlines the most common chronic disease association, the majority of which are ADs.^{ix}

Table 1. Disease associations of autoimmune liver diseases⁷

Primary biliary cirrhosis	Autoimmune hepatitis	Primary sclerosing cholangitis
Keratoconjunctivitis sicca	Autoimmune thyroiditis	Ulcerative colitis
Xerostomia	Grave’s disease	Crohn’s disease
Sjögren’s syndrome	Ulcerative colitis	Histiocytosis X
Scleroderma/CREST syndrome	Autoimmune hemolytic anemia	Rheumatoid arthritis
Rheumatoid arthritis	Idiopathic thrombocytopenia	Colorectal cancer
Autoimmune thyroiditis	Systemic lupus erythematosus	Cholangiocarcinoma
Celiac disease	Sjögren’s syndrome	Celiac disease
Mixed connective tissue disease	Polymyositis	Retroperitoneal fibrosis
Renal tubular acidosis	Mixed connective tissue disease	
	Celiac disease	
	Myasthenia gravis	

C. What's Missing in the Literature

Having lived with AIH now for 12 years, I perceive myself to be a well educated about AIH. However, I only knew that I was likely to develop a concurrent AD (not the type of AD, just the likelihood) because I read a great deal of articles after my diagnosis. The specialist who diagnosed me and followed my care, a highly trained hepatologist, never told me about the chances of developing a concurrent AD, and neither has any other hepatologist that I have followed up with since.

In fact, I was diagnosed with psoriasis at age 12, exactly 8 years prior to my diagnosis of AIH, but did not know psoriasis was an AD. If I had known that it was an AD and knew that the chances of me developing another AD were significantly high, I would like to think that I would have been more aware of my AIH symptoms and proactive about diagnosis and treatment instead of denying my symptoms and waiting more than a year to finally see a doctor for diagnosis. I could have possibly prevented the severity of liver damage and prolonged (and horrendous) corticosteroidal and immunosuppressive treatment due to the severity.

Even after explaining to my doctor that I had a concurrent AD, he dismissed the importance of watching for other symptoms of ADs, despite above cited studies about the prevalence of ADs. The studies simply do not call for patient education, but instead for more epidemiological research on the prevalence of concurrent ADs. I wondered whether or not I was the only one to have a similar experience of not receiving doctor-provided patient education, so I conducted an informal survey of ALD support group members. And I found out that out of 88 respondents from the US, Canada, UK, Serbia, Finland, and Australia, 65.1 percent were not told about the chances of developing a concurrent AD, although 86 percent wish they had been told instead of finding out either through self education or through diagnosis after worrying about symptoms for an unnecessarily long period of time. A typical response is, "I wanted to be prepared and pay attention to any symptoms to address them immediately." (See Appendix A for the survey results.)

Certainly, more rigorous epidemiological studies on the prevalence of concurrent ADs among patients with ALDs is important. In fact, among the informal survey respondents, 48.2 percent self report being diagnosed with a concurrent AD, while 14.5 percent suspect that they may have a concurrent AD. A relatively high number (20.5 percent) of respondents report having PBC and AIH overlap.

The respondents self report that the most common concurrent ADs among those with PBC, besides AIH, are Sjögren's syndrome, autoimmune thyroiditis, and Raynaud's syndrome. Among the most prevalent concurrent ADs of those with AIH, besides PBC, are autoimmune thyroiditis, Celiac disease, systemic lupus erythematosus, Sjögren's syndrome, and psoriasis. Of the four respondents who have PSC, two report having AIH overlap and one reports PBC overlap. Table 2 outlines the three ALLDs and their self-reported associated ADs, including the number of cases of each concurrent AD.

Table 2. Survey results of self-reported concurrent ADs (n=52)

Rank	Primary biliary cirrhosis (n=58)	Autoimmune hepatitis (n=43)	Primary sclerosing cholangitis (n=4)
1	Autoimmune hepatitis (29.3%)	Primary biliary cirrhosis (39.5%)	Autoimmune hepatitis (50%)
2	Sjögren’s syndrome (20.7%)	Autoimmune thyroiditis (16.3%)	Primary biliary cirrhosis (25%)
3	Autoimmune thyroiditis (13.8%)	Celiac disease (11.3%)	Systemic lupus erythematosus (25%)
4	Raynaud’s syndrome (12.1%)	Psoriasis (9.3%)	Raynaud’s syndrome (25%)
5	Rheumatoid arthritis (6.9%)	Sjögren’s syndrome (9.3%)	Psoriasis (25%)
6	Systemic lupus erythematosus (5.2%)	Systemic lupus erythematosus (9.3%)	
7	Fibromyalgia (5.2%)	Raynaud’s syndrome (7.3%)	
8	Mixed connective tissue disease (3.5%)	Interstitial colitis (4.7%)	
9	Psoriasis (3.5%)	Rheumatoid arthritis (4.7%)	
10		Sarcoidosis (4.7%)	

Note: For brevity, this table does not include the concurrent ADs reported only once, except in the case of PSC since the sample size is so small.

D. The Call for More Studies

Although I conducted an extensive literature review, I have not yet found a study that proposes patient education to help patients and providers look for warning signs of concurrent ADs. Instead the focus is on calling for more rigorous studies to determine the prevalence of concurrent autoimmune diseases. Feld and Heathcote,⁷ call for “further rigorous epidemiological studies...to truly define the incidence, prevalence, familial risk and disease associations of PBC, AIH and PSC in a variety of populations over time. This information will lead to advances in the understanding of the definition and the pathogenesis of these complex diseases.”

To help standardize future epidemiological studies of ALDs, Metcalf and James⁷ propose a set of specific guidelines to be followed:

1. stringent case inclusion criteria;
2. clear definition of date of disease onset;
3. well defined study period, area and population;
4. multiple case-finding methods;
5. rigorous tracing of all possible cases.

Feld and Heathcote⁷ describe the important of these strategies:

[The researchers observed] that 23.4 percent of patients in a study in north-east England were detected through a case-finding mechanism that included tracing all patients with positive antimitochondrial antibody testing, reviewing hospital admission records, as well as surveying all general internists in the region. It was also noted that up to 37 percent of patients in this study had not previously been identified as having PBC, despite having symptoms, signs or laboratory abnormalities consistent with this diagnosis. Together these observations suggest that a significant number of cases of PBC may be missed if studies rely on physician surveys only.

Although narrowing down prevalence rates will help health care providers in the long run, patients still need education on the chances of developing a concurrent autoimmune disease, including possible warning signs of symptoms, to lessen the severity of the AD by receiving treatment as soon as possible. And helping patients to recognize symptoms of concurrent ADs may help determine prevalence rates.

Endnotes

¹ Carmella et al.¹⁴ report that PBC typically affects women between 35 and 45 years old, although Feld and Heathcote⁷ find it typically affects women between 40 and 65 years.

¹ Feld and Heathcote⁷ write, "Despite having strong British heritages in both countries, some of this disparity likely reflects true regional variation; however, study design almost certainly accounts for a portion of the observed differences." In fact, in Victoria, Australia, Sood et al.²⁰ found higher prevalence in British, Italian, and Greek immigrants than in the native-born population.

¹ The differences between AIH types is very clinical. Zachou et al.²⁶ write, "According to the pattern of autoantibodies detected in AIH patients, a subclassification of the disease into three types was proposed in 1994. AIH type 1 (AIH-1) is characterized by the presence of antinuclear antibodies (ANA) and/or smooth muscle autoantibodies (SMA) which may associate with perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). AIH type 2 is characterized by the detection of specific autoantibodies against liver and kidney microsomal antigens (anti-LKM type 1 or infrequently type 3) and/or antibodies against liver cytosol type 1 antigen (anti-LC1). AIH type 3 is characterized by autoantibodies against soluble liver antigens (anti-SLA) or to liver-pancreas antigen (anti-LP)."

¹ Incidence and prevalence rates differ depending on the study, which researchers^{6,13,15} attribute to an inclusion of viral hepatitis prior to the introduction in 1998 of the Autoimmune Hepatitis Group Revised Scoring System, as no standardized way of evaluating patients with AIH existed previously. Feld and Heathcote⁷ write, "Clearly more study is needed to better define the global prevalence of AIH. Because of the marked heterogeneity of patient populations and the inability to exclude hepatitis C in the earlier studies of AIH, it is difficult and likely inappropriate to compare study results. A rigorous epidemiological study of AIH applying the AIH revised scoring system for diagnosis is needed to accurately define the burden of this disease."

¹ In Japan, the age of onset has shifted through the past three decades. From 1966–1975, the peak age was 40–49; from 1975–1985, the peak age of onset was 50–59 years; and as of 1999, the age has shifted to 60–69 years.¹³

¹ The frequency of human leukocyte antigens (HLA markers) that affect susceptibility to AIH varies between ethnic groups. Researchers^{30,31} find that HLA markers DRB1*0301, DRB1*0401, and DRB1*1301 are genetic risk factors for some white European and North American patients with type 1 autoimmune hepatitis. In Japanese patients, DRB1*0405 is the principal risk factor,^{30,31} while DRB1*1301 in Argentines¹² is the suspected alleles. In Italy, DRB1*0301 occurs more frequently in Italian patients with type 1 AIH.³¹ Interestingly, two different HLA markers are present in two Latin American mestizo (mixed Spanish and Amerindian ancestry) populations. In mestizo Venezuelans, type 1 AIH is associated with DRB1*1301 and DRB1*0301 alleles,^{30,31} while in mestizo Mexicans, DRB1*0404 is the suspected allele.

¹ In Japan, patients with AIH have concurrent autoimmune disorders such as RA (9.8 percent), Sjögren's syndrome (9.8 percent), thyroiditis (9.8 percent), and PBC (2 percent). Japanese patients with PBC have Sjögren's syndrome (20.8 percent), RA (5.6 percent), Raynaud's (5.4 percent), thyroiditis (4.6 percent) and UC (1.3). Those with PSC have UC (20 percent), Crohn's disease (5 percent). In Taiwan, PBC patients have thyroiditis (17 percent) and Sjögren's syndrome (2 percent), while in Thailand, AIH patients present with thyroiditis (19 percent) and PBC patients with Sicca syndrome (11 percent), thyroiditis (11 percent), and RA (11 percent).¹³ In Brazil, of 227 patients studied with AIH, 27 (11.9 percent) had associated autoimmune diseases, with the most oft cited being thyroiditis (22.2 percent), Celiac disease (14.8 percent), vitigilo (14.8 percent), mixed tissue connective disease (11.1 percent), and diabetes type 1 (11.1 percent).⁵

¹ According to Czaja,³³ "Liver tests may or may not improve after gluten restriction, and this variability of response may reflect the relationship of the celiac disease to the liver condition. Gluten restriction in celiac disease that is concurrent with rather than etiologic of the liver dysfunction may have little or no effect on the liver tests. Clinical phenotypes, however, do not predict the presence of celiac disease or its importance in the liver disorder, and the prevalence and clinical relevance of this diagnosis justify a liberal screening strategy."

¹ Despite other research^{7,22,23,27,29,30} conducted on concurrent ADs with patients who have an ALD, missing in this table for PBC are IBD, Celiac disease, and UC; for AIH, diabetes type 1 and RA.

III. DESCRIPTION OF PROPOSED RESEARCH

A. Research Question and Hypothesis

Determining the prevalence rate of concurrent ADs in patients with ALDs will assist in educating patients about the prevalence of developing a concurrent AD and their warning signs. This epidemiological and anthropology study aims to measure and assess a random sample of the population with one or more autoimmune liver diseases through the following goals:

1. Measure baseline knowledge regarding risk factors, symptoms, and treatment of most prevalent concurrent ADs (Sjögren's syndrome for those diagnosed with PBC; RA, Celiac disease, and autoimmune thyroiditis for AIH patients; and IBD for patients with PSC);
2. Document the overall prevalence of concurrent ADs and the relationship between age, gender, ethnicity, country of origin, educational level, income, and self-reported risk factors (including family history and environmental associations, e.g. history of viral infections, medications, and herbal treatment).
3. Determine the incidence of concurrent ADs based on age, gender, ethnicity, and other relevant clinical, environmental, and demographic factors.
4. Identify possible risk factors for the ADs associated with ALDs.
5. Assess health education resources and knowledge related to most prevalent associated ADs compared to a control population.

B. Subjects

The project team will enroll patients with PBC, AIH, and PBS (diagnosed and documented by stringent case inclusion criteria with a clearly defined date of disease onset) by questionnaires sent to six US tertiary referral centers with hepatology specialists and matched by random-digit-dialed controls for gender, age, ethnicity, and education level, and geographical location. Subject characteristics of the intended population group include:

1. Diagnosis of one or more ALD, with respondents with AIH have been diagnosed with the International AIH Revised Screening;
2. Age range of 18 to 60 years;

3. Female-to-male ratio depending on ALD diagnosis:
 - a. Female-to-male ratio of 13:1 among participants with PBC,
 - b. Female-to-male ratio of 4:1 among participants with AIH,
 - c. Female-to-male ratio of 1:2 among participants with PSC.
4. Based on the population determined by the 2006 American Community Survey estimates, ethnic make up of 74 percent White (from both northern and southern European backgrounds), 12 percent African American, 15 percent Latino, 4 percent Asian, and 1 percent American Indian and Native Alaskan.
5. Education level that reflect the US population in 2006, including 16 percent with less than a high school diploma, 30 percent with a high school diploma, 27 percent with some college or associate's degree, 17 percent with a bachelor's degree, and 10 percent with a graduate or professional degree.
6. The participants will be located within a 100 mile radius of tertiary referral centers for liver diseases across the US, including in Baltimore, San Diego, New York City, Miami, Dallas, and Chicago.
7. Knowledge of ADs associated with ALDs. In one control group, study participants will have not received education from their (diagnosing) physician about associated ADs, including prevalence, risk factors, and warning signs. In the other control group, study participants will have received education about associated ADs.

C. Study Design

This five-year longitudinal study will be part retrospective and part prospective study of patients (characteristics described above) seen between 2000 to 2013 who are diagnosed to have PBC, PSC, and/or AIH as per the International AIH Revised Scoring System. This study will be phased into three periods over five years.

Phase I. Months 1–6. Protocol Development.

Phase II. Months 6–54. Epidemiological and Anthropological Studies Implementation.

Phase III. Months 55–60. Final Data Analysis and Close-out of the Epidemiology Study Centers and the Data Analysis and Administrative Core.

1. Sample size

The required sample size in each group is 385 and so the total sample size is 770 people. Based on the hypothesis, the sample size was calculated to detect a difference between two proportions, i.e. a group with multiple risk factors for developing a concurrent AD and a group with without multiple risk factors (risk factors) of 10 percent with 80 percent power and significance level of 0.05 (two-sided).

2. Study setting

The prospective study will take place over a five-year period from 2008 to 2013. The retrospective part of the study will review study participants who were diagnosed with an ALD from 2002 to 2007. The main study site will be the University of Maryland, and we will work with hepatologists at five other tertiary medical centers nationwide. The following is a list of the centers who have agreed to partner with this research team as epidemiology centers.

- a. University of Maryland School of Medicine, Baltimore
- b. University of California, San Diego
- c. Mayo Foundation, Chicago
- d. Robert Wood Johnson Medical School, Piscataway NJ
- e. University of Miami
- f. University of Texas Southwestern University Medical Center, Dallas

D. Data Collection

1. Timeline

The timeline that follows is based on the National Institutes of Health timeline recommended for longitudinal chronic disease studies.⁴⁷

Phase I. Protocol Development

This phase includes the review of common and accepted definitions of ALDs and concurrent ADs. The epidemiology team will develop a standardized questionnaire to be administered to study participants based on these accepted definitions. They will establish protocols for carrying out the prevalence, incidence, and risk factor studies. The project medical anthropologist and health educator will also develop data collection instruments to assess patient education and evaluate them prior to implementation.

Year 1 (months 1-6). Develop the study protocol for the collaborative studies. The database will be established by the Data Analysis and Administrative Core for the prevalence study and initial

work will begin for the remaining studies. The database for relevant demographic and clinical information to be obtained from the parent database of the accessed studies will also be established.

Phase II. Epidemiological and Anthropological Studies Implementation

We will conduct the first study to determine prevalence (months 1–12 months of Phase II). This will be in two concurrent parts, Part A, the retrospective study, and Part B, the prospective study. Upon the establishment of the prevalence of concurrent autoimmune diseases among the participants with one or more ALDs, the incidence will be assessed over a 36-month period (months 18–54 of Phase II) retrospectively and prospectively.

During the same period of time during which the incidence study is conducted, a study of risk factors and an assessment of need for patient education will be performed. Concurrent with studies in Phase II will be analysis of the prevalence data and preparation and publication of manuscripts in peer-reviewed scientific journals. We will also perform interim analyses of findings from the incidence, risk factor, and patient education need.

Year 1 (months 7–12). Initiate the retrospective and prospective prevalence study. Refine the protocol for incidence and risk factor studies. Database development will continue by the Data Analysis and Administrative Core. Obtain relevant demographic and clinical information from parent databases.

Year 2 (12 months). Begin the retrospective and prospective incidence and risk factor studies. At the end of Year 2, begin writing papers on the design of the study and prevalence study findings. Continue database development (Data Analysis and Administrative Core). Obtain relevant demographic and clinical information from parent databases.

Year 3 (12 months). Continue incidence and risk factor studies. Implement qualitative patient education study. Manuscripts describing the prevalence will be completed in Year 3. Obtain relevant demographic and clinical information from parent databases.

Year 4 (12 months). Continue incidence study and complete risk factor studies. Continue patient education study. Interim analyses continue for these studies. Obtain relevant demographic and clinical information from parent databases.

Year 5 (months 1–6). Complete incidence and patient education studies. Interim analysis continues for these studies. Obtain final demographic and clinical information from parent databases.

2. Variables

For the retrospective part of this study, all participants will have been diagnosed over a period of five years (2002–2007) with one or more autoimmune liver diseases. For both the retrospective and prospective parts, we will collect detailed medical histories of these participants, including disease

onset, such as diagnostic indicators (laboratory results for liver functions and antibodies; liver biopsy, ultrasound, and cholangiography results); family history of autoimmune disease; genetic markers; and environmental factors; such as viral infections, medications, and herbal treatments.

In regards to independent variables, the study participants will have to be conclusively diagnosed with PBC, PSC, and/or AIH. Participants diagnosed with AIH must have been diagnosed using the International AIH Revised Scoring System.

As for measuring variables, the research team will collect contact information, including telephone number and email address, for those that agree to be a part of this study. Patients who wish to be a part of this study must sign a consent form releasing their medical records to the research team, per the HIPAA rules and IRB standards. Based on the results of the informal survey conducted for this research proposal, the feasibility of contacting study participants initially and obtaining follow-up information and their experiences seems sound. The survey respondents appear to be very interested and active in obtaining the latest research on ALDs and concurrent ADs and hold strong opinions. Although this is a small proportion of the population diagnosed with ALD, it may be construed that the sample population for this research study will also want to participate in this study.

3. Data collection instruments

The data collection instruments we will use include a modified version of the US National Health and Nutrition Examination Study (NHANES IV) questionnaire to evaluate associations between PBC, AIH, and PSC and social, demographic, personal and family medical histories, lifestyle, and environmental factors in affected individuals. To be developed by the research team are the medical record abstraction and the patient education semi-structured interview guide. We will also develop a consent form for the study participants to release their medical records.

E. Data Analyses

1. Timeline

Phase III. Final Data Analysis and Close-out of the Epidemiology Study Centers and the Data Analysis and Administrative Core

Final analysis of results from the incidence, risk factor, quality of life and functional status, and health resource utilization studies will be performed during a six-month period in Phase III. In addition, manuscripts will be prepared during this phase for publication in peer-reviewed scientific journals. The Epidemiology Study Centers and the Data Analysis/Administrative Core will also be closed-out during the final two months.

Year 5 (months 7–12). Complete final data analysis for the incidence, risk factor, and patient education studies. Prepare manuscripts and report results at scientific meetings and in peer-reviewed scientific journal articles. Close-out of both the Epidemiology Study Centers and the Data Analysis/Administrative Core will take place during months 10–12.

2. Method

To control for the possible confounding variables of age, gender, race/ethnicity and education in analyzing the prevalence of concurrent ADs, the multivariable logistic regression model will be used. In adjusting for multiple comparisons, the Bonferroni method will be applied by dividing the over all α level of .05 by the number of implied comparisons. For example, in testing for ethnic differences there are several implied comparisons including whites vs. Asians, Latinos vs. African Americans, etc. Sample weights which account for the differential selection probabilities and adjust for non-response and non-coverage will be incorporated in order to produce unbiased estimates of percentages. The standard errors will be estimated by linearization, a design-based approach.

We will analyze the study participant interviews on the need for patient education by transcribing the interviews and coding and analyzing the text for themes.

3. Data analysis software

The statistical programs SAS version 9.02 (SAS Institute Inc, Cary, NC) and SUDAAN (Research Triangle Institute, Research Triangle, NC) will be used. We plan to run cross tabs to compare prevalence for demographic data against covariables. The analysis will include logistic regression analysis to analyze trends in incidence and prevalence. The differences between different groups will be compared using t-test, the Mann Whitney U test, χ^2 , (two by two with Yates' correction) and Fisher's exact test, as appropriate. Two-sided p values < 0.05 will be considered as statistically significant.

We will transcribe the study participant interviews using a word processing software, and analyze and code the text for themes using ATLAS.ti version 5 (ATLAS.ti GmbH, Berlin, Germany).

F. Institutional Review Board

We will procure approval from the University of Maryland Institutional Review Board to conduct this study. As we will use HIPAA-protected health information, we will provide each study participants with a consent form.

G. Study Limitations

Ethical consideration must be taken into account. It is ethnically unfair if patients who develop an ALD are purposefully not told by their health care provider/diagnosing physician about the chances

of developing a concurrent AD. The provider may not tell a patient in order to protect the patient from further stress of worrying about other, although 90 percent of the informal survey respondents agree that despite being on the lookout for warning signs, they would rather be informed of the possibility of developing another. Some of the respondents perceive that because they were not informed, they did not push for a diagnosis of their symptoms and later found when finally diagnosed that their concurrent AD was at a more severe phase than expected.

To avoid this ethical conflict, we will request that all health care providers providing treatment to study participants sign an agreement to not withhold any information, including patient education of concurrent ADs (e.g. risk factors and warning signs and symptoms), from study participants.

We have found in the review of the literature that incidence and prevalence rates of ADs, including ALDs, have increased over the past three decades. We cannot control this increase, but instead hope to document it through this study. In comparing the results of the retrospective study with the prospective study, we may find that incidence and prevalence of ALDs and concurrent ADs may have increased from the retrospective over the study period. Our statistical analysis will weigh this rate of increase, if needed. However, we will document the increase, if it does occur, and publish it along with our overall findings.

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VI. PERSONNEL

Throughout the course of the pilot program, many people will be needed to fulfill important roles so that strategies can be implemented. As this project is both qualitatively and quantitatively based, it is important to have an interdisciplinary team of experts including epidemiologists and medical anthropologists.

Primary Epidemiology Study Center Team

Sarah Sug Yoon, RN, PhD

Principal Investigator and Chief
National Health and Nutrition Examination
Survey

National Center for Health Statistics, CDC
Noted clinical epidemiologist; expert on
epidemiology of chronic disease. Will oversee
the project and report findings directly to
funding agency.

TBD

Project Manager
Will manage the project and staff from start to
close out, including maintaining the budget
and supervising project teams.

Epidemiology Team

Alex S. Befeler, MD

Hepatologist
St. Louis University Medical Center
Noted autoimmune liver disease specialist. Will
provide technical assistance on diagnosis
confirmation of study participants.

Alessio Fasano, MD

Autoimmune Disease Specialist
The Center for Celiac Research, University of
Maryland

Well published autoimmune disease specialist.
Will provide technical assistance in diagnosis
and patient education of associated
autoimmune diseases.

Mary K. Washington, MD

Pathologist
Vanderbilt University Medical Center
Noted pathologist specializing in ALD. Will
provide technical assistance on diagnosis
confirmation of study participants.

TBD

Research Epidemiologist (2)
Department of Epidemiology and Biostatistics,
University of Maryland
Will design and disseminate data collection
forms, supervise quantitative data analysis,
prepare findings for presentation, and
supervise epidemiology research assistants.

Medical Anthropology Team

Jackie Donaldson-Lopez, MAA

Medical Anthropologist
Department of Anthropology, University of
Maryland

Expert in the chronic liver disease experience. Will assess patients' need for concurrent AD education and evaluate providers willingness and ability to provide patient education, and analyze interviews for common themes.

TBD (graduate student)

Research Assistant (2)
 Department of Anthropology, University of Maryland
 Will assist in interviewing patients and analyzing qualitative data.

Evaluation Team

Mary Odell Butler, PhD

Evaluator
 Battelle Centers for Public Health Research and Evaluation
 Over 30 years of evaluation experience in large scale research projects. Will conduct process evaluation early on to assess project and impact evaluation at end of project. Will write end-of-project report for funding agency.

TBD (graduate student)

Research Assistant (2)
 Department of Anthropology, University of Maryland
 Will assist with evaluation and writing evaluation report.

Data Analysis Team

TBD

Biostatistician (2)
 Department of Epidemiology and Biostatistics, University of Maryland
 Will analyze quantitative data.

TBD (graduate student)

Research Assistant
 Department of Epidemiology and Biostatistics, University of Maryland
 Will enter statistical data into computer and assist with analyzing data.

Administrative Core

TBD

Contracts Manager
 Will manage and periodically review contract.

TBD

Project Accountant
 Will process invoices and prepares balance sheets, profit and loss statements, and other financial reports.

TBD

Administrative Assistant (2)
 Will assist with administrative duties, including scheduling interviews, preparing reports, project close out, and other duties as assigned.

Secondary Epidemiology Study Center Teams

Principal Investigator

Tertiary Referral Center

Will oversee the Epidemiology Study Center at this center.

Project Coordinator

Tertiary Referral Center

Will track and report the secondary Epidemiology Study Center activities.

Data Entry Clerk

Tertiary Referral Center

Will enter quantitative data.

Administrative Assistant

Tertiary Referral Center

Will assist with administrative duties, including scheduling interviews, preparing reports, project close out, and other duties as assigned

VII. BUDGET

This budget is provided for the entire five-year length of the proposed project. Estimates are based on 2008 US dollar rates.

During Phase I (First 6 months of Year 1), the budget will be for development of the protocol by the Epidemiology Study Centers in collaboration with the Data Analysis and Administrative Core. The Epidemiology team will begin to create the database necessary to accommodate pooled data for the prevalence and incidence studies. A database for relevant clinical and demographic information obtained from the "parent" (primary) database for the ongoing studies/patient databases will also be established.

During Phase II (the second six months of Year 1, Years 2, 3, 4, and the first 6 months of Year 5), the budget reflects the initiation of the prevalence, incidence, risk factor, and patient education studies. The travel budget for Phase II is be estimated based on travel for the Principal Investigator and the Project Manager for both the Epidemiology Study Center and the Data Analysis/Administrative Core. Budgets for the Data Analysis and Administrative Core include travel for the hepatology and AD consultants.

EXPENSE DETAILS	BUDGETED	NOTES
ADMINISTRATIVE		
Salaries and wages	1,400,000.00	
Employee benefits	50,000.00	
Payroll taxes	10,000.00	
Insurance	30,000.00	
Office supplies	5,000.00	
Travel & entertainment	7,800.00	PI & PM travel to research sites
Postage	3,000.00	Shipping of materials to research sites
Furnishings	0.00	Provided by home study center
Total admin. expenses:	1,505,800.00	
SERVICE & EQUIPMENT		
Utilities	0.00	Provided by home dept/agency
Telephone and DSL	12,000.00	
Equipment purchases	3,000.00	
Rent & maintenance	0.00	Provided by home dept/agency
Computer	0.00	
Total S&E expenses:	15,000.00	
Total	\$1520,800.00	

APPENDIX A. INFORMAL SURVEY RESULTS

Conducted over a five-day period in May 2008 and sent to four online ALD support groups, this survey sought to assess the prevalence of ALDs and concurrent ADs among support group members, as well as evaluate the need for patient education. The survey results follow.

1. Epidemiology of ALDs

Question 1. Tell me about your autoimmune liver disorder (ALD). What type do you have?		
Answer Options	Response Percent	Response Count
Primary biliary cirrhosis (PBC)	50.0%	44
Autoimmune hepatitis (AIH)	26.1%	23
Primary sclerosing cholangitis (PSC)	0.0%	0
PBC and AIH	21.6%	19
PSC and PBC	0.0%	0
PSC and AIH	2.3%	2
All three	0.0%	0
<i>answered question</i>		88
<i>skipped question</i>		3

Question 2. Do you have another diagnosed or suspected AD?		
Answer Options	Response Percent	Response Count
Yes	47.7%	42
No	37.5%	33
Not sure	14.8%	13
<i>answered question</i>		88
<i>skipped question</i>		3

If you answered yes or unsure for question 3, what AD(s) have you been diagnosed with or think you have?	
Answer Options	Response Count
	49
<i>answered question</i>	49
<i>skipped question</i>	42

Number	Response Text
1	graves disease
2	psoriasis
3	Lupus, sjogren's syndrome
4	Scleroderma Sjogren's syndrome
5	Autoimmune hepatitis, celiac disease, interstitial cystitis.
6	Hashimoto's Thyroiditis
7	Graves disease, which is autoimmune hyper-thyroid, confirmed dx
8	hypoglycemia (confirmed) & lupus (suspected)
9	Sjogren's syndrome
10	questionable for Lupus & Raynaud's
11	Reynauds
12	polyarthritis, fibromyalgia, sicca,
13	Endrometrosis have had this since 1983
14	JRA and Lupus. I left 1. blank because I had Hep. A when I was 18, and now being tested for further liver functions.
15	Psoriasis arthritis
16	AD of the liver
17	Arthritis
18	Sicca Syndrome, Osteoporosis, osteoarthritis, still working on diagnosis others
19	polymalgia rheumatica, raynaud's, osteoarthritis,undifferentiated connective tissue disorder
20	Sjogren's
21	Cryptogenic hepatitis, Hashimoto's Thyroiditis
22	Sjorgrens syndome. secondary osteorporsis
23	VASOVAGAL SYNCOPE
24	PBC
25	Raynaud's
26	RA, OA, possibility of being diabetic & having a thyroid problem & looking at others!
27	Hashimoto's Thyroiditis, Raynaud's, Carpal Tunnel, Gallbladder disease, Gerd.
28	Secondary Amyloidosis, Psoriasis, type II Diabetes. The Amyloidosis is caused by a yet to be discovered AD. Although I've been tested for lots of things, my doctors have still not found the underlying disease.
29	Lupus
30	osteo arthritis; possible raynaud's
31	RA
32	Fibromyalga
33	Lupus
34	Hashimoto's Thyroiditis
35	Sjogren's Syndrome, Irritable Bowel Syndrome, GERD, Fibromyalgia
36	Sarcoidosis, E Nodosun, Cohen's Corneal Dystrophy, Hoshimotosis Thyroiditis, Celiac Sprue, Cryptitis, Coltis, Sjogren's Syndrome,
37	hypothyroidism, sicca syndrome
38	Low thyroid (diagnosed several years before AIH diagnosis), celiac sprue (tested negative twice with blood test, no biopsy yet, but stomach and joints feel better without wheat in diet)
39	sjogren
40	Allergies and autoimmune thyroiditis
41	suspect autoimmune thyroid disease/Hashimoto's

42	Psoriatic arthritis and psoriasis
43	Sarcoidosis, hypothyroidism (Hashimoto's thyroiditis), Sjögren's syndrome, Celiac disease
44	Sjogrens Disease
45	gluten intolerance
46	Autoimmune Hepatitis connective tissue disease sjorgrens syndrome borderline rheumatoid arthritis borderline thyroiditis
47	Raynauds,Osteoporosis,sjoeegrens,arthritis
48	Sicca, Osteoporosis, RA, poss. reynauds
49	Hypothyroidism osteoarthritis terminal ileitis

2. Patient Education

Question 4. When you were diagnosed with your first (or primary) AD, were you told that you (may) have an increased chance of developing another AD?		
Answer Options	Response Percent	Response Count
Yes	31.8%	28
No	63.6%	56
Not sure	4.5%	4
<i>answered question</i>		88
<i>skipped question</i>		3

Question 5. If you answered Yes to question 5, were you relieved or grateful that your health provider informed you about the chances of developing another AD?		
Answer Options	Response Percent	Response Count
Yes	69.7%	23
No	15.2%	5
Unsure	15.2%	5
<i>answered question</i>		33
<i>skipped question</i>		58

Question 6. If you answered No or Unsure to question 5, would you prefer if your health provider informed you about the chances of developing another AD?		
Answer Options	Response Percent	Response Count
Yes	85.0%	51
No	5.0%	3
Not sure	10.0%	6
<i>answered question</i>		60
<i>skipped question</i>		31

Number	Response Text
1	better to know what to expect
2	to be alert for other symptoms/signs that may appear and their causes
3	I would want to be told so I could do research and take all precautions to not get another AD.
4	There are so many of them, I wouldn't know what to look for.
5	I think it is always best to know what you have or could have, that way you can do whatever possible to prevent anything else from happening or not "freak out" when another symptom "pops" up.
6	so that I wouldn't have been so shocked to discover I had PBC
7	Knowledge is power.
8	My AIH remained a mystery, until a doctor was familiar with my graves disease and then AIH was suspected. This would have saved me valuable time.
9	So I could attempt to be proactive in preventing developing other AD's
10	It might help in diagnosis of new symptoms
11	better knowing what may lie ahead
12	Knowing about the probablility of co-existing disease would have been helpful to managing my own care
13	Be Prepared! Also be able to prevent by changing life styles
14	knowledge and not wondering what was going on for a long time.
15	didnt even tell me that endrometrosis is a AD just found out.
16	Was told of both PBC/AIH at once. didn't learn of above til later
17	I like being about to have information about my health.
18	to identify with the spymptoms and seek medical help
19	need to know, but not grateful or relieved
20	being told gives you the education to change things for your health
21	so that I might recognize symptoms early and either do preventive measures or get proper medical care as appropriate
22	uncertain
23	So I could watch out for early signs of another AD
24	In order to be prepared
25	so I would be more in tune with my body and seek medical help for any unusual symptoms
26	being aware of symptoms to be treated sooner
27	Knowledge is power
28	If something happens to me, it would be helpful to have that possibility known.To alert future physicians to the possibility.
29	Just that there is an increased chance.
30	so that the appropriate test can be taken, and I can be aware that they exist!
31	Education enables prevention and slowing down of certain progressive conditions.
32	I would like to know any issues relating to my health
33	be better informed
34	the first was a surpise and i was uninformed, this way I will have more knowledge and be better prepared to deal with it if necessary
35	may not happen and was enough initially with first diagnosis
36	because it was enough to be told that I had PBC -it was very shocking.I was drip fed information by my consultant
37	I like to know what can I expect
38	might cause unnecessary anxiety (I did read about it though)
39	so that i can work out what is going on with MY body

40	Western medicine not open to alternative treatments. I would rather research it myself.
	I'm a firm believer in preventive medicine. Knowing that I need to look out for something could only be
41	beneficial in the long run.
42	Always better to be prepared in the long run
43	to be prepared, to be aware of possible symptoms
44	I like to know and deal with the facts
45	I already have so many ADs that it really doesn't make a difference to me.
46	If I had been aware, I might have been diagnosed with PBC years earlier!
47	to be honest I think it gives me one more thing to worry about
	because I want to be proactive in my health issue the sooner I know the better mentally for my mind to get
48	around it and get prepared for the next round of things to come
49	I like to be informed about everything
50	to watch for symptoms and get treatment if needed
51	To be better prepared for what more lies ahead.
52	I want to be prepared and to notice symptoms in early stage
53	To better control another AD
	PBC was diagnosed in stage one twenty five years after first diagnosis. Not sure I would have wanted to
	worry about every possible symptom for twentyfive years but might feel differently if the PBC diagnosis
54	had been difficult or delayed.
55	I would want to be told, but it sure was depressing
56	I would want to know so it could be managed early
57	So I would be more informed about the future.
	It would make my life much easier to know what symptoms to look for. E nodosum is always followed by
	Sarcoid. I would have sought treatment sooner, which would have led to less lung damage. Also
	Lofgrens Syndrome is a combination of Hoshimotos, Sarcoid and AIH, The prior knowledge would have
58	helped me get treatment before I went into liver failure.
59	I would find out soon enough, no sense worrying now
	My AIH was a mystery for such a long time. If something else as devastating were to happen, I would want
	to help direct the medical investigation. I requested the celiac blood test, after learning AIH patients have
60	a higher risk. Knowledge is better than ignorance.
61	need to be aware of anything else we are prone to.
	I believe we are the first diagnosticians of ourselves and need to be informed so we can bring symptoms
	to the attention of our physicians. We have to be our own advocates. I was misdiagnosed with AIH and
	was on prednisone for 6 months. I found a new hepatologist at the medical center and it was he that
	took me off of pred. and put me on Urso. It wasn't long after that when my LFT's went back to normal.
62	Good luck on your paper!
	I would want to be told as I would be better able to understand treatment and discuss it with my
63	physician.
64	So I could pay attention to problems and know to address them immediately.
65	wouldn't care either way
	My daughter was diagnosed at age 14. I am her advocate and am always looking for subtle changes
	therefore any information I can get whether heartbreaking or not helps me help her to live to her full
66	potential.
67	So I can prepare for it with research.
68	preparation and knowing what is possible is important.
	because it is important to be well informed about all aspects of your case so you can make your own
69	informed decisions
70	My first diagnosis was sarcoidosis years ago, followed by others over the years. It just would've been nice

	to know about the possibility before becoming really ill with AIH. I've now been told that such things as stress might increase the risk of developing AD's - had I known this, I could've tried to avoid the high stress life style that I had prior to getting AIH. On the other hand, had I been first diagnosed now, I would've been told about the possibility. Almost 20 years ago maybe the knowledge of these diseases wasn't the same it is now.
71	Prepare mentally for additional health problems
72	hep MD told me nothing about PBC, I wanted truth
73	Don't want to be "looking" for symptoms of another disease.
74	I would have been more insistent of having further testing when told there was nothing wrong with my thyroid and that my joint pain was 'normal degeneration'.
75	better to have all the info to understand treatment
76	prevention is the best medicine
77	Relief to find problems are not imaginary.
78	Just to be kept informed of my condition
79	one can only have so much food on the plate

3. Demographics

Question 8. Please tell me about yourself.		
Answer Options	Response Percent	Response Count
Current age:	100.0%	87
Age of diagnosis of first AD:	100.0%	87
Gender:	100.0%	87
City/Town:	90.8%	79
State:	75.9%	66
Country:	98.9%	86
	<i>answered question</i>	87
	<i>skipped question</i>	4

No.	Current age:	Age of diagnosis of first AD:	Gender:	City/Town:	State:	Country:
1	64	35	female	New York	NY	USA
2	31	20	female	Silver Spring	MD	USA
3	39	39	female	Mission	KS	USA
4	52	47	Femal	Doylestown	PA	USA
5	45	40	female	Villa Park	IL	USA
6	29	25	F	Toronto		Canada
7	64	57	Female	San Francisco	CA	usa
8	48	36	female`	adelphi	MD	us

9	35	29	F	greensboro	NC	USA
10	37	33	Male	Saint Petersburg	FL	America
11	57	36	F	Philadelphia	PA	USA
12	47	47	female	Weatherford	TX	USA
13	42	30	female	Westland	MI	USA
14	69	58	F	Bend	OR	USA
15	49	46	Female	Brisbane		Australia
16	47	23	female	southgate	MI	USA
17	34	8	Female	Ottawa		Canada
18	59	50	Male	Anderson	SC	USA
19	51	50	Male	Vancouver	WA	USA
20	63	2003	female	Twillingate, NL		Canada
21	55	51	female	St. Joseph	MI	USA
22	50	49	female	Lake Havasu City	AZ	USA
23	56	40	Female	Lake Tapps	WA	USA
24	75	69	m	Bergenfield	NJ	USA
25	55	55	female	Lebanon	OR	usa
26	73	2006	f	Tulsa	OK	USA
27	48	46	female		PA	us
28	54	53	Female	Kennewick	WA	USA
29	50	48	should be gender... male			USA
30	63	61	F	Tustin	CA	U.S.A.
31	35	33	M			Canada
32	54	49	f	Melbourne		Austarlia
33	50	44	rarely (M)	Nanaimo BC		Canada
34	53	51	female	altamonte springs	FL	usa
35	64	62	female	st Augustine	FL	usa
36	30	22	female	perth		australia
37	57	48	female	NEWCASTLE UPON TYNE		ENGLAND
38	29	27	female	Senta		Serbia
39	63	52	f.			Canada
40	56	44	F	Ann Arbor	MI	US
41	45	12	no too tired! female!	London		England UK
42	66	53	F	New City	NY	USA
43	68	68	F			Canada
44	57	54	F	Tucker	GA	USA
45	50	46	femail	Newark	CA	USA
46	54	51	F	McArthurs Mills		Canada
47	59	59	F		OR	USA
48	56	I was dx'ed with Psoriasis about 10 yrs ago.	female	Swampscott	MA	USA
49	48	27	Female	Arlington	TX	USA

50	41	33	f	north arlington	NJ	usa
51	61	54	female	Rochester	NY	USA
52	71	65	female	tampa	FL	usa
53	51	49	femal	Humble	TX	USA
54	42	33	female	Federal Way	WA	usa
55	57	56	female		PA	USA
56	60	60	Female	Colorado Springs	CO	United States
57	60	58	female	Vienna	VA	USA
58	53	50	female	Holden	MA	USA
59	67	38	female	Wilton	CT	USA
60	53	44	Female	Fort Myers	FL	USA
61	69	62	female	Ketchum	ID	US
62	68	60	female	Fenton	MI	united states
63	61	26	F	Broomfield	CO	USA
64	51	43	f	Amesbury	MA	USA
65	55	48	female	Eagle Creek	OR	USA
66	51	46	F	Fredericksburg	VA	USA
67	56	49	female	Zionsville	IN	USA
68	68 years	2000	Female	Mesa	AZ	United States of America
69	55	1980	F	Stamford	CT	USA
70	59	46	female	Austin	TX	USA
71	17	14	f		KY	USA
72	78	59	F	TEmples	TX	
73	64	13	female	Roscoe	IL	USA
74	54	54	f	scituate	MD	usa
75	57	55	female	Hartford	KY	USA
76	47	31	Female	Helsinki		Finland
77	56	55	female	Oceanport	NJ	USA
78	56	55	F	MPLS	MN	us
79	56	37	Female	Attleboro	MA	USA
80	40	39	female	baton rouge	LA	united states
81	53	43	Female	Cairns		Australia
82	34	28	female	dublin		Ireland
83	56	49	Female	Billingham		England UK
84	69	52	female	Salt Lake City	UT	USA
85	62	61	f	cincinnati	OH	usa
86	54	52	female	Vancouver		Canada
87	51	38	female	Hamilton,Ontario		Canada