IDENTIFICATION OF NOVEL TARGETS FOR PSYCHOSIS IN AD WITH REAL WORLD EVIDENCE AND NETWORK ANALYSIS APPROACHES

by

Peihao Fan

Bachelor of Science, Sichuan University, 2017

Submitted to the Graduate Faculty of

School of Pharmacy in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2019

UNIVERSITY OF PITTSBURGH

School of Pharmacy

This thesis was presented

by

Peihao Fan

It was defended on

April, 2019

and approved by

Xiangqun Xie, Professor, School of Pharmacy

Lirong Wang, Assistant Professor, School of Pharmacy

Robert A Sweet, Professor, Department of Psychiatry

Junmei Wang, Associate Professor, School of Pharmacy

Thesis Director: Lirong Wang, Assistant Professor, School of Pharmacy

Novel Targets Identification for Psychosis in AD with Real World Evidence and Network Analysis Approaches

Peihao Fan, MS.

University of Pittsburgh, 2019

Alzheimer's disease (AD) is a chronic neurodegenerative disease frequently seen in the aging process and causes significant loss of life quality and financial costs. Psychotic disorder also termed as psychosis, marked by failure to differentiate illusions from reality, is a major complication of AD (AD+P). About 50% of AD patients will develop psychotic symptoms including hallucinations and delusions. Therefore, a better understanding of the connection between AD and psychosis at the molecular level is urgently needed. Novel drug targets are critical in delaying the development of psychosis in AD. In this study, Real-World Evidence (RWE) data-mining and Network analysis approaches are combined to provide an inner view of the connection between AD and psychosis and help identify novel drug targets. Statistical analysis is performed on data of medication usage from the electronic medical records of AD patients with or without psychosis symptoms (AD+P vs. AD-P), survival analysis is also conducted on time to psychosis. Results showed that Vitamin D was significantly associated with delayed time to psychosis and also used more in AD-P patients than in AD+P patients. The network analysis also identified some high-impact genes in the overlapping part of AD and psychosis, including NOTCH4, COMT, CACNA1C and DRD3 which are related to calcium homeostasis. The combined results suggest a connection between AD+P development and calcium homeostasis and may provide a new direction for drug development.

Keywords: Alzheimer's Disease; Psychosis; Vitamin D; Calcium Homeostasis; Systems Pharmacology; Real-World Evidence

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I'm deeply thankful to my advisors Dr. Xiang-Qun (Sean) Xie and Dr. Lirong Wang for their guidance and support for my research during the past two years. I would also thank Dr. Junmei Wang for his kind encouragement, suggestions and powerful technical support for my thesis. Dr. Sweet Robert also provided me valuable suggestions about the thesis. Thank all of our group members for their help and guidance. Their suggestions in each group meeting are very informative and valuable. Thank all the committee members, Dr. Xiang-Qun (Sean) Xie, Dr. Lirong Wang, Dr. Junmei Wang and Dr. Robert Sweet for the valuable suggestions.

1.0 INTRODUCTION AND BACKGROUND

1.1 ALZHEIMER'S DISEASE

Alzheimer's disease(AD) is a chronic neurodegenerative disease commonly seen in the aging process[1], and the presence of AD is responsible for a significant decrease in the quality of life for the patients[2]. It's estimated that the cost of AD is $604 billion worldwide and will triple in 2050[3]. Major risk factors of AD including aging, head injury, low education level, hyperlipidemia, hypertension, homocysteinemia, diabetes mellitus, and obesity[4-7]. The development of AD is divided into four stages based on cognitive and functional impairment: pre-dementia, early, moderate and advanced[8].

In the pre-dementia stage, the onset symptoms are easily mistakenly considered as a result of aging or stress[9] such as short term memory loss[10] and reduced daily activities[11]. Other subtle problems include decreased function in attentiveness, planning, flexibility and abstract thinking[12]. The functional loss in semantic memory is also a remarkable symptom in the onset stage of AD[12]. It's hard to catch these symptoms in this stage because these symptoms can appear long before one can be diagnosed as AD, up to eight years, and these symptoms can also be the sign of other neurological disorders. [12]. Psychotic symptoms like apathy, depressive and irritability can also be observed in this stage[13]. The preclinical stage of AD is also termed as mild cognitive impairment (MCI)[14], and it's commonly considered as the translational stage of normal aging and dementia,

and 50% to 70% of dementia is caused by AD[15-16]. The MCI with memory loss as dominating symptoms is considered as a prodromal stage of AD[17].

In the early stage of AD, the gradual decline in learning abilities and significant memory loss leads to a clear diagnosis. A small part of the patients may show different prominent symptoms other than memory loss, such as difficulties with speech and vocabulary, executive functions, perception (agnosia), or execution of movements (apraxia)[18]. Different kinds of memories influenced by AD present various patterns. The more rigid memories, like episodic memory (older memories of the person's life), semantic memory (facts learned), and implicit memory (the memory of the body on how to do things) are affected less than the freshly gained memories[19-20]. Language problem in this stage is mild and characterized by a limited vocabulary and decreased fluency in daily communication[18, 21]. Most patients are still capable of basic communication, writing and drawing tasks, but assistance may be needed when more complex speech and language are needed in daily life[18, 21-22].

The moderate stage of AD is characterized as the loss of capability in performing most common daily activities independently. Speech difficulties, reading and writing impairments and uncoordinated complex motor sequences, as well as the falling risks, grow as the progress of AD[18]. During this stage, the patients' memory problem get even worse that they may have trouble recognizing close relatives[18] as the intact long-term memory in the previous stage is under danger. Sundowning, illusionary misidentification and other delusion symptoms may appear in about 30% of the patients[18, 23]. These symptoms can create significant stress for the relatives and caregivers of the patients and moving the patients to a long-term care facility become a beneficial option[24].

In the advanced stage, the final stage of AD, patients' capabilities are very limited in taking care of themselves and largely dependent upon caregivers[18]. Language is significantly reduced to

simple words or phrases and eventually complete loss of speech[22]. However, patients can still understand emotional signals to certain extent but extreme apathy and exhaustion are commonly seen[18]. Muscle mass loss and mobility deterioration is so severe that patients are bedridden without the ability to move freely and need caregivers to feed them and take care of their personal hygiene. The cause of death is usually externally factored accompanying the long-term bed-resting lifestyle such as pressure ulcers or pneumonia, rather than AD itself[18].

1.2 PSYCHOTIC DISORDERS

Psychotic disorder, also termed as psychosis, marked by the failure to differentiate illusions from reality[25]. Symptoms may include delusions, hallucinations, disorganization and other negative symptoms[26]. Sleep problems, social withdrawal, lack of motivation, and difficulties carrying out daily activities are also observed in psychosis patients with a relatively rare pattern[25, 27-30].

Hallucinations are defined as perceptions or thoughts that occur in the absence of a corresponding external stimulus and input[31-32]. It's worth noticing that hallucinations are often confused with illusions, or perceptual distortions, which are the misperception of the external stimuli. The major difference between hallucination and illusion is that illusions based on something do exist but hallucination doesn't. Furthermore, hallucinations can have numerous forms of expressions from simple sensations like lights, colors to complex and detailed experiences, but hallucinations are generally described as being a vivid, uncontrollable experience[32]. Auditory hallucinations, particularly experiences of hearing voices that don't exist, are the most frequently observed and often the dominant feature of psychosis patients, and can

also be observed in 15% of people for general populations[33]. Auditory hallucinations heard are most commonly intelligible voices which make sense and interpretable. Frequencies and contents are significantly different among populations from different cultural and other background information. Patients who suffering auditory hallucinations can normally be able to identify the loudness, location of origin, and may be able to assign an identity to the voices. Hallucinations may contain instructions for a person to do something and it can be dangerous when combined with delusions[32, 34]. Visual hallucinations are reported in approximately a third of people with schizophrenia and often related to animate objects and changing in lights and colors. The contents of visual hallucination are mostly differed from proprioceptive information and challenge the common sense of patients, ground tilting is a frequently reported example[34-35].

Delusions are strong beliefs patients held against reality or believe in despite contradictory evidence[36]. The difference between delusional thinking and the full-down delusion is how sever does the symptom influence the patients' normal life[32]. Despite the great influence of different cultures have on delusions, multiple themes are commonly seen. The most frequently seen type of delusion is the persecutory delusion, where a person believes that an individual, organization or group is attempting to harm them. In addition, many other subtypes of delusion are also reported: 1)delusions of reference (beliefs that a particular stimulus has a special meaning that is directed at the holder of belief); 2)grandiose delusions (delusions that a person has a special power or importance); 3)thought broadcasting (the belief that one's thoughts are audible); 4)thought insertion (the belief that one's thoughts are not one's own)[32, 37].

Disorganization can be split into two categories: disorganized speech or thinking and grossly disorganized motor behavior[32]. Disorganized speech, also termed as formal thought disorder, is the disorganization of thoughts that is speculated from speech. The signature symptoms

of that are switching topics quick and often, jumping to topics that are not related to each other, incomprehensible speech, etc. Disorganized motor behavior includes many kinds of behavior pattern with no rational, like repetitive, weird, or sometimes aimless movements. Disorganized motor behavior normally doesn't include catatonia, and although it was reported as a dominant symptom in the past, it's not frequently reported nowadays. The reason behind it remains unclear, it may be a beneficial effect for a certain treatment or some factors changed within the development of the society and nutrition structure[32].

Negative psychosis symptoms (NPSs) include a variety of observations and phenomenon include reduced emotional expression, decreased motivation, and reduced spontaneous speech[38-39]. However, the treatment for the NPS is not effective due to the unclearness about its development process and mechanism.

1.3 PREVALENCE, CHARACTERISTICS, AND CONSEQUENCES OF PSYCHOSIS IN AD

1.3.1 Prevalence of psychosis in AD

Psychosis is observed as a common complication of AD and patients with dementia. Literature reports that approximately 50% of patients with AD will have psychotic symptoms (AD with psychosis, AD+P) in the following years[40]. Studies have also shown that the proportion of people having delusions vary from 10% to 73%, and the proportion of hallucinations range from 21 to 49% in a clinical population[41]. As you can see from the numbers, the probabilities in different populations vary a lot and can reach a pretty high level of risk. Particularly, the patients in a clinic

population with Alzheimer's reported 60% of them suffering from delusions and 17% of them have to hallucinations[42]. In another study focused on the population in nursing homes with dementia, more than 90% of patients showed at least one abnormal behavior. To be specific, 60% of the residents have psychosis, 42% of them have depressed mood and 82% of them showed signs of activity disturbances or aggression[43]. As for community samples, the 18-month prevalence of a population over 65 years old with dementia showed that 19% of them had delusions and 14% had hallucinations[44]. Besides, different patterns are observed between Alzheimer's dementia patients and vascular dementia patients. Delusions are more frequently seen in Alzheimer's dementia, 23% vs. 8% and agitation is less frequent, 23% vs. 33%[45]. Patients with AD tend to believe they are in danger or something bad happens on them.

AD+P patients are considered as a subgroup of patients who have more severe symptoms, includes more significant cognitive impairment and a quicker cognitive decline speed[46]. AD+P is also associated with higher rates of co-occurring agitation[47], aggression[47-48], depression[49-50], caregiver burden[51], functional impairment[52], and mortality[53] than AD−P.

Different subtypes of psychosis are studied in multiple research. Twelve major negative symptoms are selected to report as the major subtypes of psychosis in AD: delusion, hallucination, apathy, depression, aggression, anxiety, euphoria, disinhibition, irritability, aberrant motor behavior (AMB), sleep disorder and appetite disorder[54]. They can be classified into 4 sub-syndromes: hyperactivity (aggression, disinhibition, irritability, aberrant motor behavior and euphoria), psychosis (delusion, hallucination and sleep disorder), affective (depression and anxiety,) and apathy (apathy and appetite disorder)[55]. Prevalence of the psychosis in AD through the 34 studies varied from 9% to 59%[56-89]. The overall pooled prevalence of delusion was 31%

(95% CI 27–35%), hallucination was 16% (95% CI 13–18%) and sleep disorder was 39% (95% CI 30–47%)[54].

From the results of the studies mentioned above, psychosis symptoms are very frequently observed in AD, and the prevalence of NPS varied widely in different studies and populations. Age and disease durations can affect the occurrences of psychosis in AD, especially for delusion[54, 89], older people do have a higher possibility of having delusions[90]. Hallucination is reported to associate with a younger age as a contrast to delusions[57], though further study is needed to explain this correlation. The rate of AD with psychosis (AD + P) is also related to the stage of AD, early stage has a relative lower prevalence of psychosis while middle and late stage have a higher risk of psuchosis[91-92].

1.3.2 Characteristics of psychosis in AD

It's always a problem to distinguish the symptoms of AD+P and pure AD because the cognitive impairment and neuropsychiatric symptoms presented in the process are complex and working in a synergic way. The major characteristic of psychosis in AD is the occurrence of delusions and hallucinations[90, 93]. Many developments of diagnostic criteria of psychosis in AD and measurements of psychotic symptoms are made[94-96], a detailed diagnostic criteria list can be found in **Table 1**. It's important to exclude schizophrenia for the presence of psychosis symptoms. The delusions of AD+P are often paranoid type, non-bizarre, and simple contrast with the complex delusion in schizophrenia. Visual than auditory hallucinations are more frequently reported in AD, schizophrenia behaves the opposite as contrast[57, 94].

Table 1 Diagnostic criteria of psychosis in AD [94]

A. *Characteristic Symptoms*
Presence of one (or more) of the following symptoms:
1.Visual or auditory hallucinations
2.Delusions
B. *Primary Diagnosis*
All the criteria for dementia of the Alzheimer type are met
C. *Chronology of the onset of symptoms of psychosis vs. onset of symptoms of dementia*
There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia
D. *Duration and Severity*
The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer. Symptoms are severe enough to cause some disruption in patients' and/or others' functioning.
E. *Exclusion of schizophrenia and related psychotic disorders*
Criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, or Mood Disorder with Psychotic Features have never been met
F. *Relationship to delirium*
The disturbance does not occur exclusively during the course of a delirium
G. *Exclusion of other causes of psychotic symptoms*
The disturbance is not better accounted for by another general-medical condition or direct physiological effects of a substance (e.g., a drug of abuse, a medication)
Associated features: (*Specify* if associated)
With Agitation: when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression
With Negative Symptoms: when prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present
With Depression: when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present

1.3.3 Consequences of psychosis in AD

Psychosis in AD can add a significant burden on the original situation of AD patients. AD+P patients are found to have a more rapid decline speed of the cognitive and memory functions, and can significantly increase the difficulty of caregivers[97]. The negative symptoms of psychosis will attach considerable distress to the patients and worsen their mental status[98-100]. In addition to the negative effects of delusion and hallucinations may cause, AD+P is also a helpful marker for certain adverse outcomes in AD. The most associated behavior disturbance with AD+P are agitation and aggression[101-103], depressive symptoms are also increased in AD+P patients[92, 104].

More severe functional impairment, higher rates of institutionalization, worse life qualities of patients and increased mortality will also occur in the AD+P patients[89, 105-110].

1.4 NEUROLOGICAL AND GENETIC FACTORS FOR PSYCHOSIS IN ALZHEIMER'S DISEASE

1.4.1 AD genetics

The genetic mechanism and pathways are extremely complex in AD and over 100 high penetrant and high impact mutations have been reported in three genes (APP, PESN1, and PESN2) in AD early onset development[111-114]. As in the late stage, the polymorphism of APOE is reported accounted for the increased susceptibility[115-116]. Twin study showed that the development of AD has a heritable feature and the type of AD is also related to genetics in the late stage of life, but the onset age of twins can vary widely suggesting the important role of environment factors[117]. However, recent studies revealed that the genetic contribution of the genes mentioned above is quite limited, a systematic study on over 700 AD patients from 75 families suggests that the actual contribution accounted by this polymorphism in the onset of AD is down to 7%–9%[118]. In the last decade, hundreds of more AD-related genes have been reported[119-124], almost every chromosome is involved in the human genome. Many efforts were made worldwide in the past decades and hundreds of reports of genetic associations between AD and polymorphisms in genes. A public database, AlzGene (http://www.alzgene.org/), was created to help to track and to interpret the increasing amount of information[125]. Currently, the database contains 1395 studies, 695 genes, and 2973 polymorphisms.

1.4.2 Psychosis genetics

Psychosis disorders are presenting with a strong heritability pattern[126]. But the cause of psychosis at a mechanic level remains largely unclear. As a result of the difficulties of establishing connections between physiological and pathological studies in human brain, locating the potential loci may be the best way for researchers to understand the pathogenesis of psychosis[127]. Genetic studies have identified some chromosomal regions that are suggested to have linkage with psychosis symptoms, including regions of 13q, 22q[128], 18[129] and 6q[130]. Within the suspected areas, many individual genes are also reported to be connected to psychosis including NRG1 (neuregulin 1)[131-132], DTNBP1 (dystrobrevin binding protein 1)[133], G72 (DAOA)/G30 (D-amino acid oxidase activator)[134], DISC1[135] (DISC1 scaffold protein). However, no consistent patterns have been discovered yet and no pathogenically relevant variants have been established, which bring more difficulties to the study of psychosis in AD.

2.0 METHOD AND MATERIAL

Two major methods are used in this study: Real-World Evidence data-mining and Network Analysis. Real-World Evidence data-mining is a method used by many healthcare researchers and adopted by FDA to monitor post-market safety and adverse events[136]. It can also help provide information about a healthcare product, like medications, in a more real and practical situation and reveal the complex inter-influence between different factors in the clinical setting[137-138].

The first part of the Real-World Evidence analysis involving the single drug usage is a reproduction of the results reported in our recent manuscript but with different calculation environment. The original report was prepared and calculated in SAS and R but python is used in this study. In addition, significant updates are made such as the drug combination analysis and the mechanism research using network analysis. In this study, network analysis[139] is used to explore the potential linkage between psychosis and AD, and to identify the primary connecting nodes of the two processes.

Results from Real-World Evidence and Network analysis are combined to provide useful information from phenotype to mechanism level. We compared the medication history of two groups of AD populations, AD patients with or without psychotic symptoms (AD+P / AD-P), where psychotic symptoms include hallucinations and delusions. AD+P patients represent a subgroup with poor outcomes and AD-P stands for a relatively better outcome. In the process of data analysis, multiple methods are used including chi-square, survival analysis, Cox regression and PPI (protein-protein interaction) network analysis.

2.1 SUBJECTS

Subjects were participants in the University of Pittsburgh ADRC, seen between May 2000 and August 2014[140]. Subjects were included if they had an initial primary diagnosis of mild cognitive impairment (MCI) [141-142] or probable or possible AD [143] after a clinical diagnostic evaluation consisting of a baseline neurological, neuropsychological and psychiatric evaluation, laboratory studies, and brain imaging with annual re-evaluation of neurological presentation, behavioral symptoms, cognitive tests, and functioning [144-147]. Initial and annual visits included the Mini-mental State Examination (MMSE)[148]. Telephone assessments were conducted at approximately six-month intervals between annual in-person visits, and they were also conducted at the time of annual assessment for individuals unable to return to the clinic. All subjects were required to have an age of onset of cognitive problems starting $\geq$60 years old and no current or prior psychosis, including no prior personal history of a primary psychotic disorder (e.g. schizophrenia).

Psychosis was assessed at visits and by telephone using the Consortium to Establish a Registry for Alzheimer Disease Behavioral Rating Scale (BRS) which was administered to an informant knowledgeable about the patients' symptoms. The informant's relationship to the participant (available for 97.8%) and frequency of contact (available for 90.9%) was recorded. Informants were predominantly spouse (55%) or an adult child (38%). 83% had contact (5 or more days/week with the participant; 63% lived with the participant.

Patients were classified as psychotic if they had one or more of BRS items #33-45 rated as present at least three to eight days in the past month: delusional misidentification of people, self or objects; paranoia, beliefs of abandonment or infidelity; believing someone is an imposter, belief that characters on television are real; belief that there are people in or around house that aren't

there, belief that a dead person is still alive, belief that their house is not their home, auditory hallucinations, visual hallucinations. Symptoms were not rated if they occurred during an episode of delirium, were medication induced, or if the symptoms were hypnopompic or hypnogogic.

All procedures were conducted under the research protocol approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from subjects and/or their proxy.

2.2 MEDICATION INFORMATION

Information on all medications used by participants was collected at initial and annual visits, and during telephone evaluations. For AD+P patients, we only considered their medication usage from the date of the study entry to the first time of psychosis onset. For AD-P patients we considered all the available medication usage on and after the date of study entry. We selected the top 100 most used drugs from AP+P and AD-P patients and merged to get commonly used drug list consist of 123 drugs for the following analysis.

2.3 STATISTICAL ANALYSIS

Chi-square test was performed to assess the association between ever taking of each of the 100 candidate drugs during the follow-up and psychosis. Log rank test was performed to test the difference in time to psychosis from time to entry of the study between patients who have taken and have not taken each of the 100 candidate drugs during the follow-up. To adjust for multiple

testing, Benjamini & Hochberg method [149] was used to control for the false discovery rate (FDR). For those drugs statistically significantly associated with time to psychosis with FDR $\leq$ 0.1, we also performed a multivariable Cox regression with baseline MMSE, baseline age, sex, race, and education, as covariates. We used the lifelines package of python test the proportional hazard assumption[150].

The study data was maintained and managed using SPSS for Windows (v12–v15); the analyses were carried out using python packages (Pandas, Numpy, Scipy, DateTime, and Lifelines). $p<0.05$ was used as the threshold for statistical significance for all analyses except where stated otherwise.

2.4 NETWORK ANALYSIS

2.4.1 Targets inclusion criteria

Alzheimer's Disease and psychosis-related protein targets were collected from different literature and databases , including Metacore (https://portal.genego.com/), GWAS Catalog (https://www.ebi.ac.uk/GWAS/home)[151] and BaseSpace Correlation Engine (https://www.illumina.com/index-d.html)[152]. Due to the variety of information sources, targets are carefully selected based on different type of data that we believe is solid enough including RNA and miRNA expression, SNPs identified through GWAS, copy number variations (CNVs), and mutation data. The target information will be included in our study if 1) Include a primary GWAS analysis, defined as array-based genotyping and analysis of 100,000+ pre-QC SNPs selected to tag variation across the genome and without regard to gene content 2) Statistical significance (SNP-

trait p-value <1.0 x 10^{-5}) in the overall population 3) The study suggesting the association is well controlled. I choose 1.0 x 10^{-5} as the threshold of the genome-wide association rather than the stricter one 5.0 x 10^{-8} because I want to include more protein targets related to AD and psychosis to help better construct the complete structure of networks.

Signaling pathways for AD and psychosis are acquired from KEGG (http://www.genome.jp/kegg/) [153] and PANTHER Classification System (http://pantherdb.org/)[154].

In the following network analysis studies, we incorporated the protein-protein interaction (PPI) data from STRING (https://string-db.org/) [155] and Online predicted human interaction database (OPHID) (http://ophid.utoronto.ca/ophidv2.204/index.jsp)[156]. And the PPI network was constructed and analyzed with python package networkx (https://networkx.github.io/)[157]. The interaction network was shown in the molecular action view with the medium confidence level (> 0.4).

The centrality of nodes in the network is calculated based on the built-in algorithm of networkx. In detail, the degree centrality values are normalized by dividing by the maximum possible degree in a simple graph n-1 where n is the number of nodes in a network. The Eigenvector centrality is based on the power iteration method[158] and Betweenness centrality algorithm is from Ulkrik Brandes[159-162]. In order to minimize the bias caused by the amount of studies associated with different proteins, we use betweenness centrality as our primary marker in this study to lean more on the nodes' position in the network's structure, rather than the degree centrality of the nodes in the network.

The algorithm used for community detection is based on the Greedy Modularity Maximization method[163-164]. It begins with each node in its own community and joins the pair of communities that most increases modularity until no such pair exists.

3.0 RESULTS

3.1 STATISTIC RESULTS

3.1.1 Characteristics of subjects

The characteristics of the subjects are shown in **Table 1**. The demographical data showed that the subjects who developed psychosis symptoms had lower baseline MMSE, generally took fewer numbers of drugs and had lower education levels.

Table 2. Characteristics of subjects

Variable	AD-P, N=367	AD+P, N=256	DF	p value*
Follow-up, years	3.17 (2.10)	2.41 (1.80)	543	<0.001
Baseline MMSE	21.75 (4.38)	20.45 (5.16)	469	0.003
Age at baseline	79.58 (6.97)	80.9 (6.87)	544	0.02
Sex				
Female	214 (58 %)	164 (64 %)	1	0.07
Male	153 (42 %)	92 (36%)		
Race				
Asian	2 (0.3 %)	0 (0 %)	2	0.31
African-American	23(3 %)	20 (3 %)		
Caucasian	342 (55.9%)	236 (37.9 %)		
Education, years	14.10 (3.09)	13.5 (3.00)	543	0.014

AD-P: Alzheimer Disease without psychosis; AD+P: Alzheimer disease with psychosis; MMSE: Mini-mental State Examination.

Results for AD-P and AD+P are mean (SD) for continuous variables and total (%) for categorical variables.

*T-test for continuous variables and Chi-square test for sex and education, Fisher exact test for race.

3.1.2 Tests' results in AD+P and AD-P patients

In the medication dataset collected of 2000-2014 ADRC visits, a total of 478 drugs is recorded used by at least one patient before their psychosis diagnosis. The top 100 drugs (**Table 2**) are chosen by rank the usage of them and accounted for 86.5% (19141/ 22121) of all medication usage.

Table 3. List of 100 drugs and usage count

Drug Name	count	Drug Name	count	Drug Name	count	Drug Name	count
Multivitamin	1643	Metformin	193	Celecoxib	78	Quinapril	52
Donepezil	1576	Alendronate	186	Losartan	78	Trazodone	51
Aspirin	1309	Galantamine	178	Fluticasone Nasal	77	Glyburide	51
Memantine	1054	Escitalopram	177	Venlafaxine	76	Rosuvastatin	50
Calcium	760	Atenolol	171	Glipizide	75	Solifenacin	49
Levothyroxine	590	Digoxin	169	Calcium-Vitamin D	71	Bupropion	47
Simvastatin	555	Valsartan	168	Paroxetine	70	Esomeprazole	46
Ergocalciferol	553	Clopidogrel	163	Fluticasone-Salmeterol	70	Hydrochlorothiazide-Triam	46
Vitamin E	515	Potassium	157	Ibuprofen	68	Lovastatin	46
Omega-3 Polyunsaturated F	510	Diltiazem	148	Mirtazapine	68	Isosorbide	46
Lisinopril	384	Glucosamine	145	Verapamil	66	Insulin Regular	45
Ascorbic Acid	383	Acetaminophen	136	Ranitidine	65	Allopurinol	44
Metoprolol	348	Ubiquinone	124	Pyridoxine	65	Fexofenadine	42
Cyanocobalamin	332	Pravastatin	106	Nitroglycerin	64	Albuterol	42
Atorvastatin	328	Docusate	105	Raloxifene	64	Alprazolam	40
Multivitamin With Mineral	305	Tamsulosin	102	Niacin	63	Oxybutynin	38
Omeprazole	283	Risedronate	100	Loratadine	61	Fluoxetine	37
Citalopram	279	Tolterodine	98	Duloxetine	58	Quetiapine	37
Warfarin	236	Finasteride	96	Ferrous Sulfate	55	Terazosin	36
Sertraline	229	Ginkgo	92	Carvedilol	55	Conjugated Estrogens	30
Rivastigmine	227	Chondroitin	90	Pioglitazone	55	Zinc Chloride	28
Furosemide	223	Magnesium	89	Naproxen	54	Lansoprazole	28

Folic Acid	214	Lorazepam	89	Gabapentin	54	Zolpidem	26
Hydrochlorothiazide	213	Pantoprazole	88	Enalapril	53	Melatonin	24
Amlodipine	213	Ezetimibe	88	Montelukast	53	Lecithin	24

To acquire a detailed insight into drugs' effects in AD+P and AD-P patients, multiple statistical methods are adapted to comprehensively evaluate the effects.

3.1.3 Endpoint selection

Two kinds of end markers are adopted in our study, a categorical one and a continuous one. The categorical end marker is whether the patients developed psychosis, two categories, yes and no, are contained in this end marker. The continuous one is the time duration from AD diagnosis to an event including psychosis, death and censored. It's recorded in years can provide information about the effects of drugs in slowing the development of psychosis in AD.

3.1.3.1 Test results

3.1.3.1.1. Test results for single drug usage

Chi-square test, log rank test and survival analysis were performed to find out the correlation of drug usage and psychosis development in AD.

For the Chi-square test, among the 100 drugs analyzed, only Ergocalciferol (vitamin D) is significant after the false discovery rate (FDR) correction.

Table 4. Significant chi-square results for drugs

Drugs	Test statistic	P value	BH adjusted p value
Ergocalciferol	23.4	< 0.001	< 0.001

Log rank test was performed between drugs and the time to psychosis and also adjusted for FDR. Two drugs, vitamin D and multivitamin, were identified significantly associated with time to psychosis in AD patients.

Table 5. Significant results in log rank test

Drugs	Test statistic	P value	BH adjusted p value
Ergocalciferol	18.8	< 0.001	< 0.001
Multivitamin	12.3	< 0.001	0.0223
Memantine	9.28	0.00232	0.0773

Survival analysis was performed on medication usage against psychosis. 623 subjects were included in the survival analysis and 367 censored or dead in the period of study. Kaplan-Meier Estimate method was used first to estimate the survival function of the whole patients. **Figure 1** showed the estimated survival function and the cumulative function of psychosis in AD. Based on the estimation, psychosis is a pretty severe hazard in AD patients. With time increase, the risk of have psychosis is continuously growing from 44% in the first two years to 81% in sixth to eighth year (**Table 5**). Due to the elder age of AD patients, many of them dead in the period of study or dropped the study for certain reasons. This fact is the main limitation of this study, which leads to a too wide confidence interval and makes the latter part of the curve no sense. However, the curve before 6 years is pretty solid and enough to present a great overview of the development of psychosis in AD patients.

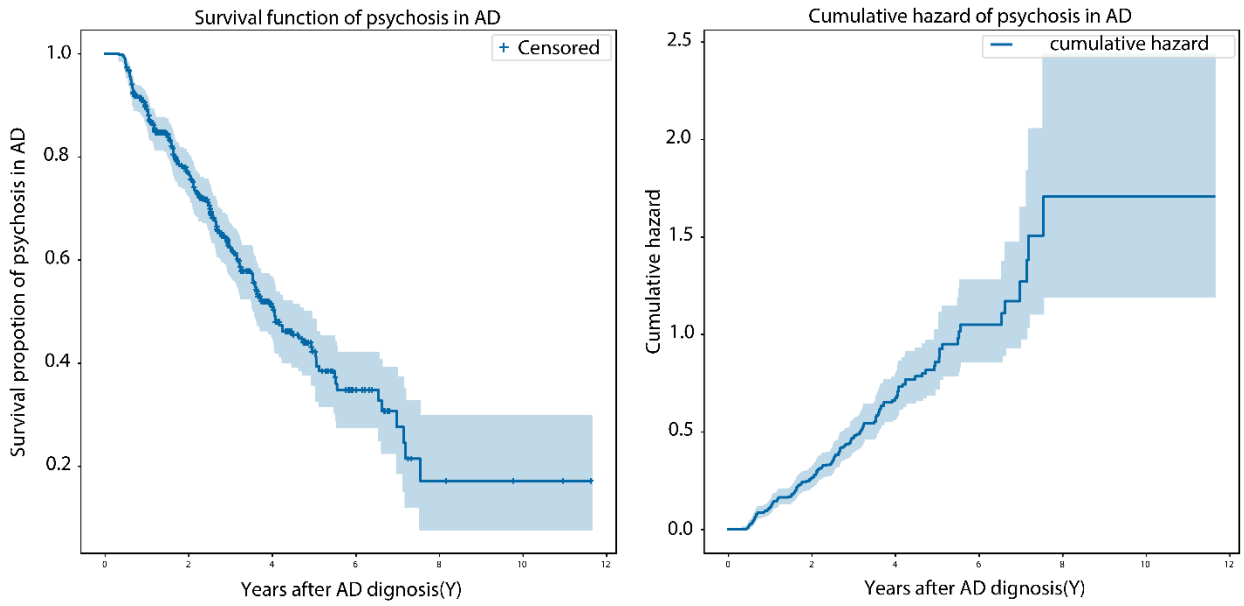

Figure 1. Survival function and cumulative hazards of psychosis in AD

The survival function and cumulative hazard of psychosis in AD are shown in the figure above. The gradually increased confidence interval is caused by the rapid censoring of subjects. The curve and confidence interval are not statistically meaningful after 6 years.

Table 6. At risk count of psychosis in AD

Time(Year)	0	2	4	6	8	10	12
At risk count	623	372	135	44	18	8	1
Percentage of change	\	40%	63%	67%	59%	55%	86%

Cox regression was performed to control for multiple variants and identify hazard ratios for single drug usage. Hazard ration and p-value are acquired for all 126 drugs, 13 of them are identified significantly related to the development of psychosis in AD (**Table 6**). However, when checking the proportional assumptions of our data, many of our variables failed due to a limited data size since we only have binary data.

Table 7. Thirteen drugs with significant results of Cox regression

Drugs	Coefficient	Hazard Ratio (HR)	SD of HR	P value
Quinapril	1.40	4.04	0.379	0.000231
Potassium	0.997	2.71	0.310	0.00131

Ergocalciferol	-0.659	0.517	0.224	0.00321
Multivitamin	-0.453	0.636	0.162	0.00523
Meloxicam	1.55	4.69	0.555	0.00532
Metformin	0.779	2.18	0.287	0.00658
Loratadine	-1.87	0.153	0.715	0.00878
Mirtazapine	0.745	2.11	0.303	0.0141
Furosemide	-0.787	0.455	0.320	0.0140
Memantine	-0.395	0.673	0.164	0.0158
Galantamine	-0.584	0.558	0.250	0.0194
Citalopram	0.443	1.56	0.201	0.0277
Pravastatin	-0.792	0.453	0.375	0.0347

3.1.3.1.2. Test results for drug combination usage.

Due to the complexity of the medication usage of elder people, drug combination is another potential factor in influencing the psychosis development in AD patients. The first step in studying co-administrated drugs is to find out the correlation between drugs. Drug combinations are identified with Cramér's V coefficient to measure the association between two nominal variables[165]. It's a method based on Pearson's chi-squared statistic and can be viewed as the association between two variables as a percentage of their maximum possible variation.

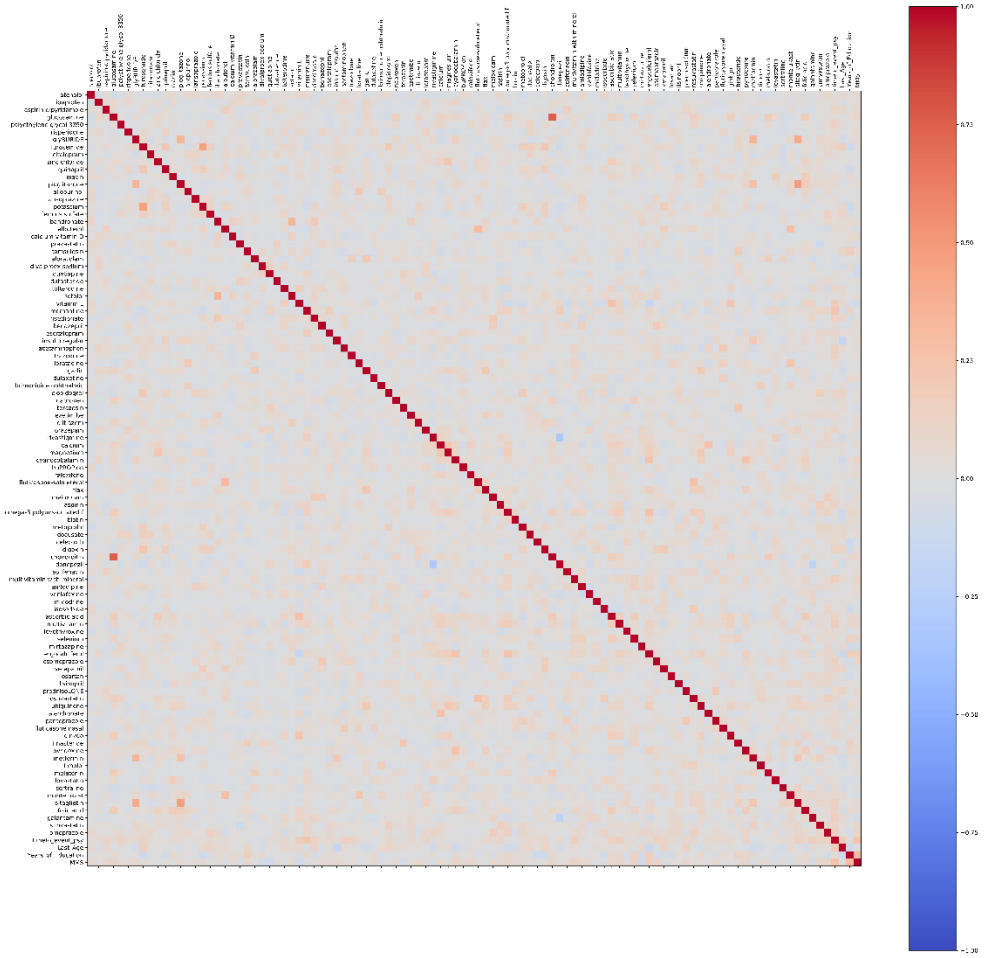

Figure 2. Heatmap of drug correlations

Correlation of drugs is shown in the figure. Generally speaking, the association among drugs are weak means they are not frequently used together. The amount of drug combinations with coefficient above 0.2 is 22 is a phenotype for the averagely low association.

As you can see from **Figure 2**, weak correlations are presented among a variety of drugs, and drugs combinations with coefficient over 0.2 are selected as drug combination objects (**Table 7**). The same procedure was performed on the 16 drug combinations.

Table 8. 22 drug combinations with coefficient over 0.2

Drug1	Drug2	Coefficient
Glucosamine	Chondroitin	0.736

glyburide	Pioglitazone	0.317
glyburide	Metformin	0.332
glyburide	Sitagliptin	0.364
Furosemide	Quinapril	0.208
Furosemide	Potassium	0.458
Furosemide	Digoxin	0.207
Pioglitazone	Metformin	0.245
Pioglitazone	Sitagliptin	0.430
Ibandronate	Sotalol	0.282
Albuterol	Fluticasone-Salmeterol	0.284
Albuterol	Montelukast	0.241
Vitamin E	Ascorbic Acid	0.270
Vitamin E	Ginkgo	0.230
Rivastigmine	Donepezil	0.308
Calcium	Magnesium	0.202
Calcium	Alendronate	0.264
Cyanocobalamin	Ergocalciferol	0.250
Cyanocobalamin	Pyridoxine	0.242
Fluticasone-Salmeterol	Rosuvastatin	0.226
Omega-3 Polyunsaturated F	Ergocalciferol	0.256
Donepezil	Galantamine	0.208

Table 9 Significant chi-square results for drug combinations

Drugs combinations	Test statistic	P value
Cyanocobalamin and Ergocalciferol	8.39	0.00378
Omega-3 Polyunsaturated F and Ergocalciferol	6.60	0.0102
Vitamin E and Ascorbic Acid	4.55	0.0329

Table 10. Significant results in log rank test

Drugs combinations	Test statistic	P value
Furosemide and Digoxin	5.71	0.0169
Omega-3 Polyunsaturated F and Ergocalciferol	5.23	0.02231
Cyanocobalamin and Ergocalciferol	4.94	0.0262

Table 11. Significant results of Cox regression

Drugs combinations	Coefficient	Hazard Ratio (HR)	SD of HR	P value

Furosemide and Digoxin	-1.21	0.297	0.571	0.0335

3.1.3.2 Test summary

3.1.3.2.1. Single drug usage

Combining the results form Chi-square, log rank test and Cox regression, Vitamin D (Ergocalciferol) is an unneglectable drug in our results. It not only enjoys a significant correlation with the occurrences of psychosis in AD but also positively related to the time interval to develop psychosis in AD patients. Furthermore, in the Cox regression, the HR of vitamin D is 0.51 meaning taking vitamin D can reduce the hazard of developing psychosis to 0.51, or 49% less likely to develop psychosis. Survival curves of Vitamin D and no Vitamin D group are shown in **Figure 2**, and the survival rate of Vitamin D group is significantly higher than the no Vitamin D group. In the 623 subjects included in our analysis, 449 (72.1%) of them have no Vitamin D usage and 173 (27.9%) have. Memantine, an NMDA receptor antagonist, is also spotted for significant correlation in both log rank test and Cox regression. In the survival analysis, Memantine presents an HR of 0.67 suggesting a protective effect towards psychosis in AD. Among the 623 subjects, 283 (45.4%) of them have Memantine usage and 339(54.6%) don't. The survival function of Memantine group and no Memantine group are shown in **Figure 3**. The groups in **Figure 2** and **Figure 3** overlapped with each other in the later part of the timeline which may indicate an insignificant correlation, but it can also be explained by the greatly reduced sample size after 6 years. The limited number of subjects may result a larger confidence interval and crossing lines.

A question remains unanswered: if Vitamin D and Memantine is used simultaneously, will the beneficial effect add up? And we will discuss this pair in the drug combinations part.

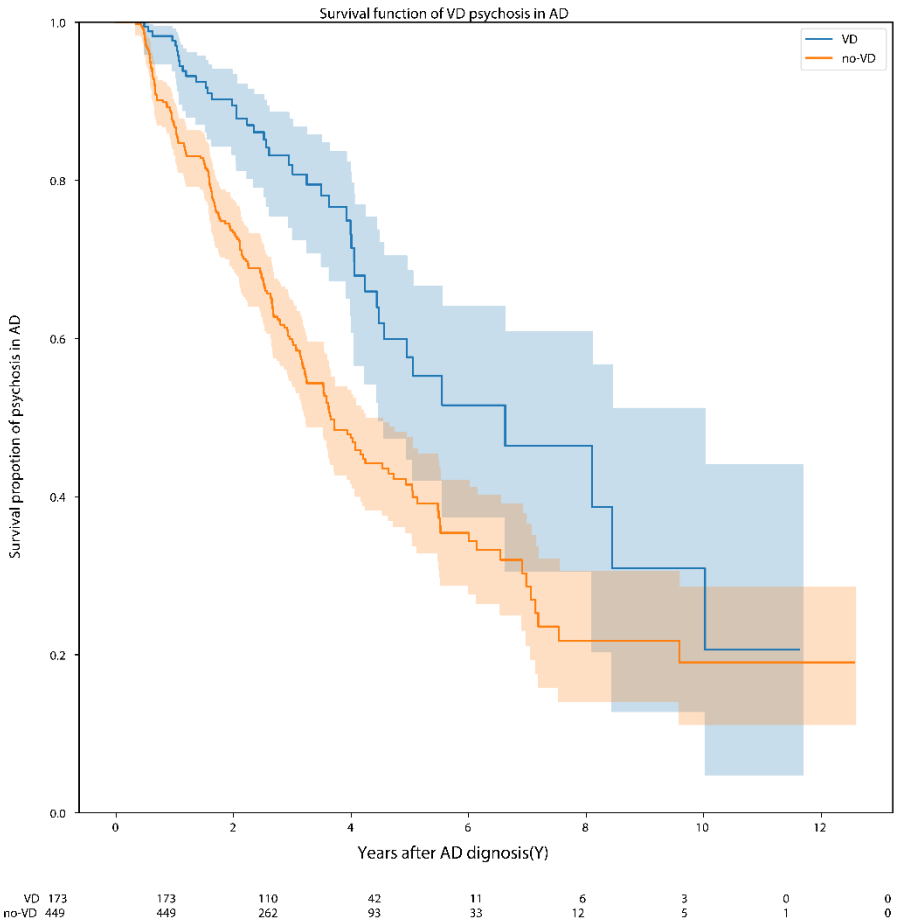

Figure 3. Survival function of psychosis in AD with and without Vitamin D

The survival functions of psychosis in AD grouped by Vitamin D treatment are shown in the figure above. The confidence intervals of two curves are separated with each other pretty well before 6 years suggesting a significant difference in the survival rate of the patient treated with and without Vitamin D.

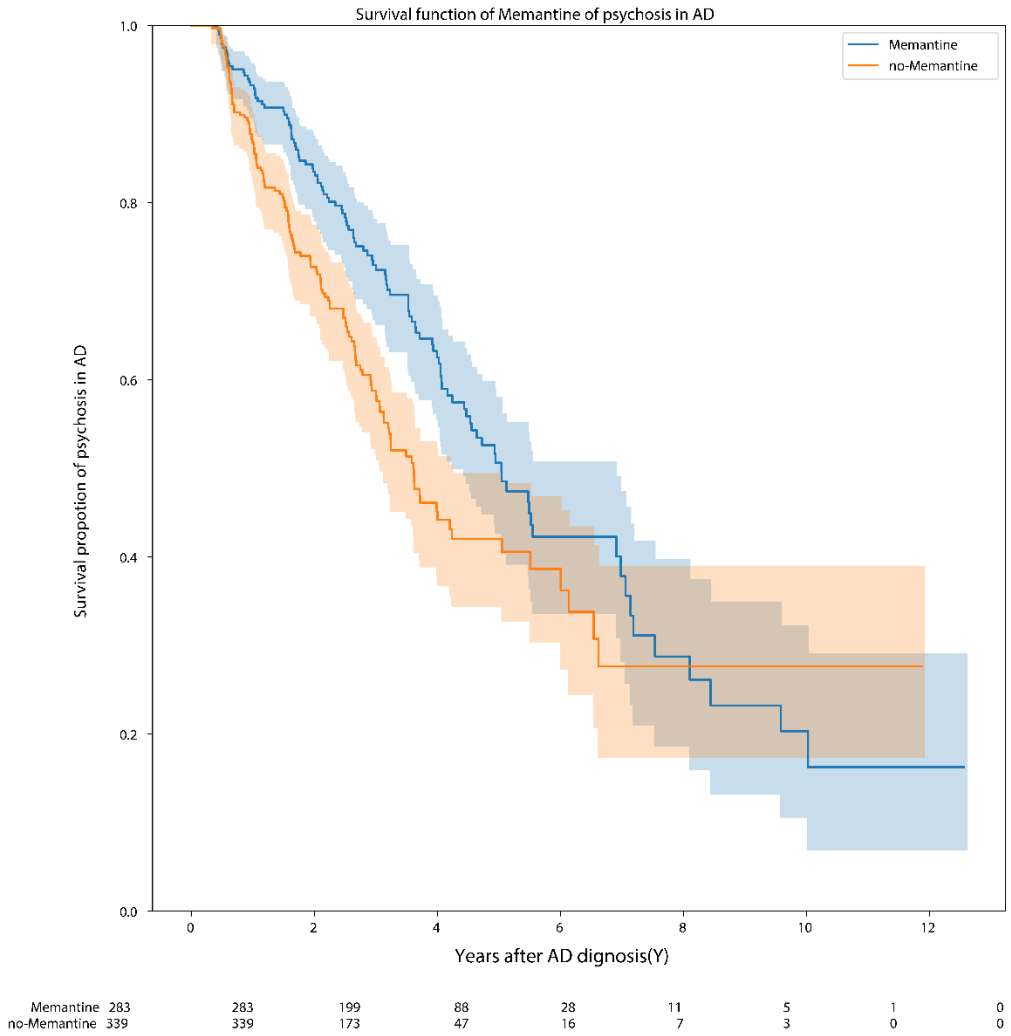

Figure 4. Survival function on psychosis in AD with and without Memantine

The survival functions of psychosis in AD grouped by Memantine treatment are shown in the figure above. The confidence intervals of two curves are slightly overlapped with each other at around 6 years but separated before that, suggesting a significant difference in the survival rate of the patient treated with and without Memantine.

3.1.3.2.2. Drug combination usage

Drug combinations are identified from the medication records using Cramér's V coefficient. As you can imagine, most of them are frequently co-administered drugs to treat or manage the same disease or symptom. As **Table 11** shown, most of the drugs' indications are chronic diseases like diabetes, hyperlipidemia and chronic obstructive pulmonary disease, which

is reasonable due to the age of the subjects. The statistic results of the drug combinations reveal an interesting result that the combinations containing Vitamin D are significant in chi-square and log rank test but not significant in Cox regression. Since the Cox regression are adjusted by baseline age, MMSE, race, gender, the significant correlation enjoyed by furosemide and digoxin may be a result of extended survival time rather than the extended time interval to develop psychosis in AD. Due to the age of the subjects, many of them died or censored before they can develop psychosis and result in an unneglectable effect to the statistic results.

As the only significant pair in the Cox regression, furosemide and digoxin, are frequently co-administered in elder patients in order to relive cardio pressure and edema. They present an HR of 0.29 with a p value of 0.03. However, the connection between these two drugs and psychosis remain unclear. The most convincing explanation is that the protective effect we observed may be the result of prolonged lifetime caused by the drugs.

Similar with the situation of furosemide and digoxin, chondroitin and glucosamine, the most correlated drug pairs among our drug combinations, are not significantly linked to our end markers and be excluded because they're both indicated for osteoarthritis.

Table 12. Overview of drug combinations

Drug	**Indication**	**Drug**	**Indication**
Glucosamine	treatment for osteoarthritis	Chondroitin	slow-acting drug for osteoarthritis (SYSADOA)
Glyburide	treatment of non-insulin-dependent diabetes mellitus (NIDDM)	Pioglitazone	manage type 2 diabetes mellitus
Glyburide	treatment of non-insulin-dependent diabetes mellitus (NIDDM)	Metformin	treating non-insulin-dependent diabetes mellitus (NIDDM)
Glyburide	treatment of non-insulin-dependent diabetes mellitus (NIDDM)	Sitagliptin	control of type 2 diabetes mellitus

Furosemide	diuretics used for edema and chronic renal insufficiency	Quinapril	angiotensin-converting enzyme (ACE) inhibitor
Furosemide	diuretics used for edema and chronic renal insufficiency	Potassium	Potassium supplements
Furosemide	diuretics used for edema and chronic renal insufficiency	Digoxin	cardiotonic glycoside used to control ventricular rate
Pioglitazone	manage type 2 diabetes mellitus	Metformin	treating non-insulin-dependent diabetes mellitus (NIDDM)
Pioglitazone	manage type 2 diabetes mellitus	Sitagliptin	control of type 2 diabetes mellitus
Ibandronate	inhibits osteoclast-mediated bone resorption	Sotalol	An adrenergic beta-antagonist that is used in the treatment of life-threatening arrhythmias.
Albuterol	beta2-adrenergic receptor agonist used in the treatment of asthma and COPD	Fluticasone-Salmeterol	beta2-adrenergic receptor agonist used for asthma and COPD
Albuterol	beta2-adrenergic receptor agonist used in the treatment of asthma and COPD	Montelukast	leukotriene receptor antagonist used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies
Vitamin E	exhibit alpha-tocopherol activity	Ascorbic Acid	an essential nutrient in human diets, and necessary to maintain connective tissue and bone
Vitamin E	exhibit alpha-tocopherol activity	Ginkgo	mainly used as memory and concentration enhancer, and anti-vertigo agent
Rivastigmine	treatment of mild to moderate dementia of the Alzheimer's type	Donepezil	a centrally acting reversible acetyl cholinesterase inhibitor mainly used for the treatment of Alzheimer's disease
Calcium	calcium supplements	Magnesium	Magnesium supplements
Calcium	calcium supplements	Alendronate	used for the treatment of osteoporosis and Paget's disease
Cyanocobalamin	Vitamin B12	Ergocalciferol	use in the management of hypocalcemia

Cyanocobalamin	Vitamin B12	Pyridoxine	the 4-methanol form of vitamin B6
Fluticasone-Salmeterol	beta2-adrenergic receptor agonist used for asthma and COPD	Rosuvastatin	antilipemic agent used to reduce plasma cholesterol levels and prevent cardiovascular disease
Omega-3 Polyunsaturated F	Omega-3 fatty acids supplements	Ergocalciferol	use in the management of hypocalcemia
Donepezil	a centrally acting reversible acetyl cholinesterase inhibitor mainly used for the treatment of Alzheimer's disease	Galantamine	used to reverse the muscular effects of gallamine triethiodide and tubocurarine, and has been studied as a treatment for Alzheimer's disease

Besides all the combinations we discussed above, the combination of Vitamin D and Memantine is also discussed because of their significant correlation with outcomes. Among our 623 subjects, 92 patients have received Vitamin D and Memantine at the same prescription, and the coefficient of them is 0.084. Since both of them are already significant in the statistic test, it's not surprising that the combination of them have a significant beneficial effect. As you can see from **Figure 6**, the survival functions of subjects grouped by whether or not receiving Vitamin D and Memantine show a good separation before 5 years due to the limitation of censoring. However, the Cox regression result for Vitamin D and Memantine is not significant. The additive effect of Vitamin D and Memantine is discussed by comparing the survival function of three groups of patients: patients taking both Vitamin D and Memantine, patients taking Vitamin D only and patients taking Memantine only. Log rank tests between these 3 groups (**Table 13**) suggest that the difference of beneficial effect between Vitamin D only and the combination of VD and Memantine is not significant, but both using VD and the combination of VD and Memantine exhibit a better effect compared to using Memantine alone. Based on the results we have, the beneficial effect of Vitamin D is further concreated for psychosis in AD, but the effect of

Memantine is not significant when added with Vitamin D. The beneficial effect of Vitamin D and Memantine combination is also not significant when comparing with using Vitamin D alone, suggesting the most part of the beneficial effect come from Vitamin D usage.

Table 13. Log rank test results for the combination of Vitamin D and Memantine of psychosis in AD

Comparison groups	Test statistic	P value
VD and Memantine against VD only	3.40	0.07
VD and Memantine against Memantine only	10.75	< 0.005
VD only against Memantine only	1.07	0.30
No VD or Memantine against Memantine only	4.37	0.04

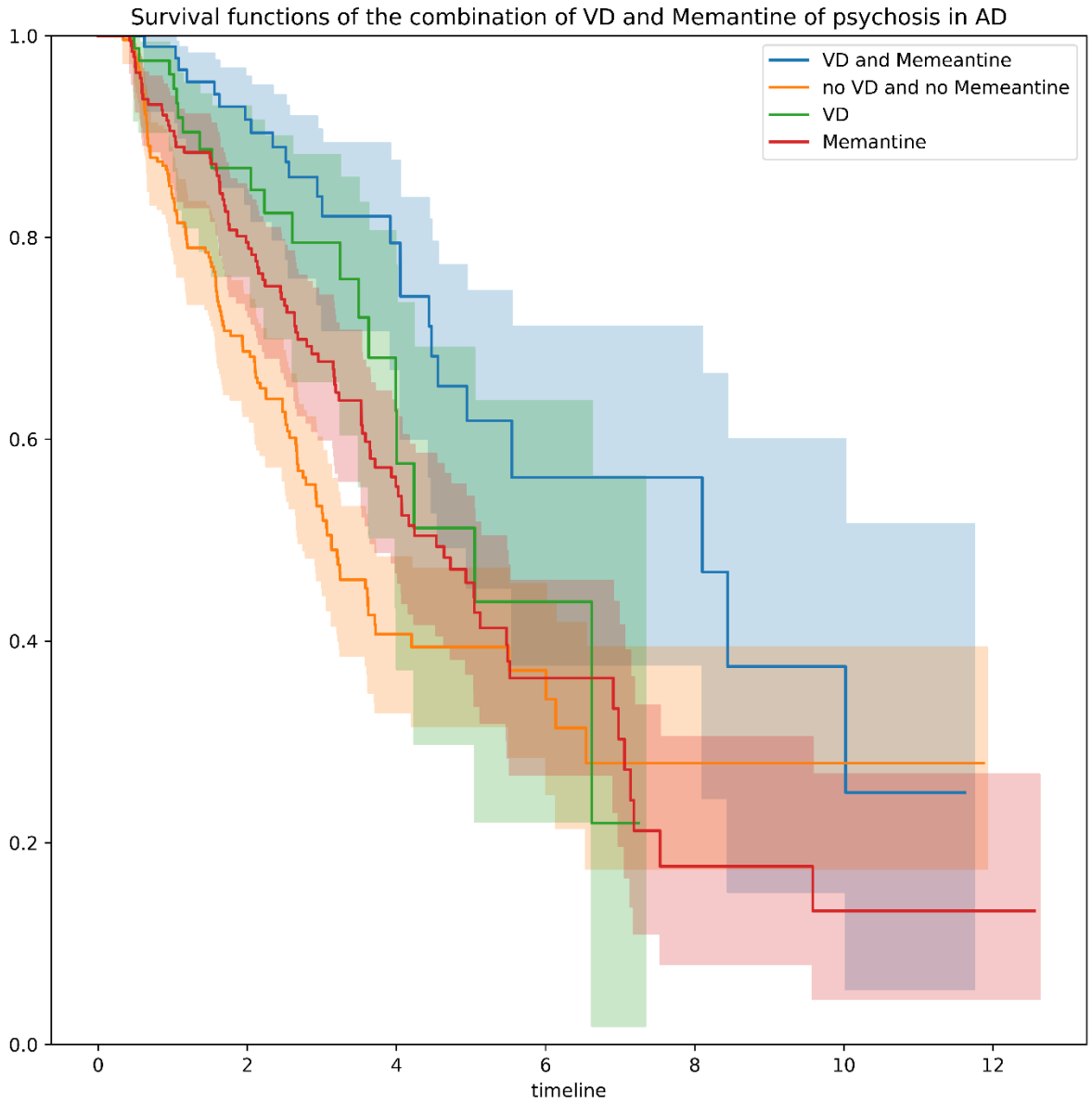

Figure 5. Survival functions of the combination of Vitamin D and Memantine of psychosis in AD

The survival functions of psychosis in AD grouped by Vitamin D and Memantine treatment and the combination of VD and Memantine are shown in the figure above. The VD and Memantine group do not contain the patients taking both drugs simultaneously. Three curves have a little bit of separation with considerable overlap.

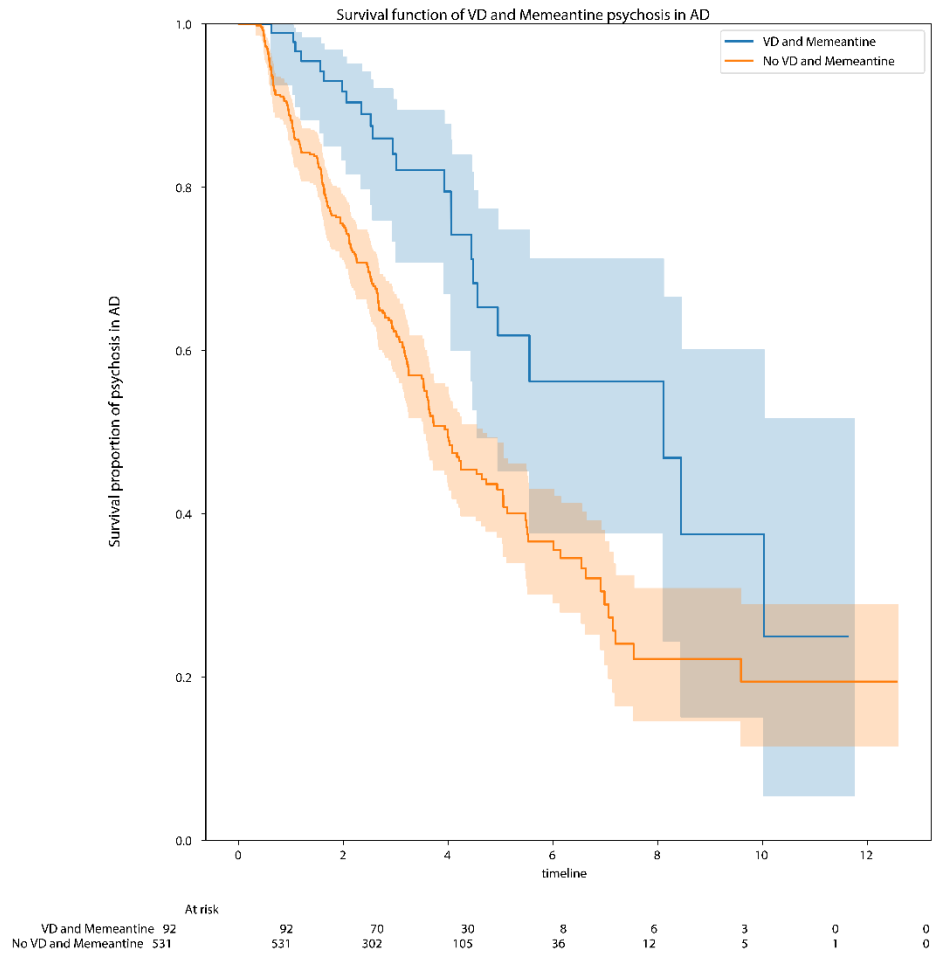

Figure 6. Survival function of VD and Memantine of psychosis in AD

The survival functions of psychosis in AD grouped by Vitamin D and Memantine treatment are shown in the figure above. The confidence intervals of two curves are slightly overlapped with each other at around 5 years but separated before that, suggesting a significant difference in the survival rate of the patient treated with and without Vitamin D and Memantine. However, it's really hard to say if the combination of two drugs is better than one.

3.2 NETWORK ANALYSIS

3.2.1 The combined network of Alzheimer's Disease and Psychosis

In order to make a better understanding of the connection between AD and psychosis and further explore the potential drug targets suggested by the previous analysis, Protein-protein interaction (PPI) network of AD and psychosis was generated. 1061 AD related protein targets and 15691 PPI data and 483 psychosis-related targets and 1361 PPI data are collected as the base of our network. Among all the protein targets collected, 90 targets are shared between AD and psychosis, including SEMA3A, TUSC3, RPN2, AMBRA1, BECN1, CACNA1C, SGK1, ADAM10, GRIN2A, FYN, ANK3, TBXAS1, EFNA5, POLN, CHRNA3, NOTCH4, GRIA1, NTRK3, IQGAP2, RELN, NOS1, GPC6, TCF7L2, TCF4, MGLL, DRD3, CHRNA2, PAK2, CTNNA2, COL25A1, COL12A1, AGER, KIF26B, PPP2R2B, TEK, KALRN, PRKG1, KSR2, COLGALT2, MEIS1, SHISA9, ZKSCAN4, PTPRG, NKAPL, CTNNA3, PDE4B, HFE, MSR1, CSMD1, COMT, APBA1, IMMP2L, ELAVL4, LRRTM4, CDH13, ZNF804A, PBRM1, LRRN2, TEP1, STXBP5L, FHIT, SYNGAP1, ZSCAN31, TENM4, ABCB1, PLCL1, RBFOX1, FSTL5, SORCS3, NKAIN2, GLIS3, NXN, MAGI2, MEGF10, MPP6, TSPAN18, FRMD4B, MTHFD1L, TMTC1, LIN28B, UXS1, BICC1, ATXN7L1, EYS, GRAMD1B, TSPAN2, ENOX1, TMEM132D, CR1 and PCNX. A weight value is assigned to all PPI in the network based on the strength of molecular interaction. The combination network of AD and psychosis has 1454 nodes and 16948 PPI interactions. It's not surprising that in **Table 14** the property of combined network followed AD due to the great disparity of the nodes number, but it can still provide a lot of useful information.

Table 14. Overview of AD and Psychosis PPI networks

	Node Number	Edge Number	Average Degree	Average Eigenvector	Average Betweenness	Average Clustering Coefficient
AD	1061	15691	29.6	0.0177	0.00167	0.324
Psychosis	483	1361	5.63	0.0229	0.00652	0.177
Combined Network	1454	16948	23.3	0.0130	0.00158	0.276

Centrality measures of the nodes are introduced in network analysis to describe how the information will spread through the network. Three different kinds of centralities are included under this parameter: Degree Centrality, Eigenvector Centrality and Betweenness Centrality. Degree Centrality, as the most simple and direct one, describes the number of connections of a particular node regardless of the direction and weight of the edges. Eigenvector Centrality includes the weight of the edges into consideration in addition to degree centrality to better describe the correction between nodes. Betweenness Centrality, as the centrality of control, represents the frequency at which a point occurs on the geodesic (shortest paths) that connected pair of points. In another way, it quantifies how many times a particular node act as a bridge in linking two ends of the network. It's obvious that the node with high Betweenness can be critical in our research for their crucial role in communication and information flow within the network.

The overview of the top 10 net-influencer in the combined network is shown in **Table 15**. The algorithm used to calculate these values are described in the method part. It's not surprising that the results in the 3 centralities overlapped with each other a lot since they're all measuring the importance of the node in the whole network from different angels, and it's pretty obvious that the top 10 nodes do have very high values when compared with the average value, 10-fold ratio at least, a better view is provided in **Figure 7** that only a few nodes take position at the upper-right corner. This phenomenon suggesting that though there are 1454 of nodes in the network, a small

group of nodes, such as the top 10 nodes shown in the table, are extremely connected and enjoy a critical role in the signaling process and information flow within the network.

Table 15. Overview of net-influencer in the combined network

Degree	Eigenvector	Betweenness
INS(0.200)	GAPDH(0.158)	APP(0.0552)
AKT1(0.199)	AKT1(0.158)	AKT1(0.0528)
GAPDH(0.191)	INS(0.157)	INS(0.0497)
APP(0.186)	ALB(0.157)	TP53(0.0451)
ALB(0.184)	IL6(0.149)	FYN(0.0382)
TP53(0.175)	TNF(0.141)	GRIA1(0.0348)
IL6(0.162)	MAPK3(0.138)	GAPDH(0.0345)
MAPK3(0.153)	TP53(0.138)	ALB(0.0247)
TNF(0.149)	VEGFA(0.136)	CACNA1C(0.0245)
VEGFA(0.142)	CASP3(0.127)	RBFOX1(0.0209)

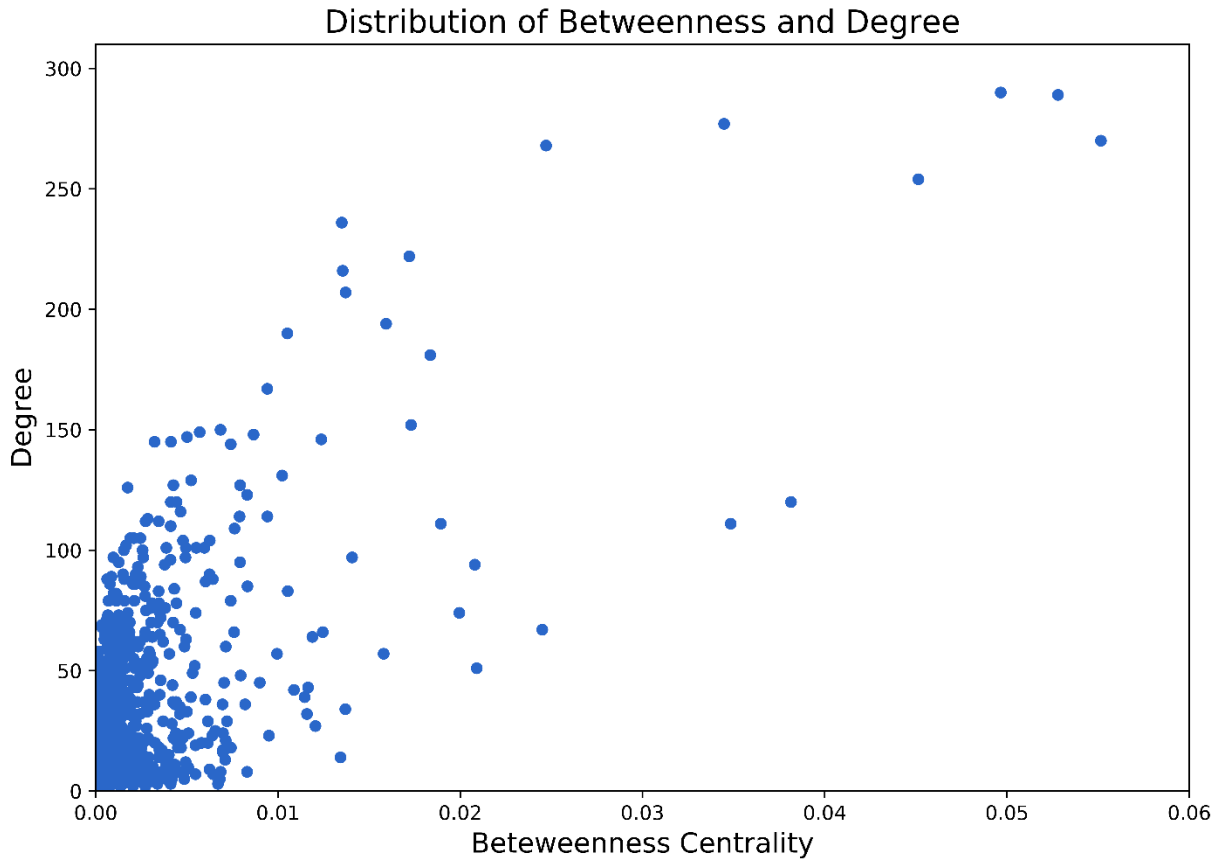

Figure 7. Distribution of degree and betweenness of nodes in the combined network

The figure above showed the distribution of degrees and betweenness of the nodes in the combined network. It's obvious that the absolute most of the nodes have very low degrees and betweenness centrality while a very small group of nodes, like the top 10 nodes, enjoy a very high centrality compared to others. This phenomenon suggesting that the information flow within the network is greatly controlled and regulated by the small group of nodes.

After identifying the critical targets in the network, the function of these targets is the next question we need to answer. To do that, we need to identify the underlying pathways represented by those nodes and therefore establish a connection between protein targets and biological functions. 10 communities are detected as relatively separated components of the network (**Figure 8**). Among the 10 detected communities, 7 communities, excluding 7, 8 and 9, contain enough nodes to be actually biological meaningful and when sort the network based on the community and the nodes' betweenness, every community have one or a few nodes enjoy a significant higher Betweenness value and acting as the portal connecting the community to the other parts of the network (**Figure 9**). Among the top 10 targets we mentioned above (**Table 15**), they're divided into different communities like APP, FYN, GAPDH and INS and it further illustrates the importance of these nodes in the combined network. These detected communities represent different biological pathways that participating in the development of psychosis in AD and a target-pathway mapping was conducted in order to find the pathways most likely get involved.

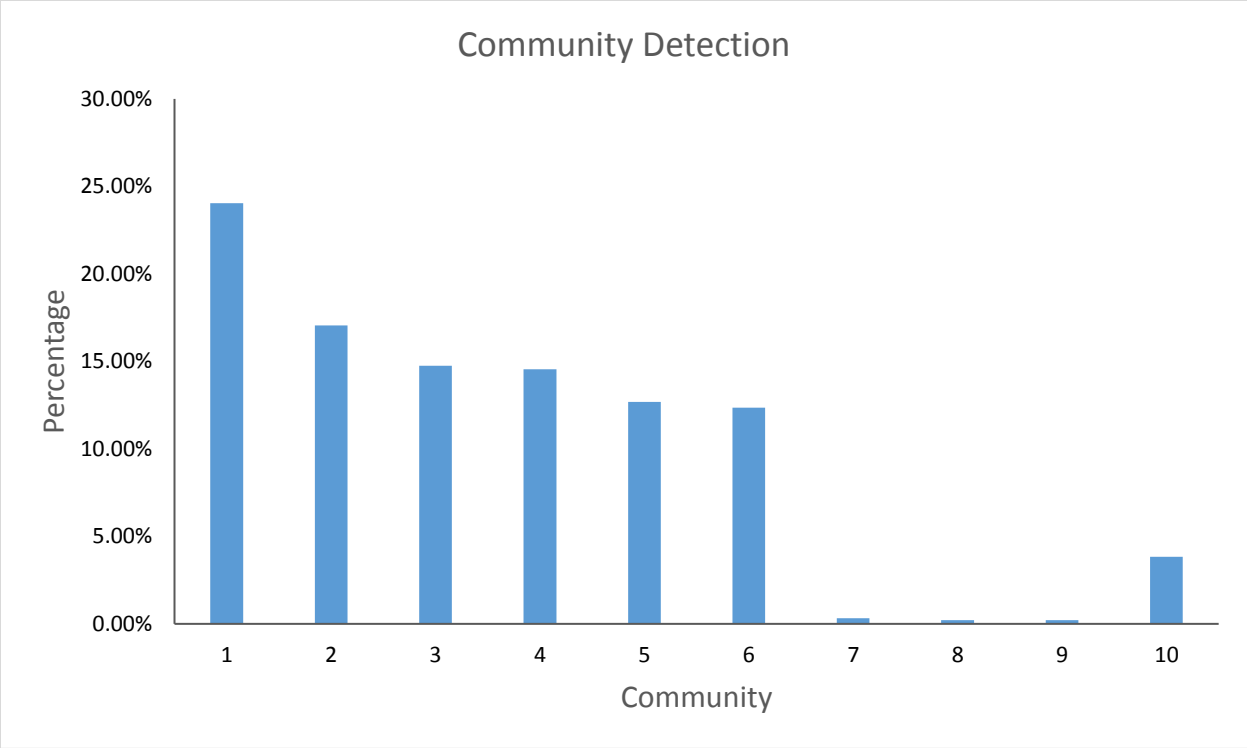

Figure 8. Overview of community detection

Results of community detection are shown in the figure above. 7 meaningful communities are detected, and targets count are shown in the figure. These communities are constructed with similar targets amounts and can be the representatives for different functions involved biologically.

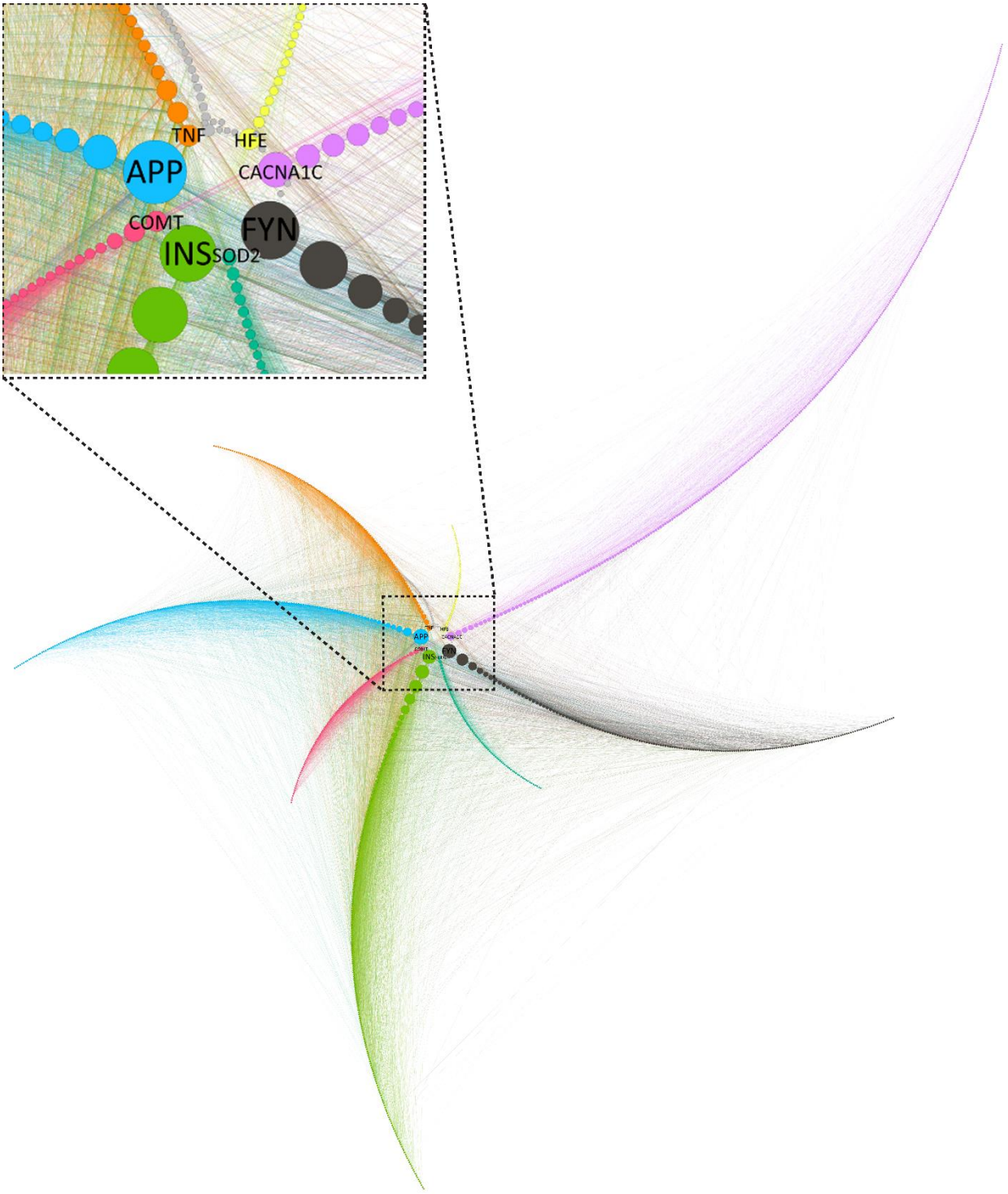

Figure 9. Overview of community interaction

Community interactions are showed above incorporated with the betweenness centrality data of nodes. The node size represents the betweenness centrality of nodes while the bigger node enjoys a higher betweenness level. It's very clear that the high impact nodes, nodes with high betweenness

centrality, are evenly distributed to communities and function as the main gateway for information exchange and interactions. It also suggests that the architecture of the combined network is a big system formed by several sub-networks that connect with each other through a small hub, most of the targets in the network work mostly with the targets within their communities.

The target-pathway mapping returned a solid result with a very low p-value, meaning that the targets in these communities are highly accordant with the targets in the pathways recorded in the database. The result also contains a lot of pathways that are closely related to AD and neurological disorders (**Table 16**), such as the Huntington disease pathway, Alzheimer disease-presenilin pathway, p53 pathway and Alzheimer disease-amyloid secretase pathway.

Table 16. Target-pathway mapping results

Community	**Pathways**	**P-value**
Community 1	FAS signaling pathway (P00020)	< 0.001
Community 1	Ras Pathway (P04393)	< 0.001
Community 1	PDGF signaling pathway (P00047)	< 0.001
Community 1	Angiotensin II-stimulated signaling through G proteins and beta-arrestin (P05911)	< 0.001
Community 1	Interleukin signaling pathway (P00036)	0.00236
Community 1	Wnt signaling pathway (P00057)	0.00121
Community 1	Huntington disease (P00029)	0.00367
Community 1	p53 pathway (P00059)	0.00459
Community 1	Alzheimer disease-presenilin pathway (P00004)	0.00138
Community 1	p38 MAPK pathway (P05918)	0.0132
Community 1	Parkinson disease (P00049)	0.0135
Community 1	Integrin signaling pathway (P00034)	0.0294
Community 2	Ionotropic glutamate receptor pathway (P00037)	< 0.001
Community 2	Muscarinic acetylcholine receptor 1 and 3 signaling pathway (P00042)	< 0.001
Community 2	5HT1 type receptor-mediated signaling pathway (P04373)	< 0.001
Community 2	Enkephalin release (P05913)	< 0.001
Community 2	Synaptic vesicle trafficking (P05734)	< 0.001
Community 2	Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway (P00027)	< 0.001
Community 2	Metabotropic glutamate receptor group II pathway (P00040)	< 0.001
Community 2	Endothelin signaling pathway (P00019)	0.00296
Community 2	Opioid proopiomelanocortin pathway (P05917)	0.00136
Community 3	Alzheimer disease-amyloid secretase pathway (P00003)	< 0.001
Community 4	Apoptosis signaling pathway (P00006)	< 0.001

Community 5	Plasminogen activating cascade (P00050)	< 0.001
Community 5	Cholesterol biosynthesis (P00014)	0.0223
Community 6	Cadherin signaling pathway (P00012)	0.0494
Community 10	Cell-cell junction organization (R-HSA-421270)	0.00992
Community 10	Nectin/Necl trans heterodimerization (R-HSA-420597)	0.0177
Community 10	Cell junction organization (R-HSA-446728)	0.0275

Figure 10 provides a more direct way to exhibit the results of target-pathway mapping. The radius of the sectors is calculated by log (1/p-value) and the angle of the sector is the percentage of targets contained in this sector. As you can see from **Figure 10,** community 1 and community 2 are mapped to many pathways with high credibility. It's fairly understandable because these two communities contain the largest amount of targets and may result in mismatches.

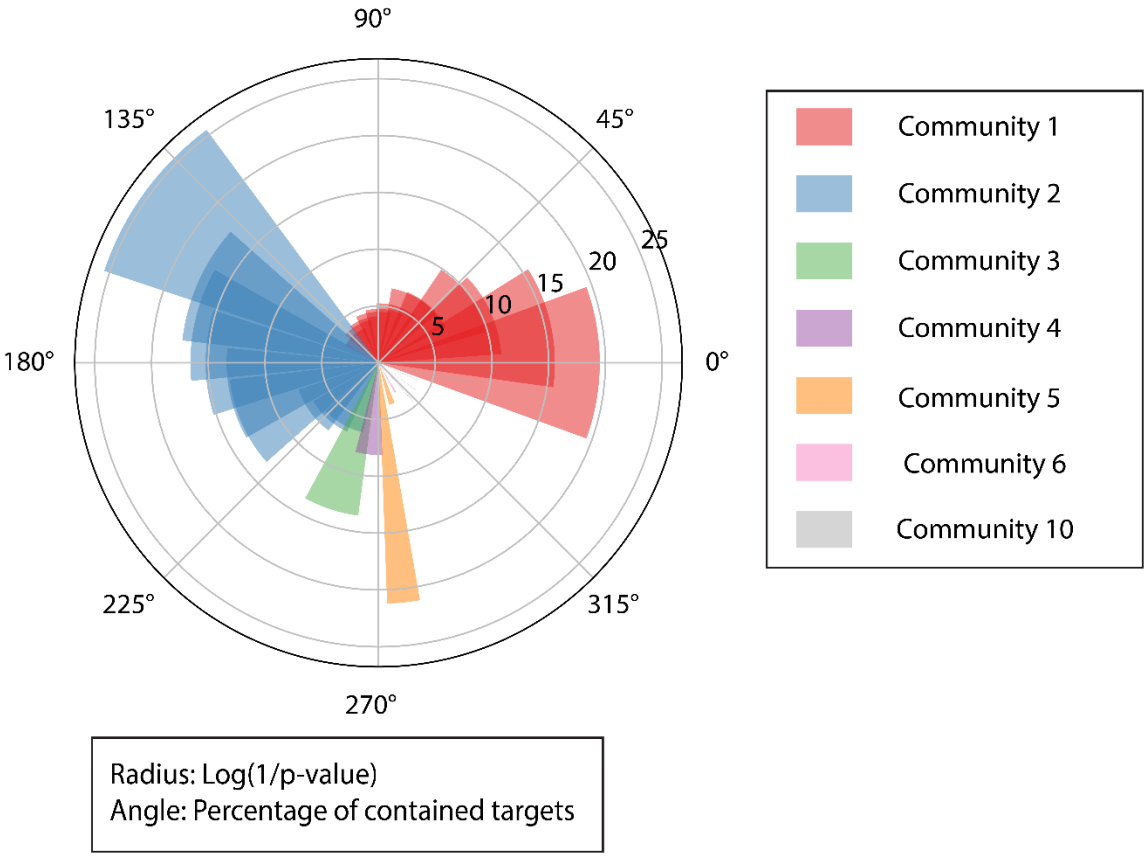

Figure 10. Distribution of targets and p-value for target-pathway mapping results

Results of pathway mapping are shown in the figure. The radius represents the p-value of the mapping, higher bars have a smaller p-value and the angle of the bar represent the percentage of contained targets. It's natural that the first two communities are matched to different pathways because they have relatively more targets and protein target can function in different pathways.

3.2.2 Overlapping proteins between AD and Psychosis

Since the object of this study is to study the development of psychosis in AD, the overlapping targets between AD and psychosis are a group of targets that we should pay additional attention to. The net-influence parameters of the 90 overlapped targets are shown in **Table 17**. Most targets in the overlapping part enjoy a Betweenness above average which side support the bridging role of the shared targets.

Table 17. Overview of net-influencer for overlapping proteins

Target	Degree	Eigenvector	Betweenness
SEMA3A	0.0220	0.0140	0.0046
TUSC3	0.0048	0.0002	0.0025
RPN2	0.0048	0.0006	0.0019
AMBRA1	0.0055	0.0031	0.0002
BECN1	0.0509	0.0522	0.020
CACNA1C	0.0461	0.0179	0.0245
SGK1	0.033	0.0317	0.008
ADAM10	0.0571	0.0473	0.0105
GRIN2A	0.0647	0.0357	0.0208
FYN	0.0826	0.0623	0.0382
ANK3	0.0268	0.006	0.0115
TBXAS1	0.0083	0.0036	0.0021
EFNA5	0.0255	0.0177	0.0042
POLN	0.0055	0.0022	0.0026
CHRNA3	0.0117	0.0028	0.0012
NOTCH4	0.020	0.0139	0.0072
GRIA1	0.0764	0.0428	0.0348
NTRK3	0.0248	0.0183	0.007
IQGAP2	0.0055	0.0041	0.0038

RELN	0.0392	0.0249	0.0158
NOS1	0.044	0.0432	0.0119
GPC6	0.0145	0.0038	0.0071
TCF7L2	0.0296	0.019	0.0117
TCF4	0.020	0.0145	0.0062
MGLL	0.0172	0.0106	0.0066
DRD3	0.0482	0.0315	0.0043
CHRNA2	0.0145	0.0041	0.0007
PAK2	0.0241	0.0185	0.0046
CTNNA2	0.022	0.0054	0.0116
COL25A1	0.0124	0.0051	0.0035
COL12A1	0.011	0.0051	0.0015
AGER	0.0303	0.0437	0.0042
KIF26B	0.0055	0.0009	0.0007
PPP2R2B	0.0234	0.0110	0.0137
TEK	0.0262	0.0343	0.0060
KALRN	0.0289	0.0132	0.0109
PRKG1	0.0310	0.0253	0.0070
KSR2	0.0103	0.0061	0.0022
COLGALT2	0.0076	0.0009	0.0009
MEIS1	0.0117	0.0047	0.0020
SHISA9	0.0096	0.0038	0.0006
ZKSCAN4	0.0055	0.0017	0.0069
PTPRG	0.0151	0.0093	0.0021
NKAPL	0.0055	0.0001	0.0043
CTNNA3	0.0124	0.0027	0.0024
PDE4B	0.02	0.0082	0.0037
HFE	0.0186	0.0099	0.0121
MSR1	0.0248	0.0202	0.0082
CSMD1	0.0138	0.0012	0.0058
COMT	0.0454	0.0207	0.0125
APBA1	0.0248	0.0102	0.0044
IMMP2L	0.0124	0.0014	0.0047
ELAVL4	0.0165	0.0142	0.0051
LRRTM4	0.0062	0.0004	0.0006
CDH13	0.0110	0.0055	0.0023
ZNF804A	0.0151	0.0021	0.0048
PBRM1	0.0096	0.0083	0.0026
LRRN2	0.0028	0	0.0009
TEP1	0.0062	0.0056	0.0050
STXBP5L	0.0124	0.0015	0.0074

FHIT	0.0165	0.0114	0.0044
SYNGAP1	0.0193	0.0068	0.0013
ZSCAN31	0.0034	0	0.0003
TENM4	0.0076	0.0008	0.0017
ABCB1	0.0310	0.0364	0.009
PLCL1	0.0028	0.0002	0.0002
RBFOX1	0.0351	0.0090	0.0209
FSTL5	0.0048	0.0002	0.0019
SORCS3	0.0055	0.0019	0.0045
NKAIN2	0.0041	0.0002	0.0003
GLIS3	0.0069	0.0027	0.0031
NXN	0.0083	0.0014	0.0017
MAGI2	0.0145	0.0060	0.0044
MEGF10	0.0034	0.0014	0.0003
MPP6	0.0055	0.0010	0.0003
TSPAN18	0.0028	0	0.0004
FRMD4B	0.0021	0	0.0002
MTHFD1L	0.0103	0.0020	0.0006
TMTC1	0.0034	0.0015	0.0001
LIN28B	0.0034	0.004	0.0012
UXS1	0.0048	0.002	0.0064
BICC1	0.0055	0.0004	0.0083
ATXN7L1	0.0048	0.0001	0.0019
EYS	0.0069	0.0018	0.0024
GRAMD1B	0.0028	0.0001	0.0027
TSPAN2	0.0048	0.0008	0.0018
ENOX1	0.0014	0	0
TMEM132D	0.0048	0.0046	0.0055
CR1	0.0124	0.0128	0.0004
PCNX	0.0014	0	0.0001

Figure 11 shows the distribution of connectivity parameters of overlapping targets. Even in the overlapping part of the network, the average betweenness centrality remains relatively low and a few nodes, like FYN and GRIA1, possess a much higher connectivity than other nodes. This observation suggest that even though 90 targets are found overlapped between psychosis and AD, only a few of them is the “bridge” for the transferring of information.

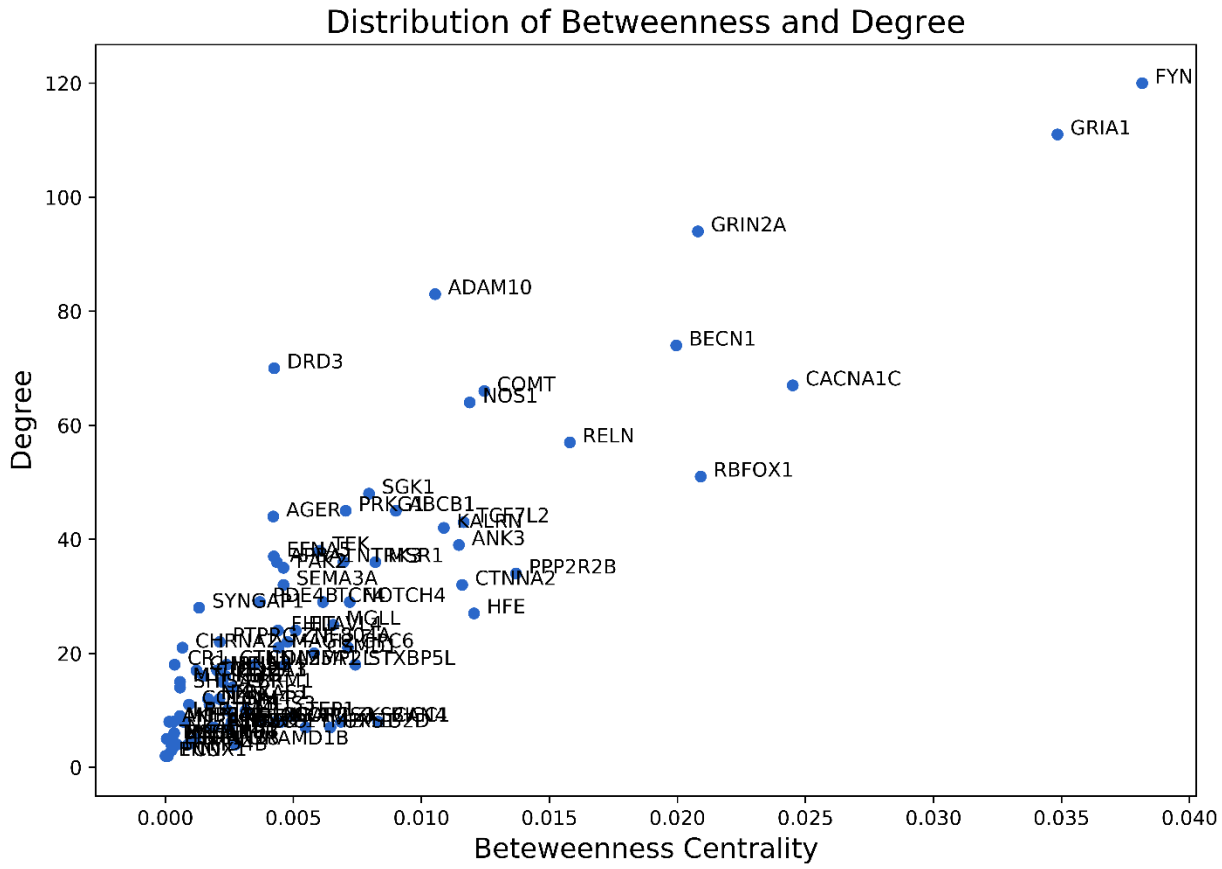

Figure 11. Distribution of degree and betweenness of overlapping proteins between psychosis and AD

The figure above showed the distribution of degrees and betweenness of the nodes in the overlapping part of psychosis and AD. FYN and DRIA1, as members of top 10 targets, enjoy a far larger degree and betweenness centrality.

3.2.3 Vitamin D in network analysis

In the previous statistical analysis, Vitamin D is the most frequently seen name in the results. Therefore, we'd like to explore what happens when Vitamin D related targets are included in the network. Protein targets related to Vitamin D are acquired from online databases like AD and psychosis, the PPI information is also collected following previous procedures. 89 targets and 344 PPI data are collected. Among the 89 targets related to Vitamin D, 21 targets are shared

between the combined network of AD and psychosis and 5 of them are in the overlapping part between AD and psychosis, including COMT, DRD3, CACNA1C, NOTCH4, and AMBRA1. Net influence parameters are calculated for these 21 targets and sorted by their Betweenness centrality.

Table 18. Overview of Vitamin D network

	Node Number	Edge Number	Average Degree	Average Eigenvector	Average Betweenness	Average Clustering Coefficient
Vitamin D	89	344	7.73	0.076	0.018	0.43

Table 19. Overview of net-influencer for overlapping proteins between Vitamin D and combined network

	Betweenness	Degree	Eigenvector
CACNA1C	0.0245	0.0461	0.0179
COMT	0.0125	0.0454	0.0207
NOTCH4	0.0072	0.02	0.0139
DRD3	0.0043	0.0482	0.0315
CD36	0.0024	0.022	0.0149
EGR1	0.0022	0.0619	0.0716
CCL2	0.0018	0.0867	0.1026
DLX5	0.0010	0.0062	0.0034
CYP1A1	0.0008	0.0227	0.0174
A2M	0.0006	0.0358	0.0352
VDR	0.0006	0.0282	0.0409
TGFB2	0.0006	0.0296	0.0388
TIMP3	0.0006	0.0268	0.032
CD14	0.0006	0.0227	0.021
CYP19A1	0.0004	0.0296	0.040
NME1	0.0003	0.0227	0.0202
HSD11B1	0.0002	0.0131	0.0090
MMP12	0.0002	0.0227	0.0297
AMBRA1	0.0002	0.0055	0.0031
ALOX15	0.0001	0.0117	0.0154
GIG25	0.0001	0.0145	0.0142

After sorted by the Betweenness, CACNA1C, COMT, NOTCH4and DRD3 ranked as the highest four targets. The reason for that may be their position in the overlapping part of the

combined network allow them to function more as a bridge to link different components of the network, which also suggest a therapeutic potential in interfering the development of psychosis in AD. Therefore, these four targets gained our special interest.

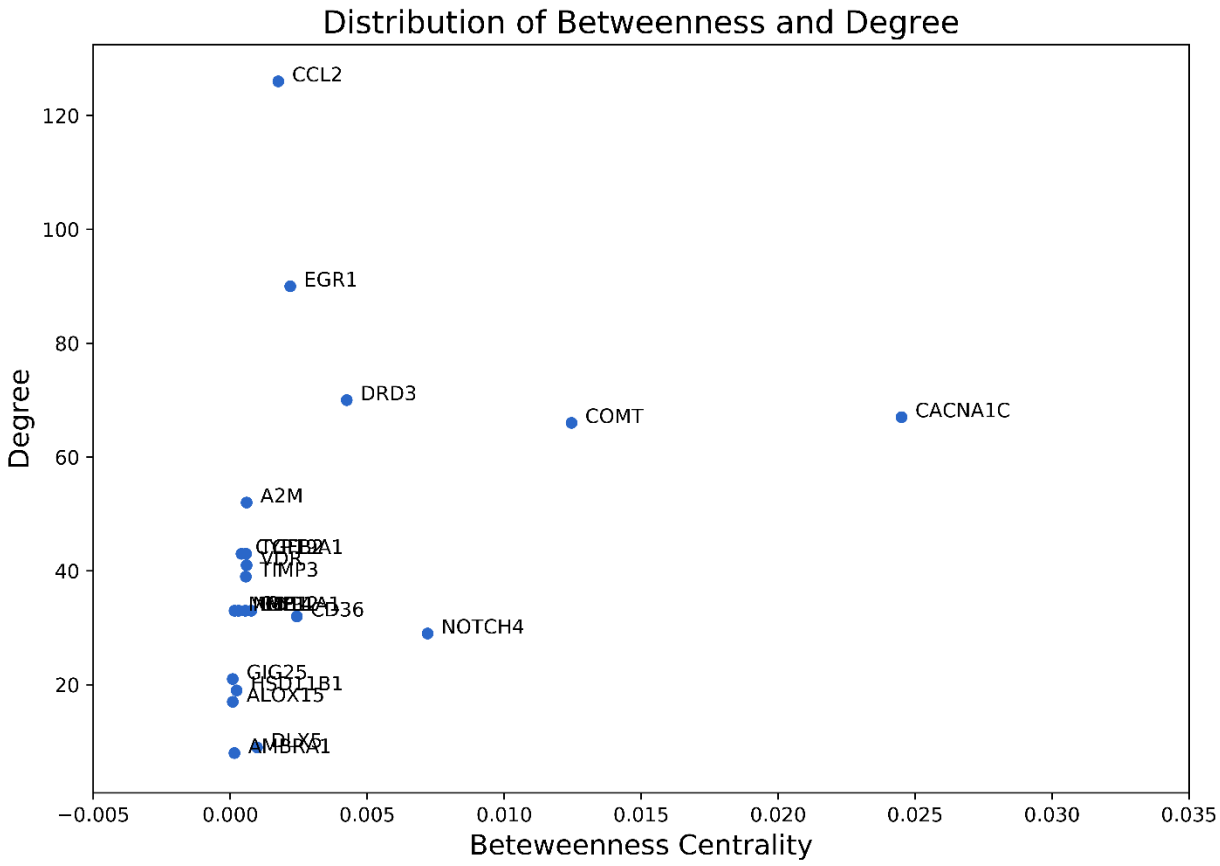

Figure 12. Distribution of degree and Betweenness of overlapping targets between the combined network and Vitamin D

The figure above showed the distribution of degrees and betweenness of the nodes in the overlapping part of psychosis and Vitamin D. Some familiar names like NOTCH4, COMT and CACNA1C are noticed with their potential influence in regulating the information flow between psychosis and AD under Vitamin D's effect. Therefore, an explanation at the mechanism level for Vitamin D's beneficial effect is drawn.

NOTCH4

NOTCH4 is the abbreviation for notch receptor 4, is a receptor for membrane-bound ligands Jagged1, Jagged2 and Delta1 proteins functioning in the regulation of cell-fate determination. It plays an important role in the implementation of differentiation, proliferation and apoptotic programs and the regulation signaling pathway for branching morphogenesis in the development of vascular system[166]. NOTCH4 also regulates the interactions between physically adjacent cells by binding between Notch family receptors and their cognate ligands. It's reported to be related to neurological disorders like schizophrenia, schizoaffective disorder and paranoid[167]. It's also related to the initial tumor perfusion[168-169] and angiogenesis[170]. NOTCH4 is very selectively expressed in vascular endothelial cells and may be the least studied mammalian Notch receptors. It's found abundantly expressed in growing vascular endothelial cells but lower in established capillary beds[170]. The stability of functional NOTCH4 heterodimers requires the participation of Ca^{2+}[171]. No drug is reported to target on NOTCH4 for now.

COMT

COMT is the abbreviation of catechol-O-methyltransferase, it functions as the catalyst for the transfer of a methyl group from S-adenosylmethionine to catecholamines[172], it can bind with different kinds of neurotransmitters such as dopamine, epinephrine, and norepinephrine[173-174]. Through the O-methylation, it plays a critical way in degrading the catecholamine transmitters[174]. In addition to its function in the metabolism of endogenous substances, COMT is also an important player in the metabolism of catechol drugs used in the treatment of several kinds of diseases like hypertension, asthma, and Parkinson disease[173]. COMT is reported having two different forms in tissues, a soluble form (S-COMT) and a membrane-bound form (MB-COMT). The major differences between S-COMT and MB-COMT due to their different structure: N-termini, variations in the transcription process are produced through the use of alternative translation

initiation sites and promoters. COMT is connected to schizophrenia, AD and amphetamine-related disorders[175], and reported for the value in predicting cognitive decline and psychosis[176]. The activity of COMT can be significantly reduced by around 60% by the presence of Ca^{2+}[177], and COMT could in turn influence the expression of calcium transporter in duodenum, kidney and placenta[178]. The current finding suggesting that the serum levels of calcium can be affected by COMT inhibitors or calcium supplementation, which indicating its involvement in the maintenance of calcium metabolism (such as resorption, absorption and re-absorption of calcium ions) in human body[178-182]. Four drugs, Tolcapone, Entacapone, Opicapone and Epinephrine, are approved targeting on COMT. First three of them take COMT as the primary target and indicated for Parkinson Disease.

CACNA1C

CACNA1C is the abbreviation for calcium voltage-gated channel subunit alpha1 C. Calcium channels directly influence the influx of calcium ions into the cell upon membrane polarization. The alpha-1 subunit consists of 24 transmembrane segments and forms the channel through which calcium ions pass into the cell. The calcium channel is constructed by four blocks: alpha-1, alpha-2/delta and gamma, one unit of each of them will form a unit of calcium channel. Multiple isoforms are reported of these proteins, the reason may be that either they are encoded by different genes or they are the result of different splicing segments of transcripts, and some of the isoforms may not be able to produce functional ion channel subunits[166]. CACNA1C is found related to AD and bipolar disorder in GWAS study[183-184], and it's also related to arteriosclerosis[185] and brain neoplasms[186]. Many medications, especially dihydropyridine calcium channel blockers, target on CACNA1C and commonly used in hypertension and other diseases.

DRD3

DRD3 is the abbreviation of dopamine receptor D3, the function of DRD3 is regulated by the G proteins through the inhibition of adenylyl and cyclase[187]. This receptor is majorly located in the limbic areas of brain and this area is associated with cognitive, emotional, and endocrine functions. Variations of this gene are related to a higher risk of hereditary essential tremor 1[188-189]. Alternative splicing of this gene in the transcription process may result in encoding different isoforms that are functionally impaired. DRD3 is actively studied of its role in multiple neuro disorders such as Parkinson's disease, bipolar disorder and schizophrenia with a varied conclusion. Some reports denied the linkage between DRD3 and psychotic symptoms[190] while others hold an opposite opinion[191]. It's also reported that the activation of DRD3 can reduce the secretion of insulin from β-cells[192], this correlation can be explained by a theory that after the activation of DRD3 by dopamine, the Gβγ complex is released and can interact directly with voltage-gated calcium channels, and this theory is verified with results from in vitro experiments[193-194]. DRD3 is also a popular drug target in treating schizophrenia, drug addiction and Parkinson's disease[195] and exhibits an effect of an antidepressant.

4.0 DISCUSSION

Combining the results of RWE studies and network analysis, an obvious connection between calcium homeostasis and AD+P is revealed. Based on the statistic results of clinical data, vitamin D is the most potential and significant candidate in delaying the development in psychosis in AD with positive effects in both the occurrences of AD+P and the time to develop psychosis in AD. The network analysis thus provides a unique view to explain this observation: Vitamin D is related to several protein targets that play critical roles in the combined network of psychosis and AD. These targets locate among the overlapping part of psychosis and AD which allow them maximum influence the signaling and information transition process. Literature can be found reporting that vitamin D deficiency is more frequently observed in patients of psychotic disorders[196-198], the serum level of vitamin D of psychosis patients is significantly lower than healthy patients[198]. But our study is the first to present that taking vitamin D can effectively prevent the development of psychosis in AD. The significant results of Vitamin D and Memantine is also reported in other literatures[199-200] and give birth to a clinical trial to validate the effect of oral Vitamin D3 in AD patients taking Memantine (NCT01409694). Parathyroid hormone (PTH) is another important factor modulating calcium homeostasis and neurological status and with significant connections toward cognitive function and dementia[201]. Hyperparathyroidism, characterized by elevated/high PTH levels, has been associated with many chronic conditions including impaired cognitive function and dementia[202-203]. Elevated PTH is reported to relate to decreased brain blood flow[204] and increased conversion of 1,25-dihydroxyvitamin D which is the active type of Vitamin D[205]. Since elevated PTH is a natural response in the calcium pathways against calcium deficiency, which indicates that in the AD patients the calcium homeostasis is

disturbed and increase vitamin D intake is pointing at the same direction with elevated PYH level. Both Vitamin D and PTH function to restore the calcium homeostasis and can further affect each other. Since PTH, Vitamin D and calcium are in a negative feedback loop, it's hard to identify their role in the chain reaction restoring homeostasis by elevating Vitamin D and PTH is the direction suggested by our studies and other reports.

5.0 CONCLUSION AND FUTURE SPECULATION

In this study, we applied Real-World Evidence and Network analysis approached to the clinical medication data and protein-protein interaction data in order to have a better understanding of the connection between AD and psychosis in both symptom level and mechanism level. The results of both approaches suggest a strong correlation between AD+P and calcium homeostasis, including the alternation of PTH and Vitamin D and several high-impact targets in the PPI network such as NOTCH4, COMT, CACNA1C and DRD3. Multiple network analysis method like centrality and community detection is also helpful in discovering the architecture of biological networks and identifying novel drug targets. To conclude, the results from this study provided a solid ground for the beneficial effect of Vitamin D and the connection between psychosis symptoms in AD and calcium homeostasis and identified a group of targets that Vitamin D apply its effect with, pointing a potential path for further researches and drug development for Alzheimer's Disease management.

In the future, the direction of change of these regulated genes are out next focus point. Since COMT, DRD3 and CACNA1C all have marketed drugs targeted on them, if we know the alteration direction needed to protect our brain against psychosis in AD, we'll be able to repurpose the existing drugs or design novel compounds targeted on these targets based on the structure of known medication.

I'd also like to mention the major limitation of this study. 1) The age of the subjects are elder people, so they may not allow a long enough observation time to distinguish the effect of the drug of interest and other factors like the chronic disease they suffering, and thus bring bias and false positive into our analysis. 2) Because the absence of dosage data, the classification of drug

usage are restrained at binominal, which may cloud the different phenomenon under different administrations like as a treatment or just supplementary. 3) The network analysis is biased by the amount of studies associated with different proteins, meaning that the extensively studied protein targets will have more protein-protein interactions that than the less studied targets even it may not be the truth. Application of betweenness centrality can help minimize this bias but may not be able to eliminate it completely.

Future studies can be conducted following our conclusions and understandings. In order to further clarify the mechanism of psychosis in AD and the role of Vitamin D, differentially expressed genes (DEGs) can be a great hint in exploring the fundamental biological changes in AD+P patients and provide more detailed explanations for the possible role of calcium homeostasis. More comprehensive, detailed and well-controlled clinical studies is another great method in the future study if we can include the dosage information, complications and their corresponding gene expression data. Network analysis can also be further modified with directional PPI data and the fold change of gene expression under disease condition.

APPENDIX A Reference list for genes and official full names

Gene	Official Full Name
A2M	Alpha-2-macroglobulin
ABCB1	Multidrug resistance protein 1
ADAM10	Disintegrin and metalloproteinase domain-containing protein 10
AGER	Advanced glycosylation end product-specific receptor
AKT1	RAC-alpha serine/threonine-protein kinase
ALB	Albumin
ALOX15	Arachidonate 15-lipoxygenase
AMBRA1	Activating molecule in BECN1-regulated autophagy protein 1
ANK3	Ankyrin-3
APBA1	Amyloid-beta A4 precursor protein-binding family A member 1
APOE	Apolipoprotein E
APP	Amyloid beta precursor protein
ATXN7L1	Ataxin-7-like protein 1
BECN1	Beclin-1
BICC1	Protein bicaudal C homolog 1
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C
CASP3	Caspase 3
CCL2	C-C motif chemokine 2
CD14	Monocyte differentiation antigen CD14
CD36	Monocyte differentiation antigen CD36
CDH13	Cadherin-13
CHRNA2	Neuronal acetylcholine receptor subunit alpha-2
CHRNA3	Neuronal acetylcholine receptor subunit alpha-3
CHRNA7	Neuronal acetylcholine receptor subunit alpha-7
COL12A1	Collagen alpha-1(XII) chain
COL25A1	Collagen alpha-1(XXV) chain
COLGALT2	Procollagen galactosyltransferase 2
COMT	Catechol O-methyltransferase
CR1	Complement receptor type 1
CSMD1	CUB and sushi domain-containing protein 1
CTNNA2	Catenin alpha-2
CTNNA3	Catenin alpha-3
CYP1A1	Cytochrome P450 1A1
DISC1	Disrupted in schizophrenia 1 protein

DRD3	D(3) dopamine receptor
EFNA5	Ephrin-A5
EGR1	Early growth response protein 1
ELAVL4	ELAV-like protein 4
ENOX1	Ecto-NOX disulfide-thiol exchanger 1
EYS	Protein eyes shut homolog
FHIT	Bis(5'-adenosyl)-triphosphatase
FRMD4B	FERM domain-containing protein 4B
FSTL5	Follistatin-related protein 5
FYN	FYN proto-oncogene, Src family tyrosine kinase
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GIG25	Serpin family A member 3
GLIS3	Zinc finger protein GLIS3
GPC6	Glypican-6
GRAMD1B	GRAM domain containing 1B
GRIA1	Glutamate ionotropic receptor AMPA type subunit 1
GRIN2A	Glutamate receptor ionotropic, NMDA 2A
HFE	Hereditary hemochromatosis protein
HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1
HTR2A	5-hydroxytryptamine receptor 2A
IL6	Interleukin-6
IMMP2L	Mitochondrial inner membrane protease subunit 2
INS	Insulin
IQGAP2	Ras GTPase-activating-like protein
KALRN	Kalirin
KIF26B	Kinesin-like protein
KSR2	Kinase suppressor of Ras 2
LIN28B	Protein lin-28 homolog B
LRRN2	Leucine rich repeat neuronal 2
LRRTM4	Leucine-rich repeat transmembrane neuronal protein 4
MAGI2	Membrane-associated guanylate kinase
MAPK1	Mitogen-activated protein kinase 1
MAPK3	Mitogen-activated protein kinase 3
MEGF10	Multiple epidermal growth factor-like domains protein 10
MEIS1	Homeobox protein Meis1
MGLL	Monoglyceride lipase
MMP12	Macrophage metalloelastase
MPP6	MAGUK p55 subfamily member 6
MSR1	Macrophage scavenger receptor types I and II

MTHFD1L	Monofunctional C1-tetrahydrofolate synthase
NKAIN2	Sodium/potassium-transporting ATPase subunit beta-1-interacting protein 2
NKAPL	NKAP-like protein
NME1	Nucleoside diphosphate kinase A
NOS1	Nitric oxide synthase, brain
NOTCH4	Neurogenic locus notch homolog protein 4
NRG1	Pro-neuregulin-1, membrane-bound isoform
NTRK3	NT-3 growth factor receptor
NXN	Nucleoredoxin
PAK2	Serine/threonine-protein kinase PAK 2
PBRM1	Protein polybromo-1
PCNX	Pecanex-like protein 1
PDE4B	AMP-specific 3',5'-cyclic phosphodiesterase 4B
PGBD1	Piggybac transposable element-derived protein 1
PLCL1	Inactive phospholipase C-like protein 1
POLN	DNA polymerase nu
PPP2R2B	Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B beta isoform
PRKG1	cGMP-dependent protein kinase 1
PTPRG	Receptor-type tyrosine-protein phosphatase gamma
RBFOX1	RNA binding fox-1 homolog 1
RELN	Reelin
RGS4	Regulator of G-protein signaling 4
RPN2	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2
RTN4R	Reticulon-4 receptor
S100A8	Protein S100-A8
SEMA3A	Semaphorin-3A
SGK1	Serine/threonine-protein kinase Sgk1
SHISA9	Protein shisa-9
SORCS3	Sortilin related VPS10 domain containing receptor 3
STXBP5L	Syntaxin-binding protein 5-like
SYNGAP1	Ras/Rap GTPase-activating protein SynGAP
TBXAS1	Thromboxane-A synthase; Cytochrome P450 family 5
TCF4	Transcription factor 4
TCF7L2	Transcription factor 7-like 2
TEK	Angiopoietin-1 receptor
TENM4	Teneurin-4
TEP1	Telomerase protein component 1
TIMP3	Metalloproteinase inhibitor 3
TMEM132D	Transmembrane protein 132D

TMTC1	Transmembrane and tetratricopeptide repeat containing 1
TNF	Tumor necrosis factor
TP53	Cellular tumor antigen p53
TSPAN18	Tetraspanin-18
TSPAN2	Tetraspanin-2
TUSC3	Tumor suppressor candidate 3
UXS1	UDP-glucuronic acid decarboxylase 1
VDR	Vitamin D3 receptor
VEGFA	Vascular endothelial growth factor A
ZKSCAN4	Zinc finger protein with KRAB and SCAN domains 4
ZNF804A	Zinc finger protein 804A
ZSCAN26	Zinc finger and SCAN domain-containing protein 26
ZSCAN31	Zinc finger and SCAN domain-containing protein 31

APPENDIX B Baseline characteristics of subjects grouped by usage of Vitamin D

Variable	VD, N=173	No VD, N=450	DF	p value*
Follow-up, years	3.00 (2.02)	2.80 (2.01)	309	0.271
Baseline MMSE	22.3 (3.92)	20.8 (4.97)	392	0.001
Age at baseline	78.7 (6.73)	80.7 (6.95)	321	0.001
Sex				
Female	108 (62.4 %)	269(59.9 %)	1	0.62
Male	65 (37.6 %)	180(40.1%)		
Race				
Asian	1 (0.578 %)	1 (0.222 %)	2	0.31
African-American	11(6.36 %)	32 (7.11 %)		
Caucasian	161 (93.1%)	416 (92.4 %)		
Education, years	14.7 (2.87)	13.5 (3.08)	332	<0.001

MMSE: Mini-mental State Examination.

Results for AD-P and AD+P are mean (SD) for continuous variables and total (%) for categorical variables.

T-test for continuous variables, Chi-square test for sex and education, Fisher exact test for race.

APPENDIX C Description of data source and studies involved

Data source description for psychosis related protein targets

	Data source database	Associated targets reports	Unique targets count
Alzheimer's disease	GWAS catalog	1489*	1061
	Metacore	769	
	BaseSpace	81	
Psychosis	GWAS catalog	2639*	483
	Metacore	67	
	BaseSpace	100	

***Repeat reports of association were not removed**

APPENDIX D Details of AD and Psychosis related studies

PSYCHOSIS RELATED ASSOCIATION STUDIES

Studies	PubMed ID	First Author	Date	Journal	Association count
Genome-wide association study of schizophrenia in ashkenazi jews.	26198764	Goes fs	7/21/2015	Am j med genet b neuropsychiatr genet	649
Genome-wide association study detected novel susceptibility genes for schizophrenia and shared trans-populations/diseases genetic effect.	30285260	Ikeda m	10/3/2018	Schizophr bull	485
Meta-analysis of gwas of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia.	28540026	Anney rjl	5/22/2017	Mol autism	301
Genome-wide association study of paliperidone efficacy.	27846195	Li q	11/11/2016	Pharmacogenet genomics	249
Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia.	28991256	Li z	10/9/2017	Nat genet	222
Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions	29483656	Pardinas af	2/26/2018	Nat genet	108

under strong background selection.					
Biological insights from 108 schizophrenia-associated genetic loci.	25056061	Ripke s	7/22/2014	Nature	98
Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis.	23453885	Smoller jw	2/27/2013	Lancet	74
Five novel loci associated with antipsychotic treatment response in patients with schizophrenia: a genome-wide association study.	29503163	Yu h	3/1/2018	Lancet psychiatry	50
Genome-wide association studies of smooth pursuit and antisaccade eye movements in psychotic disorders: findings from the b-snip study.	29064472	Lencer r	10/24/2017	Transl psychiatry	36
A molecular pathway analysis informs the genetic risk for arrhythmias during antipsychotic treatment.	29064910	Kure fischer e	10/23/2017	Int clin psychopharmacol	34
Genome-wide association study in a swedish population yields support for greater cnv and mhc involvement in schizophrenia compared with bipolar disorder.	22688191	Bergen se	6/12/2012	Mol psychiatry	28
Genome-wide association analysis identifies 13 new risk loci for schizophrenia.	23974872	Ripke s	8/25/2013	Nat genet	27
Genome-wide association study identifies five new schizophrenia loci.	21926974	Ripke s	9/18/2011	Nat genet	25

Genome-wide association analysis to predict optimal antipsychotic dosage in schizophrenia: a pilot study.	26821981	Koga at	1/28/2016	J neural transm (vienna)	21
Association of polygenic score for schizophrenia and hla antigen and inflammation genes with response to lithium in bipolar affective disorder: a genome-wide association study.	29121268	Amare at	11/9/2017	Jama psychiatry	16
Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or schizophrenia reveal eight novel genetic loci for depression.	30626913	Amare at	1/9/2019	Mol psychiatry	16
Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms.	23212062	Fanous ah	12/1/2012	Am j psychiatry	16
A comprehensive family-based replication study of schizophrenia genes.	23894747	Aberg ka	2/1/2013	Jama psychiatry	14
Identifying the genetic risk factors for treatment response to lurasidone by genome-wide association study: a meta-analysis of samples from three independent clinical trials.	29730043	Li j	5/2/2018	Schizophr res	13
Genome-wide association study identifies common variants associated with	25944848	Athanasiu l	5/5/2015	J psychopharmacol	12

pharmacokinetics of psychotropic drugs.					
Genome-wide association study of multiplex schizophrenia pedigrees.	22885689	Levinson df	9/1/2012	Am j psychiatry	11
Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia.	27400856	Legge se	7/12/2016	Mol psychiatry	10
Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia.	24280982	Ruderfer dm	11/26/2013	Mol psychiatry	10
Common variants on 2p16.1, 6p22.1 and 10q24.32 are associated with schizophrenia in han chinese population.	27922604	Yu h	12/6/2016	Mol psychiatry	9
Common variants conferring risk of schizophrenia.	19571808	Stefansson h	7/1/2009	Nature	7
The common variants implicated in microstructural abnormality of first episode and drug-naã¯ve patients with schizophrenia.	28924203	Ren hy	9/18/2017	Sci rep	7
A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype.	19023125	Potkin sg	11/20/2008	Schizophr bull	6
Genetic underpinnings of left superior temporal gyrus thickness in patients with schizophrenia.	26249676	Wolthusen rp	8/7/2015	World j biol psychiatry	6
Genomewide association for schizophrenia in the catie study: results of stage 1.	18347602	Sullivan pf	3/18/2008	Mol psychiatry	6

Genetic predictors of risk and resilience in psychiatric disorders: a cross-disorder genome-wide association study of functional impairment in major depressive disorder, bipolar disorder, and schizophrenia.	24039173	Mcgrath lm	9/13/2013	Am j med genet b neuropsychiatr genet	5
Gwas meta analysis identifies tsnare1 as a novel schizophrenia / bipolar susceptibility locus.	24166486	Sleiman p	10/29/2013	Sci rep	5
Common polygenic variation contributes to risk of schizophrenia and bipolar disorder.	19571811	Purcell sm	7/1/2009	Nature	4
Evidence for genetic contribution to the increased risk of type 2 diabetes in schizophrenia.	30470734	Hackinger s	11/23/2018	Transl psychiatry	4
Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci.	23358160	Borglum ad	1/29/2013	Mol psychiatry	4
Infection and inflammation in schizophrenia and bipolar disorder: a genome wide study for interactions with genetic variation.	25781172	Avramopoulos d	3/17/2015	Plos one	4
A genome-wide association study of early gamma-band response in a schizophrenia case-control sample.	28922980	Konte b	9/19/2017	World j biol psychiatry	3
Bcl9 and c9orf5 are associated with negative symptoms in schizophrenia: meta-	23382809	Xu c	1/29/2013	Plos one	3

analysis of two genome-wide association studies.					
Gene variants associated with schizophrenia in a norwegian genome-wide study are replicated in a large european cohort.	20185149	Athanasiu l	2/23/2010	J psychiatr res	3
Genome-wide association analysis of eye movement dysfunction in schizophrenia.	30120336	Kikuchi m	8/17/2018	Sci rep	3
Genome-wide association analysis with gray matter volume as a quantitative phenotype in first-episode treatment-naã¯ve patients with schizophrenia.	24086445	Wang q	9/24/2013	Plos one	3
Identification of loci associated with schizophrenia by genome-wide association and follow-up.	18677311	O'donovan mc	7/30/2008	Nat genet	3
A genome-wide association study in individuals of african ancestry reveals the importance of the duffy-null genotype in the assessment of clozapine-related neutropenia.	30647433	Legge se	1/15/2019	Mol psychiatry	2
Common variants on 8p12 and 1q24.2 confer risk of schizophrenia.	22037555	Shi y	10/30/2011	Nat genet	2
Common variants on chromosome 6p22.1 are associated with schizophrenia.	19571809	Shi j	7/1/2009	Nature	2
Dock4 and ceacam21 as novel schizophrenia candidate genes in the jewish population.	21682944	Alkelai a	6/20/2011	Int j neuropsychopharmacol	2
Genome-wide association analysis of age at onset in	21688384	Wang ks	6/17/2011	Am j med genet b neuropsychiatr genet	2

schizophrenia in a european-american sample.					
Genome-wide association study identifies a susceptibility locus for schizophrenia in han chinese at 11p11.2.	22037552	Yue wh	10/30/2011	Nat genet	2
Genome-wide association study implicates hla-c*01:02 as a risk factor at the major histocompatibility complex locus in schizophrenia.	22883433	Irish schizophrenia genomics consortium and the wellcome trust case control consortium 2	8/7/2012	Biol psychiatry	2
Genome-wide association study of treatment refractory schizophrenia in han chinese.	22479419	Liou yj	3/27/2012	Plos one	2
Pharmacogenomic study of clozapine-induced agranulocytosis/granulocytopenia in a japanese population.	26876947	Saito t	2/11/2016	Biol psychiatry	2
A genetic locus in 7p12.2 associated with treatment resistant schizophrenia.	25223841	Li j	9/13/2014	Schizophr res	1
A genome-wide association study for quantitative traits in schizophrenia in china.	21679298	Ma x	6/16/2011	Genes brain behav	1
A genome-wide association study in 574 schizophrenia trios using dna pooling.	18332876	Kirov g	3/11/2008	Mol psychiatry	1
Common variants on xq28 conferring risk of schizophrenia in han chinese.	24043878	Wong eh	9/16/2013	Schizophr bull	1

Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia.	17522711	Lencz t	3/20/2007	Mol psychiatry	1
Evidence for shared genetic risk between methamphetamine-induced psychosis and schizophrenia.	23594818	Ikeda m	4/17/2013	Neuropsychopharmacology	1
Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women.	18282107	Shifman s	2/15/2008	Plos genet	1
Genome-wide association study implicates ndst3 in schizophrenia and bipolar disorder.	24253340	Lencz t	11/19/2013	Nat commun	1
Genome-wide association study with the risk of schizophrenia in a korean population.	26531332	Kim lh	11/14/2015	Am j med genet b neuropsychiatr genet	1
Heritability informed power optimization (hipo) leads to enhanced detection of genetic associations across multiple traits.	30289880	Qi g	10/5/2018	Plos genet	1
Whole-genome-wide association study in the bulgarian population reveals hhat as schizophrenia susceptibility gene.	23142968	Betcheva et	11/7/2012	Psychiatr genet	1

ALZHEIMER'S DISEASE RELATED ASSOCIATION STUDIES

Studies	PubMed ID	First Author	Date	Association Count
Gwas on family history of Alzheimer's disease.	29777097	Marioni Re	5/18/2018	221
Family-based association analyses of imputed genotypes reveal genome-wide significant association of Alzheimer's disease with osbpl6, ptprg, and pdcl3.	26830138	Herold C	2/2/2016	203
Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk.	30617256	Jansen Ie	1/7/2019	141
Two novel loci, cobl and slc10a2, for Alzheimer's disease in african americans.	27770636	Mez J	10/20/2016	123
A novel alzheimer disease locus located near the gene encoding tau protein.	25778476	Jun G	3/17/2015	50
Genome-wide association study of the rate of cognitive decline in Alzheimer's disease.	23535033	Sherva R	3/24/2013	44
Genetic data and cognitively defined late-onset Alzheimer's disease subgroups.	30514930	Mukherjee S	12/4/2018	33
Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease.	24162737	Lambert Jc	10/27/2013	33
Genome-wide association study of Alzheimer's disease	29274321	Chung J	12/20/2017	31

endophenotypes at prediagnosis stages.				
Genome-wide association study of Alzheimer's disease with psychotic symptoms.	22005930	Hollingworth P	10/18/2011	19
Genetic risk factors for the posterior cortical atrophy variant of Alzheimer's disease.	26993346	Schott Jm	3/15/2016	18
Genome-wide association with mri atrophy measures as a quantitative trait locus for Alzheimer's disease.	21116278	Furney Sj	11/30/2010	17
Rare coding variants in plcg2, abi3, and trem2 implicate microglial-mediated innate immunity in Alzheimer's disease.	28714976	Sims R	9/1/2017	17
Transethnic genome-wide scan identifies novel Alzheimer's disease loci.	28183528	Jun Gr	2/6/2017	15
Apoe and bche as modulators of cerebral amyloid deposition: a florbetapir pet genome-wide association study.	23419831	Ramanan Vk	2/19/2013	13
Genome-wide association analysis of age-at-onset in Alzheimer's disease.	22005931	Kamboh Mi	10/18/2011	13
Genome-wide association and linkage study in the amish detects a novel candidate late-onset alzheimer disease gene.	22881374	Cummings Ac	9/1/2012	13
A comprehensive genetic association study of alzheimer disease in african americans.	22159054	Logue Mw	12/1/2011	11
Single-nucleotide polymorphisms are associated with cognitive decline at Alzheimer's disease conversion within mild cognitive impairment patients.	28560309	Lee E	4/23/2017	11
Common variants at ms4a4/ms4a6e, cd2ap, cd33 and epha1 are associated with	21460841	Naj Ac	4/3/2011	9

late-onset Alzheimer's disease.				
Genome-wide association study of Alzheimer's disease.	22832961	Kamboh Mi	5/15/2012	8
Genetic determinants of survival in patientswith alzheimerâ€™s disease.	25649651	Wang X	2/3/2015	7
Genome-wide association study of csf biomarkers abeta1-42, t-tau, and p-tau181p in the adni cohort.	21123754	Kim S	12/1/2010	7
Gwas of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease.	23562540	Cruchaga C	4/4/2013	6
Genome-wide analysis reveals novel genes influencing temporal lobe structure with relevance to neurodegeneration in Alzheimer's disease.	20197096	Stein Jl	3/1/2010	5
Genome-wide association study of csf levels of 59 Alzheimer's disease candidate proteins: significant associations with proteins involved in amyloid processing and inflammation.	25340798	Kauwe Js	10/23/2014	5
Genome-wide scan of copy number variation in late-onset Alzheimer's disease.	20061627	Heinzen El	9/11/2009	5
Overrepresentation of glutamate signaling in Alzheimer's disease: network-based pathway enrichment using meta-analysis of genome-wide association studies.	24755620	Perez-Palma E	4/22/2014	5
The membrane-spanning 4-domains, subfamily a (ms4a) gene cluster contains a common variant associated with Alzheimer's disease.	21627779	Antunez C	5/31/2011	5
Common variants at abca7, ms4a6a/ms4a4e, epha1, cd33	21460840	Hollingworth P	4/3/2011	4

and cd2ap are associated with Alzheimer's disease.				
Dementia revealed: novel chromosome 6 locus for late-onset alzheimer disease provides genetic evidence for folate-pathway abnormalities.	20885792	Naj Ac	9/23/2010	4
A genome-wide association study of late-onset Alzheimer's disease in a japanese population.	26049409	Hirano A	6/5/2015	3
Abcc9 gene polymorphism is associated with hippocampal sclerosis of aging pathology.	24770881	Nelson Pt	4/27/2014	3
F-box/lrr-repeat protein 7 is genetically associated with Alzheimer's disease.	26339675	Tosto G	6/18/2015	3
Genome-wide association study identifies variants at clu and cr1 associated with Alzheimer's disease.	19734903	Lambert Jc	9/6/2009	3
Genome-wide association study identifies variants at clu and picalm associated with Alzheimer's disease.	19734902	Harold D	9/6/2009	3
Genome-wide association study implicates a chromosome 12 risk locus for late-onset alzheimer disease.	19118814	Beecham Gw	1/3/2009	3
Pharmacogenomics in Alzheimer's disease: a genome-wide association study of response to cholinesterase inhibitors.	23374588	Martinelli-Boneschi F	1/29/2013	3
A genome-wide association study for late-onset Alzheimer's disease using dna pooling.	18823527	Abraham R	9/29/2008	2
A large scale multivariate parallel ica method reveals novel imaging-genetic relationships for Alzheimer's disease in the adni cohort.	22245343	Meda Sa	1/8/2012	2
Alzheimer disease pathology in cognitively healthy elderly: a genome-wide study.	20452100	Kramer Pl	5/6/2010	2

Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to apoe.	18976728	Bertram L	10/29/2008	2
Hidden heterogeneity in Alzheimer's disease: insights from genetic association studies and other analyses.	29107063	Yashin Ai	10/26/2017	2
Meta-analysis for genome-wide association study identifies multiple variants at the bin1 locus associated with late-onset Alzheimer's disease.	21390209	Hu X	2/24/2011	2
Sorl1 is genetically associated with late-onset Alzheimer's disease in japanese, koreans and caucasians.	23565137	Miyashita A	4/2/2013	2
Suclg2 identified as both a determinator of csf aî²1-42 levels and an attenuator of cognitive decline in Alzheimer's disease.	25027320	Ramirez A	7/15/2014	2
Variants in the atp-binding cassette transporter (abca7), apolipoprotein e ïµ4,and the risk of late-onset alzheimer disease in african americans.	23571587	Reitz C	4/10/2013	2
A high-density whole-genome association study reveals that apoe is the major susceptibility gene for sporadic late-onset Alzheimer's disease.	17474819	Coon Kd	4/1/2007	1
A potential endophenotype for Alzheimer's disease: cerebrospinal fluid clusterin.	26545630	Deming Y	9/25/2015	1
Candidate single-nucleotide polymorphisms from a genomewide association study of alzheimer disease.	17998437	Li H	11/12/2007	1
Cdk5rap2 gene and tau pathophysiology in late-onset sporadic Alzheimer's disease.	29360470	Miron J	1/19/2018	1

Examination of the current top candidate genes for ad in a genome-wide association study.	19125160	Feulner Tm	1/7/2009	1
Gab2 alleles modify Alzheimer's risk in apoe epsilon4 carriers.	17553421	Reiman Em	6/7/2007	1
Genetic variation in pcdh11x is associated with susceptibility to late-onset Alzheimer's disease.	19136949	Carrasquillo Mm	1/11/2009	1
Genome-wide analysis of genetic loci associated with alzheimer disease.	20460622	Seshadri S	5/12/2010	1
Genome-wide association of familial late-onset Alzheimer's disease replicates bin1 and clu and nominates cugbp2 in interaction with apoe.	21379329	Wijsman Em	2/17/2011	1
Genome-wide haplotype association study identifies the frmd4a gene as a risk locus for Alzheimer's disease.	22430674	Lambert Jc	3/20/2012	1
Shared genetic contribution to ischaemic stroke and Alzheimer's disease.	26913989	Traylor M	2/23/2016	1
Sorl1 as an Alzheimer's disease predisposition gene?	17975299	Webster Ja	11/1/2007	1
Variant of trem2 associated with the risk of Alzheimer's disease.	23150908	Jonsson T	11/14/2012	1

BIBLIOGRAPHY

1. Dickson, D. W.; Crystal, H. A.; Mattiace, L. A.; Masur, D. M.; Blau, A. D.; Davies, P.; Yen, S.-H.; Aronson, M. K., Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiol. Aging* **1992,** *13* (1), 179-189.
2. Thorgrimsen, L.; Selwood, A.; Spector, A.; Royan, L.; de Madariaga Lopez, M.; Woods, R.; Orrell, M., Whose quality of life is it anyway?: The validity and reliability of the Quality of Life-Alzheimer's Disease (QoL-AD) scale. *Alzheimer Dis. Assoc. Disord.* **2003,** *17* (4), 201-208.
3. Wimo, A.; Prince, M., World Alzheimer Report. *The global economic impact of dementia. Alzheimer's Disease International* **2010**.
4. Rosendorff, C.; Beeri, M. S.; Silverman, J. M., Cardiovascular risk factors for Alzheimer's disease. *The American journal of geriatric cardiology* **2007,** *16* (3), 143-149.
5. Barnes, D. E.; Yaffe, K., The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology* **2011,** *10* (9), 819-828.
6. Van Den Heuvel, C.; Thornton, E.; Vink, R., Traumatic brain injury and Alzheimer's disease: a review. *Prog. Brain Res.* **2007,** *161*, 303-316.
7. Sharp, E. S.; Gatz, M., The relationship between education and dementia an updated systematic review. *Alzheimer Dis. Assoc. Disord.* **2011,** *25* (4), 289.
8. Sperling, R. A.; Aisen, P. S.; Beckett, L. A.; Bennett, D. A.; Craft, S.; Fagan, A. M.; Iwatsubo, T.; Jack Jr, C. R.; Kaye, J.; Montine, T. J., Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia* **2011,** *7* (3), 280-292.
9. Waldemar, G.; Dubois, B.; Emre, M.; Georges, J.; McKeith, I. G.; Rossor, M.; Scheltens, P.; Tariska, P.; Winblad, B., Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur. J. Neurol.* **2007,** *14* (1), e1-e26.
10. Burns, A.; Iliffe, S., Alzheimer's disease. *BMJ* **2009,** *338*.
11. Nygård, L., Instrumental activities of daily living: a stepping-stone towards Alzheimer's disease diagnosis in subjects with mild cognitive impairment? *Acta Neurol. Scand.* **2003,** *107* (s179), 42-46.
12. Bäckman, L.; Jones, S.; Berger, A.-K.; Laukka, E. J.; Small, B. J., Multiple cognitive deficits during the transition to Alzheimer's disease. *Journal of Internal Medicine* **2004,** *256* (3), 195-204.
13. Murray, E.; Buttner, E.; Price, B., Depression and psychosis in neurological practice. *Daroff R, Fenichel G, Jankovic J, Mazziotta J. Bradley's neurology in clinical practice.(6th ed.). Philadelphia, PA: Elsevier/Saunders. ISBN* **2012**, 1-4377.
14. Arnáiz, E.; Almkvist, O., Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. *Acta Neurol. Scand.* **2003,** *107* (s179), 34-41.
15. Burns, A.; Iliffe, S., Dementia. *BMJ* **2009,** *338*.
16. Bachman, D.; Wolf, P. A.; Linn, R.; Knoefel, J.; CobbS, J.; Belanger, A.; D'agostino, R.; White, L., Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurology* **1992,** *42* (1), 115-115.

17. Grundman, M.; Petersen, R. C.; Ferris, S. H.; et al., Mild cognitive impairment can be distinguished from alzheimer disease and normal aging for clinical trials. *Arch. Neurol.* **2004,** *61* (1), 59-66.
18. Förstl, H.; Kurz, A., Clinical features of Alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience* **1999,** *249* (6), 288-290.
19. Carlesimo, G. A.; Oscar-Berman, M., Memory deficits in Alzheimer's patients: A comprehensive review. *Neuropsychol. Rev.* **1992,** *3* (2), 119-169.
20. Jelicic, M.; Bonebakker, A. E.; Bonke, B., Implicit Memory Performance of Patients With Alzheimer's Disease: A Brief Review. *Int. Psychogeriatr.* **1995,** *7* (3), 385-392.
21. Taler, V.; Phillips, N. A., Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review. *Journal of Clinical and Experimental Neuropsychology* **2008,** *30* (5), 501-556.
22. Frank, E. M., Effect of Alzheimer's disease on communication function. *J. S. C. Med. Assoc.* **1994,** *90* (9), 417-23.
23. Ladislav Volicer; David G. Harper; Barbara C. Manning; Rachel Goldstein; Andrew Satlin, Sundowning and Circadian Rhythms in Alzheimer's Disease. *Am. J. Psychiatry* **2001,** *158* (5), 704-711.
24. Gold, D. P.; Reis, M. F.; Markiewicz, D.; Andres, D., When Home Caregiving Ends: A Longitudinal Study of Outcomes for Caregivers of Relatives with Dementia. *J. Am. Geriatr. Soc.* **1995,** *43* (1), 10-16.
25. Kapur, S., Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American journal of Psychiatry* **2003,** *160* (1), 13-23.
26. Verdoux, H.; van Os, J., Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophr. Res.* **2002,** *54* (1), 59-65.
27. Rutter, M.; Greenfeld, D.; Lockyer, L., A five to fifteen year follow-up study of infantile psychosis: II. Social and behavioural outcome. *The British Journal of Psychiatry* **1967,** *113* (504), 1183-1199.
28. Kampman, O.; Laippala, P.; Väänänen, J.; Koivisto, E.; Kiviniemi, P.; Kilkku, N.; Lehtinen, K., Indicators of medication compliance in first-episode psychosis. *Psychiatry Res.* **2002,** *110* (1), 39-48.
29. Mulder, C. L.; Koopmans, G. T.; Hengeveld, M. W., Lack of motivation for treatment in emergency psychiatry patients. *Soc. Psychiatry Psychiatr. Epidemiol.* **2005,** *40* (6), 484-488.
30. Haddock, G.; McCarron, J.; Tarrier, N.; Faragher, E., Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol. Med.* **1999,** *29* (4), 879-889.
31. Asaad, G.; Shapiro, B., Hallucinations: theoretical and clinical overview. *The American journal of psychiatry* **1986**.
32. Black, D. W.; Grant, J. E.; American Psychiatric, A., *DSM-5 TM guidebook the essential companion to the Diagnostic and statistical manual of mental disorders, fifth edition*. American Psychiatric Publishing: Washington, DC, 2014.
33. Posey, T. B.; Losch, M. E., Auditory hallucinations of hearing voices in 375 normal subjects. *Imagin. Cogn. Pers.* **1983,** *3* (2), 99-113.
34. Forest, D. A.; University of, E.; Department of, P., Phenomenology of schizophrenia. University of Edinburgh: Edinburgh, 1973.

35. Waters, F.; Collerton, D.; Ffytche, D. H.; Jardri, R.; Pins, D.; Dudley, R.; Blom, J. D.; Mosimann, U. P.; Eperjesi, F.; Ford, S., Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. *Schizophrenia bulletin* **2014,** *40* (Suppl_4), S233-S245.
36. Corlett, P. R.; Murray, G. K.; Honey, G. D.; Aitken, M. R.; Shanks, D. R.; Robbins, T. W.; Bullmore, E. T.; Dickinson, A.; Fletcher, P. C., Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain* **2007,** *130* (9), 2387-2400.
37. Appelbaum, P. S.; Robbins, P. C.; Roth, L. H., Dimensional approach to delusions: comparison across types and diagnoses. *Am. J. Psychiatry* **1999,** *156* (12), 1938-1943.
38. Kirkpatrick, B.; Fenton, W. S.; Carpenter, W. T.; Marder, S. R., The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr. Bull.* **2006,** *32* (2), 214-219.
39. Crow, T., Positive and negative schizophrenic symptoms and the role of dopamine. *The British Journal of Psychiatry* **1980,** *137* (4), 383-386.
40. Murray, P. S.; Kumar, S.; Demichele-Sweet, M. A.; Sweet, R. A., Psychosis in Alzheimer's disease. *Biological psychiatry* **2014,** *75* (7), 542-52.
41. LEBOVICI, S., THE PSYCHOPATHOLOGY OF DEMENTIA. *Gaz. Med. Fr.* **1980,** *87* (26), 3299-&.
42. Burns, A. In *Psychiatric symptoms and behavioural disturbances in the dementias*, Vienna, Springer Vienna: Vienna, 1997; pp 27-35.
43. Brodaty, H.; Draper, B.; Saab, D.; Low, L.-F.; Richards, V.; Paton, H.; Lie, D., Psychosis, depression and behavioural disturbances in Sydney nursing home residents: prevalence and predictors. *Int. J. Geriatr. Psychiatry* **2001,** *16* (5), 504-512.
44. Lyketsos, C. G.; Sheppard, J.-M. E.; Steinberg, M.; Tschanz, J. A. T.; Norton, M. C.; Steffens, D. C.; Breitner, J. C. S., Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *Int. J. Geriatr. Psychiatry* **2001,** *16* (11), 1043-1053.
45. Lyketsos, C. G.; Steinberg, M.; Tschanz, J. T.; Norton, M. C.; Steffens, D. C.; Breitner, J. C., Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am. J. Psychiatry* **2000,** *157* (5), 708-714.
46. Ropacki, S. A.; Jeste, D. V., Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am. J. Psychiatry* **2005,** *162* (11), 2022-30.
47. Gilley, D. W.; Wilson, R. S.; Beckett, L. A.; Evans, D. A., Psychotic symptoms and physically aggressive behavior in Alzheimer's disease. *J. Am. Geriatr. Soc.* **1997,** *45* (9), 1074-9.
48. Sweet, R. A.; Pollock, B. G.; Sukonick, D. L.; Mulsant, B. H.; Rosen, J.; Klunk, W. E.; Kastango, K. B.; DeKosky, S. T.; Ferrell, R. E., The 5-HTTPR polymorphism confers liability to a combined phenotype of psychotic and aggressive behavior in Alzheimer disease. *Int. Psychogeriatr.* **2001,** *13* (4), 401-9.
49. Lyketsos, C. G.; Sheppard, J. M.; Steinberg, M.; Tschanz, J. A.; Norton, M. C.; Steffens, D. C.; Breitner, J. C., Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *Int. J. Geriatr. Psychiatry* **2001,** *16* (11), 1043-53.
50. Sweet, R. A.; Bennett, D. A.; Graff-Radford, N. R.; Mayeux, R., Assessment and familial aggregation of psychosis in Alzheimer's disease from the National Institute on Aging Late Onset Alzheimer's Disease Family Study. *Brain* **2010,** *133* (Pt 4), 1155-62.
51. Kaufer, D. I.; Cummings, J. L.; Christine, D.; Bray, T.; Castellon, S.; Masterman, D.; MacMillan, A.; Ketchel, P.; DeKosky, S. T., Assessing the impact of neuropsychiatric symptoms

in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J. Am. Geriatr. Soc.* **1998,** *46* (2), 210-5.
52. Scarmeas, N.; Brandt, J.; Albert, M.; Hadjigeorgiou, G.; Papadimitriou, A.; Dubois, B.; Sarazin, M.; Devanand, D.; Honig, L.; Marder, K.; Bell, K.; Wegesin, D.; Blacker, D.; Stern, Y., Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch. Neurol.* **2005,** *62* (10), 1601-8.
53. Wilson, R. S.; Tang, Y.; Aggarwal, N. T.; Gilley, D. W.; McCann, J. J.; Bienias, J. L.; Evans, D. A., Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology* **2006,** *26* (2), 68-75.
54. Zhao, Q.-F.; Tan, L.; Wang, H.-F.; Jiang, T.; Tan, M.-S.; Tan, L.; Xu, W.; Li, J.-Q.; Wang, J.; Lai, T.-J.; Yu, J.-T., The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J. Affect. Disord.* **2016,** *190*, 264-271.
55. Aalten, P.; Verhey, F. R. J.; Boziki, M.; Bullock, R.; Byrne, E. J.; Camus, V.; Caputo, M.; Collins, D.; De Deyn, P. P.; Elina, K.; Frisoni, G.; Girtler, N.; Holmes, C.; Hurt, C.; Marriott, A.; Mecocci, P.; Nobili, F.; Ousset, P. J.; Reynish, E.; Salmon, E.; Tsolaki, M.; Vellas, B.; Robert, P. H., Neuropsychiatric Syndromes in Dementia. *Dement. Geriatr. Cogn. Disord.* **2007,** *24* (6), 457-463.
56. Binetti, G. a.; Bianchetti, A.; Padovani, A.; Lenzi, G.; Leo, D. D.; Trabucchi, M., Delusions in Alzheimer's disease and multi‐infarct dementia. *Acta Neurologica Scandinavica* **1993,** *88* (1), 5-9.
57. Burns, A.; Jacoby, R.; Levy, R., Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. *The British Journal of Psychiatry* **1990,** *157* (1), 86-94.
58. Cohen, D.; Eisdorfer, C.; Gorelick, P.; Paveza, G.; Luchins, D. J.; Freels, S.; Ashford, J. W.; Semla, T.; Levy, P.; Hirschman, R., Psychopathology associated with Alzheimer's disease and related disorders. *J. Gerontol.* **1993,** *48* (6), M255-M260.
59. Mega, M. S.; Cummings, J. L.; Fiorello, T.; Gornbein, J., The spectrum of behavioral changes in Alzheimer's disease. *Neurology* **1996,** *46* (1), 130-135.
60. Chow, T.; Liu, C.; Fuh, J.; Leung, V.; Tai, C.; Chen, L. W.; Wang, S.; Chiu, H.; Lam, L.; Chen, Q., Neuropsychiatric symptoms of Alzheimer's disease differ in Chinese and American patients. *International Journal of Geriatric Psychiatry* **2002,** *17* (1), 22-28.
61. Lyketsos, C. G.; Baker, L.; Warren, A.; Steele, C.; Brandt, J.; Steinberg, M.; Kopunek, S.; Baker, A., Depression, delusions, and hallucinations in Alzheimer's disease: no relationship to apolipoprotein E genotype. *J. Neuropsychiatry Clin. Neurosci.* **1997,** *9* (1), 64-67.
62. Hirono, N.; Mori, E.; Yasuda, M.; Ikejiri, Y.; Imamura, T.; Shimomura, T.; Ikeda, M.; Hashimoto, M.; Yamashita, H., Factors associated with psychotic symptoms in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **1998,** *64* (5), 648-652.
63. Hart, D.; Craig, D.; Compton, S.; Critchlow, S.; Kerrigan, B.; McIlroy, S.; Passmore, A., A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **2003,** *18* (11), 1037-1042.
64. Mirakhur, A.; Craig, D.; Hart, D.; McLlroy, S.; Passmore, A., Behavioural and psychological syndromes in Alzheimer's disease. *International journal of geriatric psychiatry* **2004,** *19* (11), 1035-1039.
65. Lopez, O. L.; Becker, J. T.; Sweet, R. A., Non-cognitive symptoms in mild cognitive impairment subjects. *Neurocase* **2005,** *11* (1), 65-71.
66. Moran, M.; Lynch, C.; Walsh, C.; Coen, R.; Coakley, D.; Lawlor, B., Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Med.* **2005,** *6* (4), 347-352.

67. Fuh, J.; Wang, S.; Cummings, J., Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *J. Neurol. Neurosurg. Psychiatry* **2005,** *76* (10), 1337-1341.
68. Gormley, N.; Rizwan, M.; Lovestone, S., Clinical predictors of aggressive behaviour in Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **1998,** *13* (2), 109-115.
69. Harwood, D. G.; Barker, W. W.; Ownby, R. L.; Bravo, M.; Aguero, H.; Duara, R., Depressive symptoms in Alzheimer's disease: an examination among community-dwelling Cuban American patients. *The American Journal of Geriatric Psychiatry* **2000,** *8* (1), 84-91.
70. Haupt, M.; Kurz, A.; Jänner, M., A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* **2000,** *11* (3), 147-152.
71. Di Iulio, F.; Palmer, K.; Blundo, C.; Casini, A. R.; Gianni, W.; Caltagirone, C.; Spalletta, G., Occurrence of neuropsychiatric symptoms and psychiatric disorders in mild Alzheimer's disease and mild cognitive impairment subtypes. *Int. Psychogeriatr.* **2010,** *22* (4), 629-640.
72. Fernández, M.; Gobartt, A. L.; Balañá, M., Behavioural symptoms in patients with Alzheimer's disease and their association with cognitive impairment. *BMC Neurol.* **2010,** *10* (1), 87.
73. Martínez, M. F.; Flores, J. C.; De Las Heras, S. P.; Lekumberri, A. M.; Menocal, M. G.; Imirizaldu, J. J. Z., Prevalence of neuropsychiatric symptoms in elderly patients with dementia in Mungialde County (Basque Country, Spain). *Dement. Geriatr. Cogn. Disord.* **2008,** *25* (2), 103-108.
74. Ikeda, M.; Shigenobu, K.; Fukuhara, R.; Hokoishi, K.; Nebu, A.; Maki, N.; Nomura, M.; Komori, K.; Tanabe, H., Delusions of Japanese patients with Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **2003,** *18* (6), 527-532.
75. Karttunen, K.; Karppi, P.; Hiltunen, A.; Vanhanen, M.; Välimäki, T.; Martikainen, J.; Valtonen, H.; Sivenius, J.; Soininen, H.; Hartikainen, S., Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **2011,** *26* (5), 473-482.
76. Mizrahi, R.; Starkstein, S. E.; Jorge, R.; Robinson, R. G., Phenomenology and clinical correlates of delusions in Alzheimer disease. *The American journal of geriatric psychiatry* **2006,** *14* (7), 573-581.
77. Nakaaki, S.; Murata, Y.; Sato, J.; Shinagawa, Y.; Hongo, J.; Tatsumi, H.; Hirono, N.; Mimura, M.; Furukawa, T. A., Association between apathy/depression and executive function in patients with Alzheimer's disease. *Int. Psychogeriatr.* **2008,** *20* (5), 964-975.
78. Senanarong, V.; Cummings, J.; Fairbanks, L.; Mega, M.; Masterman, D.; O'connor, S.; Strickland, T., Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. *Dement. Geriatr. Cogn. Disord.* **2004,** *17* (1-2), 14-20.
79. Tatsch, M. F.; de Campos Bottino, C. M.; Azevedo, D.; Hototian, S. R.; Moscoso, M. A.; Folquitto, J. C.; Scalco, A. Z.; Louzã, M. R., Neuropsychiatric symptoms in Alzheimer disease and cognitively impaired, nondemented elderly from a community-based sample in Brazil: prevalence and relationship with dementia severity. *The American journal of geriatric psychiatry* **2006,** *14* (5), 438-445.
80. Teri, L.; Ferretti, L. E.; Gibbons, L. E.; Logsdon, R. G.; McCurry, S. M.; Kukull, W. A.; McCormick, W. C.; Bowen, J. D.; Larson, E. B., Anxiety in Alzheimer's disease: Prevalence and comorbidity. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* **1999,** *54* (7), M348-M352.

81. Tractenberg, R. E.; Weiner, M. F.; Patterson, M. B.; Teri, L.; Thal, L. J., Comorbidity of psychopathological domains in community-dwelling persons with Alzheimer's disease. *J. Geriatr. Psychiatry Neurol.* **2003,** *16* (2), 94-99.
82. Tractenberg, R. E.; Weiner, M. F.; Thal, L. J., Estimating the prevalence of agitation in community-dwelling persons with Alzheimer's disease. *The Journal of neuropsychiatry and clinical neurosciences* **2002,** *14* (1), 11-18.
83. Treiber, K. A.; Lyketsos, C. G.; Corcoran, C.; Steinberg, M.; Norton, M.; Green, R. C.; Rabins, P.; Stein, D. M.; Welsh-Bohmer, K. A.; Breitner, J. C., Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int. Psychogeriatr.* **2008,** *20* (3), 538-553.
84. Tunnard, C.; Whitehead, D.; Hurt, C.; Wahlund, L.; Mecocci, P.; Tsolaki, M.; Vellas, B.; Spenger, C.; Kłoszewska, I.; Soininen, H., Apathy and cortical atrophy in Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **2011,** *26* (7), 741-748.
85. Van der Mussele, S.; Le Bastard, N.; Vermeiren, Y.; Saerens, J.; Somers, N.; Mariën, P.; Goeman, J.; De Deyn, P. P.; Engelborghs, S., Behavioral symptoms in mild cognitive impairment as compared with Alzheimer's disease and healthy older adults. *Int. J. Geriatr. Psychiatry* **2013,** *28* (3), 265-275.
86. Van Vliet, D.; De Vugt, M. E.; Aalten, P.; Bakker, C.; Pijnenburg, Y. A.; Vernooij-Dassen, M. J.; Koopmans, R. T.; Verhey, F. R., Prevalence of neuropsychiatric symptoms in young-onset compared to late-onset Alzheimer's disease–part 1: findings of the two-year longitudinal NeedYD-study. *Dement. Geriatr. Cogn. Disord.* **2012,** *34* (5-6), 319-327.
87. Wilson, R. S.; Gilley, D. W.; Bennett, D. A.; Beckett, L. A.; Evans, D. A., Hallucinations, delusions, and cognitive decline in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **2000,** *69* (2), 172-177.
88. Aalten, P.; Verhey, F. R.; Boziki, M.; Brugnolo, A.; Bullock, R.; Byrne, E. J.; Camus, V.; Caputo, M.; Collins, D.; De Deyn, P. P., Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. *Dement. Geriatr. Cogn. Disord.* **2008,** *25* (1), 1-8.
89. Bassiony, M. M.; Steinberg, M. S.; Warren, A.; Rosenblatt, A.; Baker, A. S.; Lyketsos, C. G., Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. *International journal of geriatric psychiatry* **2000,** *15* (2), 99-107.
90. Devanand, D. P.; Miller, L.; Richards, M.; Marder, K.; Bell, K.; Mayeux, R.; Stern, Y., The Columbia University scale for psychopathology in Alzheimer's disease. *Archives of neurology* **1992,** *49* (4), 371-376.
91. Drevets, W. C.; Rubin, E. H., Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol. Psychiatry* **1989,** *25* (1), 39-48.
92. Sweet, R. A.; Bennett, D. A.; Graff-Radford, N. R.; Mayeux, R.; Group*, N. I. o. A. L.-O. A. s. D. F. S., Assessment and familial aggregation of psychosis in Alzheimer's disease from the National Institute on Aging Late Onset Alzheimer's Disease Family Study. *Brain* **2010,** *133* (4), 1155-1162.
93. Wragg, R. E.; Jeste, D. V., Overview of depression and psychosis in Alzheimer's disease. *The American journal of psychiatry* **1989,** *146* (5), 577.
94. Jeste, D. V.; Finkel, S. I., Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. *The American Journal of Geriatric Psychiatry* **2000,** *8* (1), 29-34.

95. Reisberg, B.; Borenstein, J.; Salob, S. P.; Ferris, S. H., Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *The Journal of clinical psychiatry* **1987**.
96. Cummings, J. L.; Mega, M.; Gray, K.; Rosenberg-Thompson, S.; Carusi, D. A.; Gornbein, J., The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **1994,** *44* (12), 2308-2308.
97. Kaufer, D. I.; Cummings, J. L.; Christine, D.; Bray, T.; Castellon, S.; Masterman, D.; MacMillan, A.; Ketchel, P.; DeKosky, S. T., Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J. Am. Geriatr. Soc.* **1998,** *46* (2), 210-215.
98. Tariot, P. N.; Mack, J. L.; Patterson, M. B.; Edland, S. D., The behavior rating scale for dementia of the consortium to establish a registry for Alzheimer's disease. *The American journal of psychiatry* **1995,** *152* (9), 1349.
99. Rubin, E. H.; Drevets, W. C.; Burke, W. J., The nature of psychotic symptoms in senile dementia of the Alzheimer type. *Topics in geriatrics* **1988,** *1* (1), 16-20.
100. Association, A. s., 2013 Alzheimer's disease facts and figures. *Alzheimer's & dementia* **2013,** *9* (2), 208-245.
101. Gilley, D. W.; Whalen, M. E.; Wilson, R. S.; Bennett, D. A., Hallucinations and associated factors in Alzheimer's disease. *The Journal of neuropsychiatry and clinical neurosciences* **1991**.
102. Gilley, D. W.; Wilson, R. S.; Beckett, L. A.; Evans, D. A., Psychotic symptoms and physically aggressive behavior in Alzheimer's disease. *J. Am. Geriatr. Soc.* **1997,** *45* (9), 1074-1079.
103. Sweet, R. A.; Pollock, B. G.; Sukonick, D. L.; Mulsant, B. H.; Rosen, J.; Klunk, W. E.; Kastango, K. B.; DeKosky, S. T.; Ferrell, R. E., The 5-HTTPR polymorphism confers liability to a combined phenotype of psychotic and aggressive behavior in Alzheimer disease. *Int. Psychogeriatr.* **2001,** *13* (4), 401-409.
104. Lyketsos, C. G.; Sheppard, J. M. E.; Steinberg, M.; Tschanz, J. A. T.; Norton, M. C.; Steffens, D. C.; Breitner, J. C., Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *Int. J. Geriatr. Psychiatry* **2001,** *16* (11), 1043-1053.
105. Scarmeas, N.; Brandt, J.; Albert, M.; Hadjigeorgiou, G.; Papadimitriou, A.; Dubois, B.; Sarazin, M.; Devanand, D.; Honig, L.; Marder, K., Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch. Neurol.* **2005,** *62* (10), 1601-1608.
106. Rabins, P. V.; Mace, N. L.; Lucas, M. J., The impact of dementia on the family. *JAMA* **1982,** *248* (3), 333-335.
107. Cummings, J.; Diaz, C.; Levy, M.; Binetti, G.; Litvan, I. In *Neuropsychiatric Syndromes in Neurodegenerative Disease: Frequency and Signficance*, Semin. Clin. Neuropsychiatry, 1996; pp 241-247.
108. Wilson, R.; Tang, Y.; Aggarwal, N.; Gilley, D.; McCann, J.; Bienias, J.; Evans, D., Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology* **2006,** *26* (2), 68-75.
109. Lyketsos, C. G.; Carrillo, M. C.; Ryan, J. M.; Khachaturian, A. S.; Trzepacz, P.; Amatniek, J.; Cedarbaum, J.; Brashear, R.; Miller, D. S., Neuropsychiatric symptoms in Alzheimer's disease. Elsevier: 2011.
110. Geda, Y. E.; Schneider, L. S.; Gitlin, L. N.; Miller, D. S.; Smith, G. S.; Bell, J.; Evans, J.; Lee, M.; Porsteinsson, A.; Lanctôt, K. L., Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *Alzheimer's & dementia* **2013,** *9* (5), 602-608.

111. Tanzi, R. E.; Bertram, L., New Frontiers in Alzheimer's Disease Genetics. *Neuron* **2001,** *32* (2), 181-184.
112. St George-Hyslop, P. H., Molecular genetics of Alzheimer's disease. *Biol. Psychiatry* **2000,** *47* (3), 183-199.
113. Donald L. Price; Rudolph E. Tanzi; Borchelt, D. R.; Sisodia, S. S., ALZHEIMER'S DISEASE: Genetic Studies and Transgenic Models. *Annu. Rev. Genet.* **1998,** *32* (1), 461-493.
114. Bertram, L.; Lill, C. M.; Tanzi, R. E., The genetics of Alzheimer disease: back to the future. *Neuron* **2010,** *68* (2), 270-281.
115. Corder, E. H.; Saunders, A. M.; Strittmatter, W. J.; Schmechel, D. E.; Gaskell, P. C.; Small, G.; Roses, A. D.; Haines, J.; Pericak-Vance, M. A., Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **1993,** *261* (5123), 921-923.
116. Mattsson, N.; Groot, C.; Jansen, W. J.; Landau, S. M.; Villemagne, V. L.; Engelborghs, S.; Mintun, M. M.; Lleo, A.; Molinuevo, J. L.; Jagust, W. J., Prevalence of the apolipoprotein E ε4 allele in amyloid β positive subjects across the spectrum of Alzheimer's disease. *Alzheimer's & Dementia* **2018**.
117. Gatz, M.; Pedersen, N. L.; Berg, S.; Ahlbom, A.; Johansson, B.; Winblad, B.; Johansson, K.; Viitanen, M.; Mortimer, J. A.; Posner, S. F., Heritability for Alzheimer's Disease: The Study of Dementia in Swedish Twins. *The Journals of Gerontology: Series A* **1997,** *52A* (2), M117-M125.
118. Daw, E. W.; Payami, H.; Nemens, E. J.; Nochlin, D.; Bird, T. D.; Schellenberg, G. D.; Wijsman, E. M., The Number of Trait Loci in Late-Onset Alzheimer Disease. *The American Journal of Human Genetics* **2000,** *66* (1), 196-204.
119. Tanzi, R. E., A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorders. *The Journal of Clinical Investigation* **1999,** *104* (9), 1175-1179.
120. Bertram, L.; Tanzi, R. E., Of replications and refutations: The status of Alzheimer's disease genetic research. *Curr. Neurol. Neurosci. Rep.* **2001,** *1* (5), 442-450.
121. Bennett, R. E.; Robbins, A. B.; Hu, M.; Cao, X.; Betensky, R. A.; Clark, T.; Das, S.; Hyman, B. T., Tau induces blood vessel abnormalities and angiogenesis-related gene expression in P301L transgenic mice and human Alzheimer's disease. *Proceedings of the National Academy of Sciences* **2018,** *115* (6), E1289-E1298.
122. Reiman, E. M.; Chen, K.; Liu, X.; Bandy, D.; Yu, M.; Lee, W.; Ayutyanont, N.; Keppler, J.; Reeder, S. A.; Langbaum, J. B., Fibrillar amyloid-β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences* **2009,** *106* (16), 6820-6825.
123. Tanzi, R. E.; Bertram, L., Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell* **2005,** *120* (4), 545-555.
124. Selkoe, D. J., Alzheimer's disease: genes, proteins, and therapy. *Physiol. Rev.* **2001,** *81* (2), 741-766.
125. Bertram, L.; McQueen, M. B.; Mullin, K.; Blacker, D.; Tanzi, R. E., Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat. Genet.* **2007,** *39* (1), 17.
126. McGuffin, P.; Rijsdijk, F.; Andrew, M.; Sham, P.; Katz, R.; Cardno, A., The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **2003,** *60* (5), 497-502.
127. DeMichele-Sweet, M. A. A.; Weamer, E. A.; Klei, L.; Vrana, D. T.; Hollingshead, D. J.; Seltman, H. J.; Sims, R.; Foroud, T.; Hernandez, I.; Moreno-Grau, S.; Tárraga, L.; Boada, M.;

Ruiz, A.; Williams, J.; Mayeux, R.; Lopez, O. L.; Sibille, E. L.; Kamboh, M. I.; Devlin, B.; Sweet, R. A., Genetic risk for schizophrenia and psychosis in Alzheimer disease. *Mol. Psychiatry* **2017,** *23*, 963.
128. Badner, J. A.; Gershon, E. S., Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol. Psychiatry* **2002,** *7* (4), 405-11.
129. Berrettini, W., Evidence for shared susceptibility in bipolar disorder and schizophrenia. *Am. J. Med. Genet. C Semin. Med. Genet.* **2003,** *123c* (1), 59-64.
130. Craddock, N.; O'Donovan, M. C.; Owen, M. J., The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J. Med. Genet.* **2005,** *42* (3), 193-204.
131. Stefansson, H.; Sigurdsson, E.; Steinthorsdottir, V.; Bjornsdottir, S.; Sigmundsson, T.; Ghosh, S.; Brynjolfsson, J.; Gunnarsdottir, S.; Ivarsson, O.; Chou, T. T.; Hjaltason, O.; Birgisdottir, B.; Jonsson, H.; Gudnadottir, V. G.; Gudmundsdottir, E.; Bjornsson, A.; Ingvarsson, B.; Ingason, A.; Sigfusson, S.; Hardardottir, H.; Harvey, R. P.; Lai, D.; Zhou, M.; Brunner, D.; Mutel, V.; Gonzalo, A.; Lemke, G.; Sainz, J.; Johannesson, G.; Andresson, T.; Gudbjartsson, D.; Manolescu, A.; Frigge, M. L.; Gurney, M. E.; Kong, A.; Gulcher, J. R.; Petursson, H.; Stefansson, K., Neuregulin 1 and susceptibility to schizophrenia. *Am. J. Hum. Genet.* **2002,** *71* (4), 877-92.
132. Stefansson, H.; Sarginson, J.; Kong, A.; Yates, P.; Steinthorsdottir, V.; Gudfinnsson, E.; Gunnarsdottir, S.; Walker, N.; Petursson, H.; Crombie, C.; Ingason, A.; Gulcher, J. R.; Stefansson, K.; St Clair, D., Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. *Am. J. Hum. Genet.* **2003,** *72* (1), 83-7.
133. Straub, R. E.; Jiang, Y.; MacLean, C. J.; Ma, Y.; Webb, B. T.; Myakishev, M. V.; Harris-Kerr, C.; Wormley, B.; Sadek, H.; Kadambi, B.; Cesare, A. J.; Gibberman, A.; Wang, X.; O'Neill, F. A.; Walsh, D.; Kendler, K. S., Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *Am. J. Hum. Genet.* **2002,** *71* (2), 337-48.
134. Chumakov, I.; Blumenfeld, M.; Guerassimenko, O.; Cavarec, L.; Palicio, M.; Abderrahim, H.; Bougueleret, L.; Barry, C.; Tanaka, H.; La Rosa, P.; Puech, A.; Tahri, N.; Cohen-Akenine, A.; Delabrosse, S.; Lissarrague, S.; Picard, F. P.; Maurice, K.; Essioux, L.; Millasseau, P.; Grel, P.; Debailleul, V.; Simon, A. M.; Caterina, D.; Dufaure, I.; Malekzadeh, K.; Belova, M.; Luan, J. J.; Bouillot, M.; Sambucy, J. L.; Primas, G.; Saumier, M.; Boubkiri, N.; Martin-Saumier, S.; Nasroune, M.; Peixoto, H.; Delaye, A.; Pinchot, V.; Bastucci, M.; Guillou, S.; Chevillon, M.; Sainz-Fuertes, R.; Meguenni, S.; Aurich-Costa, J.; Cherif, D.; Gimalac, A.; Van Duijn, C.; Gauvreau, D.; Ouellette, G.; Fortier, I.; Raelson, J.; Sherbatich, T.; Riazanskaia, N.; Rogaev, E.; Raeymaekers, P.; Aerssens, J.; Konings, F.; Luyten, W.; Macciardi, F.; Sham, P. C.; Straub, R. E.; Weinberger, D. R.; Cohen, N.; Cohen, D., Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* **2002,** *99* (21), 13675-80.
135. Blackwood, D. H.; Fordyce, A.; Walker, M. T.; St Clair, D. M.; Porteous, D. J.; Muir, W. J., Schizophrenia and affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *Am. J. Hum. Genet.* **2001,** *69* (2), 428-33.
136. Jarow, J. P.; LaVange, L.; Woodcock, J., Multidimensional evidence generation and FDA regulatory decision making: defining and using "real-world" data. *Jama* **2017,** *318* (8), 703-704.
137. Sherman, R. E.; Anderson, S. A.; Dal Pan, G. J.; Gray, G. W.; Gross, T.; Hunter, N. L.; LaVange, L.; Marinac-Dabic, D.; Marks, P. W.; Robb, M. A., Real-world evidence—what is it and what can it tell us. *N Engl J Med* **2016,** *375* (23), 2293-2297.

138. Wechsler, J., FDA Moves to Broaden Acceptance of Real-World Evidence in Clinical Research. *Applied Clinical Trials* **2017,** *26* (9/10), 7-7.
139. Bu, D.; Zhao, Y.; Cai, L.; Xue, H.; Zhu, X.; Lu, H.; Zhang, J.; Sun, S.; Ling, L.; Zhang, N.; Li, G.; Chen, R., Topological structure analysis of the protein–protein interaction network in budding yeast. *Nucleic Acids Res.* **2003,** *31* (9), 2443-2450.
140. Weamer, E. A.; DeMichele-Sweet, M. A.; Cloonan, Y. K.; Lopez, O. L.; Sweet, R. A., Incident Psychosis in Subjects With Mild Cognitive Impairment or Alzheimer's Disease. *J. Clin. Psychiatry* **2016,** *77* (12), e1564-e1569.
141. Albert, M. S.; DeKosky, S. T.; Dickson, D.; Dubois, B.; Feldman, H. H.; Fox, N. C.; Gamst, A.; Holtzman, D. M.; Jagust, W. J.; Petersen, R. C.; Snyder, P. J.; Carrillo, M. C.; Thies, B.; Phelps, C. H., The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers. Dement* **2011,** *7* (3), 270-279.
142. Petersen, R. C., Mild cognitive impairment as a diagnostic entity. *J Intern. Med* **2004,** *256* (3), 183-194.
143. McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E. M., Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* **1984,** *34*, 939-944.
144. Lopez, O. L.; Becker, J. T.; Chang, Y. F.; Sweet, R. A.; Aizenstein, H.; Snitz, B.; Saxton, J.; McDade, E.; Kamboh, M. I.; DeKosky, S. T.; Reynolds, C. F., III; Klunk, W. E., The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's disease. *Am. J. Psychiatry* **2013,** *170* (9), 1051-1058.
145. Lopez, O. L.; Becker, J. T.; Klunk, W. E.; Saxton, J.; Hamilton, R. L.; Kaufer, D. I.; Sweet, R. A.; Cidis Meltzer, C.; Wisniewski, S. R.; Kamboh, M. I.; DeKosky, S. T., Research evaluation and diagnosis of probable Alzheimer's disease over the last two decades. I. *Neurology* **2000,** *55*, 1854-1862.
146. Lopez, O. L.; Becker, J. T.; Klunk, W. E.; Saxton, J.; Hamilton, R. L.; Kaufer, D.; Sweet, R. A.; Cidis Meltzer, C.; Wisniewski, S. R.; Kamboh, M. I.; DeKosky, S. T., Research evaluation and diagnosis of possible Alzheimer's disease over the last two decades. II. *Neurology* **2000,** *55*, 1863-1869.
147. Wilkosz, P. A.; Seltman, H. J.; Devlin, B.; Weamer, E. A.; Lopez, O. L.; DeKosky, S. T.; Sweet, R. A., Trajectories of cognitive decline in Alzheimer's disease. *Int. Psychogeriatr* **2010,** *22* (2), 281-290.
148. Folstein, M. F.; Folstein, S. E.; McHugh, P. R., "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res* **1975,** *12* (3), 189-198.
149. Benjamini, Y.; Hochberg, Y., Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the royal statistical society. Series B (Methodological)* **1995**, 289-300.
150. Cameron Davidson-Pilon, J. K., Ben Kuhn, Paul Zivich, Andrew Fiore-Gartland, Luis Moneda, Gabriel, Danie lWIlson, Alex Parij, Kyle Stark, Steven Anton, Lilian Besson, Jona , Harsh Gadgil, Dave Golland, Sean Hussey, Javad Noorbakhsh, Andreas Klintberg, Joanne Jordan, Jeff Rose, Isaac Slavitt, Eric Martin, Eduardo Ochoa, Dylan Albrecht, dhuynh, Denis Zgonjanin, Daniel Chen, Chris Fournier, Arturo, André F. Rendeiro *CamDavidsonPilon/lifelines: v0.18.4*, 2019.

151. Buniello, A.; MacArthur, J. A. L.; Cerezo, M.; Harris, L. W.; Hayhurst, J.; Malangone, C.; McMahon, A.; Morales, J.; Mountjoy, E.; Sollis, E., The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res.* **2018,** *47* (D1), D1005-D1012.
152. Eberle, M. A.; Fritzilas, E.; Krusche, P.; Källberg, M.; Moore, B. L.; Bekritsky, M. A.; Iqbal, Z.; Chuang, H.-Y.; Humphray, S. J.; Halpern, A. L., A reference data set of 5.4 million phased human variants validated by genetic inheritance from sequencing a three-generation 17-member pedigree. *Genome Res.* **2017,** *27* (1), 157-164.
153. Kanehisa, M.; Goto, S., KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res* **2000,** *28* (1), 27-30.
154. Mi, H.; Muruganujan, A.; Casagrande, J. T.; Thomas, P. D., Large-scale gene function analysis with the PANTHER classification system. *Nat. Protoc.* **2013,** *8*, 1551.
155. Jensen, L. J.; Kuhn, M.; Stark, M.; Chaffron, S.; Creevey, C.; Muller, J.; Doerks, T.; Julien, P.; Roth, A.; Simonovic, M.; Bork, P.; von Mering, C., STRING 8--a global view on proteins and their functional interactions in 630 organisms. *Nucleic Acids Res* **2009,** *37* (Database issue), D412-6.
156. Brown, K. R.; Jurisica, I., Online predicted human interaction database. *Bioinformatics* **2005,** *21* (9), 2076-82.
157. Aric A. Hagberg, D. A. S., Pieter J. Swart *Exploring Network Structure, Dynamics, and Function using NetworkX*, Proceedings of the 7th Python in Science Conference, 2008.
158. Bonacich, P., Power and centrality: A family of measures. *American journal of sociology* **1987,** *92* (5), 1170-1182.
159. Brandes, U., A faster algorithm for betweenness centrality. *Journal of mathematical sociology* **2001,** *25* (2), 163-177.
160. Brandes, U., On variants of shortest-path betweenness centrality and their generic computation. *Social Networks* **2008,** *30* (2), 136-145.
161. Brandes, U.; Pich, C., Centrality estimation in large networks. *International Journal of Bifurcation and Chaos* **2007,** *17* (07), 2303-2318.
162. Freeman, L. C., A set of measures of centrality based on betweenness. *Sociometry* **1977**, 35-41.
163. Newman, M. E., Communities, modules and large-scale structure in networks. *Nat. Phys.* **2012,** *8* (1), 25.
164. Clauset, A.; Newman, M. E.; Moore, C., Finding community structure in very large networks. *Physical review E* **2004,** *70* (6), 066111.
165. Cramer, H., Mathematical methods of statistics, Princeton Univ. *Press, Princeton, NJ* **1946**.
166. Consortium, T. U., UniProt: a worldwide hub of protein knowledge. *Nucleic Acids Res.* **2018,** *47* (D1), D506-D515.
167. Ujike, H.; Takehisa, Y.; Takaki, M.; Tanaka, Y.; Nakata, K.; Takeda, T.; Kodama, M.; Fujiwara, Y.; Yamamoto, A.; Kuroda, S., NOTCH4 gene polymorphism and susceptibility to schizophrenia and schizoaffective disorder. *Neurosci. Lett.* **2001,** *301* (1), 41-44.
168. Krebs, L. T.; Xue, Y.; Norton, C. R.; Shutter, J. R.; Maguire, M.; Sundberg, J. P.; Gallahan, D.; Closson, V.; Kitajewski, J.; Callahan, R., Notch signaling is essential for vascular morphogenesis in mice. *Genes Dev.* **2000,** *14* (11), 1343-1352.

169. Costa, M. J.; Wu, X.; Cuervo, H.; Srinivasan, R.; Bechis, S. K.; Cheang, E.; Marjanovic, O.; Gridley, T.; Cvetic, C. A.; Wang, R. A., Notch4 is required for tumor onset and perfusion. *Vascular cell* **2013,** *5* (1), 7.
170. James, A. C.; Szot, J. O.; Iyer, K.; Major, J. A.; Pursglove, S. E.; Chapman, G.; Dunwoodie, S. L., Notch4 reveals a novel mechanism regulating Notch signal transduction. *Biochim. Biophys. Acta* **2014,** *1843* (7), 1272-1284.
171. Rand, M. D.; Grimm, L. M.; Artavanis-Tsakonas, S.; Patriub, V.; Blacklow, S. C.; Sklar, J.; Aster, J. C., Calcium depletion dissociates and activates heterodimeric notch receptors. *Molecular and cellular biology* **2000,** *20* (5), 1825-1835.
172. Chen, J.; Lipska, B. K.; Halim, N.; Ma, Q. D.; Matsumoto, M.; Melhem, S.; Kolachana, B. S.; Hyde, T. M.; Herman, M. M.; Apud, J., Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *The American Journal of Human Genetics* **2004,** *75* (5), 807-821.
173. Egan, M. F.; Goldberg, T. E.; Kolachana, B. S.; Callicott, J. H.; Mazzanti, C. M.; Straub, R. E.; Goldman, D.; Weinberger, D. R., Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences* **2001,** *98* (12), 6917-6922.
174. Zubieta, J.-K.; Heitzeg, M. M.; Smith, Y. R.; Bueller, J. A.; Xu, K.; Xu, Y.; Koeppe, R. A.; Stohler, C. S.; Goldman, D., COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. *Science* **2003,** *299* (5610), 1240-1243.
175. Shifman, S.; Bronstein, M.; Sternfeld, M.; Pisanté-Shalom, A.; Lev-Lehman, E.; Weizman, A.; Reznik, I.; Spivak, B.; Grisaru, N.; Karp, L., A highly significant association between a COMT haplotype and schizophrenia. *The American Journal of Human Genetics* **2002,** *71* (6), 1296-1302.
176. Gothelf, D.; Eliez, S.; Thompson, T.; Hinard, C.; Penniman, L.; Feinstein, C.; Kwon, H.; Jin, S.; Jo, B.; Antonarakis, S. E.; Morris, M. A.; Reiss, A. L., COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nat. Neurosci.* **2005,** *8*, 1500.
177. Weinshilboum, R. M.; Raymond, F. A., Calcium inhibition of rat liver catechol-O-methyltransferase. *Biochem. Pharmacol.* **1976,** *25* (5), 573-579.
178. Yang, H.; Ahn, C.; Jeung, E.-B., Differential expression of calcium transport genes caused by COMT inhibition in the duodenum, kidney and placenta of pregnant mice. *Mol. Cell. Endocrinol.* **2015,** *401*, 45-55.
179. Horwitz, M. J.; Hodak, S. P.; Stewart, A. F., Non-parathyroid hypercalcemia. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th edn. American Society for Bone and Mineral Research: Washington, DC* **2009**, 307-312.
180. Silverberg, S. J.; Bilezikian, J. P., Primary hyperparathyroidism: still evolving? *J. Bone Miner. Res.* **1997,** *12* (5), 856-862.
181. Quiram, D.; Weinshilboum, R. M., CATECHOL ‐ O ‐ METHYLTRANSFERASE IN RAT ERYTHROCYTE AND THREE OTHER TISSUES: COMPARISON OF BIOCHEMICAL PROPERTIES AFTER REMOVAL OF INHIBITORY CALCIUM 1. *J. Neurochem.* **1976,** *27* (5), 1197-1203.
182. Papaleo, F.; Crawley, J. N.; Song, J.; Lipska, B. K.; Pickel, J.; Weinberger, D. R.; Chen, J., Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. *J. Neurosci.* **2008,** *28* (35), 8709-8723.
183. Hollingworth, P.; Sweet, R.; Sims, R.; Harold, D.; Russo, G.; Abraham, R.; Stretton, A.; Jones, N.; Gerrish, A.; Chapman, J.; Ivanov, D.; Moskvina, V.; Lovestone, S.; Priotsi, P.; Lupton,

M.; Brayne, C.; Gill, M.; Lawlor, B.; Lynch, A.; Craig, D.; McGuinness, B.; Johnston, J.; Holmes, C.; Livingston, G.; Bass, N. J.; Gurling, H.; McQuillin, A.; Holmans, P.; Jones, L.; Devlin, B.; Klei, L.; Barmada, M. M.; Demirci, F. Y.; DeKosky, S. T.; Lopez, O. L.; Passmore, P.; Owen, M. J.; O'Donovan, M. C.; Mayeux, R.; Kamboh, M. I.; Williams, J., Genome-wide association study of Alzheimer's disease with psychotic symptoms. *Mol. Psychiatry* **2012,** *17* (12), 1316-27.
184. Ferreira, M. A.; O'Donovan, M. C.; Meng, Y. A.; Jones, I. R.; Ruderfer, D. M.; Jones, L.; Fan, J.; Kirov, G.; Perlis, R. H.; Green, E. K.; Smoller, J. W.; Grozeva, D.; Stone, J.; Nikolov, I.; Chambert, K.; Hamshere, M. L.; Nimgaonkar, V. L.; Moskvina, V.; Thase, M. E.; Caesar, S.; Sachs, G. S.; Franklin, J.; Gordon-Smith, K.; Ardlie, K. G.; Gabriel, S. B.; Fraser, C.; Blumenstiel, B.; Defelice, M.; Breen, G.; Gill, M.; Morris, D. W.; Elkin, A.; Muir, W. J.; McGhee, K. A.; Williamson, R.; MacIntyre, D. J.; MacLean, A. W.; St, C. D.; Robinson, M.; Van Beck, M.; Pereira, A. C.; Kandaswamy, R.; McQuillin, A.; Collier, D. A.; Bass, N. J.; Young, A. H.; Lawrence, J.; Ferrier, I. N.; Anjorin, A.; Farmer, A.; Curtis, D.; Scolnick, E. M.; McGuffin, P.; Daly, M. J.; Corvin, A. P.; Holmans, P. A.; Blackwood, D. H.; Gurling, H. M.; Owen, M. J.; Purcell, S. M.; Sklar, P.; Craddock, N., Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat. Genet.* **2008,** *40* (9), 1056-8.
185. Tiwari, S.; Zhang, Y.; Heller, J.; Abernethy, D. R.; Soldatov, N. M., Atherosclerosis-related molecular alteration of the human CaV1.2 calcium channel alpha1C subunit. *Proc. Natl. Acad. Sci. U. S. A.* **2006,** *103* (45), 17024-9.
186. Lee, R. S.; Stewart, C.; Carter, S. L.; Ambrogio, L.; Cibulskis, K.; Sougnez, C.; Lawrence, M. S.; Auclair, D.; Mora, J.; Golub, T. R.; Biegel, J. A.; Getz, G.; Roberts, C. W., A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *J. Clin. Invest.* **2012,** *122* (8), 2983-8.
187. Dubertret, C.; Gorwood, P.; Ades, J.; Feingold, J.; Schwartz, J. C.; Sokoloff, P., Meta‐analysis of DRD3 gene and schizophrenia: ethnic heterogeneity and significant association in Caucasians. *Am. J. Med. Genet.* **1998,** *81* (4), 318-322.
188. Bakker, P. R.; van Harten, P. N.; van Os, J., Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: a meta analysis. *Schizophr. Res.* **2006,** *83* (2-3), 185-192.
189. Malhotra, A.; Goldman, D.; Buchanan, R.; Rooney, W.; Clifton, A.; Kosmidis, M.; Breier, A.; Pickar, D., The dopamine D 3 receptor (DRD3) Ser 9 Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. *Mol. Psychiatry* **1998,** *3* (1), 72.
190. Craig, D.; Hart, D. J.; Carson, R.; McIlroy, S. P.; Passmore, A. P., Psychotic symptoms in Alzheimer's disease are not influenced by polymorphic variation at the dopamine receptor DRD3 gene. *Neurosci. Lett.* **2004,** *368* (1), 33-36.
191. McGuire, V.; Den Eeden, S. K. V.; Tanner, C. M.; Kamel, F.; Umbach, D. M.; Marder, K.; Mayeux, R.; Ritz, B.; Ross, G. W.; Petrovitch, H.; Topol, B.; Popat, R. A.; Costello, S.; Manthripragada, A. D.; Southwick, A.; Myers, R. M.; Nelson, L. M., Association of DRD2 and DRD3 polymorphisms with Parkinson's disease in a multiethnic consortium. *J. Neurol. Sci.* **2011,** *307* (1), 22-29.
192. Ustione, A.; Piston, D. W.; Harris, P. E., Minireview: dopaminergic regulation of insulin secretion from the pancreatic islet. *Mol. Endocrinol.* **2013,** *27* (8), 1198-1207.
193. Ustione, A.; Piston, D. W., Dopamine synthesis and D3 receptor activation in pancreatic β-cells regulates insulin secretion and intracellular [Ca2+] oscillations. *Mol. Endocrinol.* **2012,** *26* (11), 1928-1940.

194. Caldwell, B.; Ustione, A.; Piston, D., Fluorescence fluctuation spectroscopy to detect interactions between dopamine receptors and calcium channel in pancreatic β-cells. *Biophysical Journal* **2014,** *106* (2), 718a.
195. Joyce, J. N.; Millan, M. J., Dopamine D3 receptor agonists for protection and repair in Parkinson's disease. *Curr. Opin. Pharmacol.* **2007,** *7* (1), 100-5.
196. Belvederi Murri, M.; Respino, M.; Masotti, M.; Innamorati, M.; Mondelli, V.; Pariante, C.; Amore, M., Vitamin D and psychosis: Mini meta-analysis. *Schizophr. Res.* **2013,** *150* (1), 235-239.
197. Rey‐Sánchez, P.; Lavado‐García, J. M.; Canal‐Macías, M. L.; Gómez‐Zubeldia, M. A.; Roncero‐Martín, R.; Pedrera‐Zamorano, J. D., Ultrasound bone mass in schizophrenic patients on antipsychotic therapy. *Hum. Psychopharmacol. Clin. Exp.* **2009,** *24* (1), 49-54.
198. Jamilian, H.; Bagherzadeh, K.; Nazeri, Z.; Hassanijirdehi, M., Vitamin D, parathyroid hormone, serum calcium and phosphorus in patients with schizophrenia and major depression. *International journal of psychiatry in clinical practice* **2013,** *17* (1), 30-34.
199. Annweiler, C.; Beauchet, O., Possibility of a new anti-alzheimer's disease pharmaceutical composition combining memantine and vitamin D. *Drugs Aging* **2012,** *29* (2), 81-91.
200. Annweiler, C.; Fantino, B.; Parot-Schinkel, E.; Thiery, S.; Gautier, J.; Beauchet, O., Alzheimer's disease--input of vitamin D with mEmantine assay (AD-IDEA trial): study protocol for a randomized controlled trial. *Trials* **2011,** *12*, 230.
201. Usdin, T. B.; Gruber, C.; Bonner, T. I., Identification and functional expression of a receptor selectively recognizing parathyroid hormone, the PTH2 receptor. *J. Biol. Chem.* **1995,** *270* (26), 15455-8.
202. Papageorgiou, S. G.; Christou, Y.; Kontaxis, T.; Bonakis, A.; Anagnostouli, M.; Potagas, C.; Kalfakis, N., Dementia as presenting symptom of primary hyperparathyroidism: favourable outcome after surgery. *Clin. Neurol. Neurosurg.* **2008,** *110* (10), 1038-40.
203. Yu, N.; Donnan, P. T.; Flynn, R. W.; Murphy, M. J.; Smith, D.; Rudman, A.; Leese, G. P., Increased mortality and morbidity in mild primary hyperparathyroid patients. The Parathyroid Epidemiology and Audit Research Study (PEARS). *Clin. Endocrinol. (Oxf.)* **2010,** *73* (1), 30-4.
204. Cermik, T. F.; Kaya, M.; Ugur-Altun, B.; Bedel, D.; Berkarda, S.; Yigitbasi, O. N., Regional cerebral blood flow abnormalities in patients with primary hyperparathyroidism. *Neuroradiology* **2007,** *49* (4), 379-85.
205. Murray, T. M.; Rao, L. G.; Divieti, P.; Bringhurst, F. R., Parathyroid hormone secretion and action: evidence for discrete receptors for the carboxyl-terminal region and related biological actions of carboxyl- terminal ligands. *Endocr. Rev.* **2005,** *26* (1), 78-113.