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**EARLY DETECTION OF ALZHEIMER'S
DISEASE USING MACHINE LEARNING
ALGORITHMS**

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Master's Thesis

Supervisor

Prof. Dr. Osman Nuri UÇAN

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DEDICATION

First and foremost, I am thankful to Almighty Allah that by His grace and bounty, I am able to write my MSc thesis. I ask sincerity in all my actions from Almighty Allah and I quote the verse from the Holy Quran “Say: My prayer, my offering, my life and my death are for Allah, the Lord of all the world” (Chapter Al-’An‘am, verse 162).

I AM DEEPLY INDEBTED to my supervisor Prof. Dr. Osman Nuri Ucan for his kind interest, generous support and constant advice throughout the past three and half years. I have benefitted tremendously from his rare insight, his ample intuition and his exceptional knowledge. This thesis would never have been written without his tireless and patient mentoring. It is my very great privilege to have been one of his research students.

I am so grateful to my fabulous family, who have pushed themselves to the extreme ends to ensure that I continue my education to the highest level. Truly without your prayers, love, sacrifices and support, I would not have reached this point in my life and this MSc research work would not have been possible.

ABSTRACT

EARLY DETECTION OF ALZHEIMER'S DISEASE USING MACHINE LEARNING ALGORITHMS

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Alzheimer's disease (AD) is one of the most frequent neurological causes of death globally. Globally, the number of AD patients is growing dramatically. Manually diagnosing AD by a neurologist is time-consuming and may not always provide accurate results. The classification of AD using brain imaging has shown promising, less time-consuming results.

This research two main contributions: 1) Conduct the state-of-the-art of AD, and 2) Using Machine Learning (ML), develop three models for classifying AD cases.

In the first part, we investigate the background of AD history, brain imaging techniques for AD, and AD classification methods. After that, we introduce ML approaches in health diseases. According to the literature, for AD classification, ADNI and OASIS are the most used publicly available online data sources. Therefore, we search on how many these two datasets have been utilized during 2020-2022 on three highly ranked scientific databases: IEEE, Science Direct, and Springer. Next, we study, the main substantial risk (protective) factors influencing AD's deterioration (improvement). Lastly, we analyzed in depth 20 articles published recently.

In the second part, we developed our study models: MLP, KNN and NB. The models have been trained and tested using the OASIS dataset. The evaluations were conducted regarding the accuracy, recall, F-measure, TPR, and FPR. The comparisons demonstrate that MLP achieve the best outcomes. Furthermore, the verification demonstrated that MLP (of this study) outperformed its counterpart's models.

Keywords: Alzheimer's Disease, Machine Learning, Naive Bayes, KNN, MLP, OASIS.

TABLE OF CONTENTS

	<u>Pages</u>
ABSTRACT.....	vi
LIST OF TABLES	x
LIST OF FIGURES	xi
ABBREVIATIONS.....	xiii
1. INTRODUCTION.....	1
1.1 INTRODUCTION.....	1
1.2 RESEARCH MOTIVATION	2
1.3 PROBLEM STATEMENT	2
1.4 AIM AND OBJECTIVES.....	3
1.4.1 Aim.....	3
1.4.2 Objectives.....	3
1.5 RESEARCH METHODOLOGY	3
1.6 RESEARCH ORGANIZATION	4
2. BACKGROUND AND LITERATURE REVIEW.....	6
2.1 INTRODUCTION.....	6
2.2 BASICS AND BACKGROUND.....	8
2.2.1 AD vs. MIC	8
2.2.2 The History of the AD.....	9
2.3 BRAIN IMAGING TECHNIQUES FOR AD.....	9
2.3.1 Preliminaries.....	9
2.3.2 Magnetic Resonance Image (MRI)	10
2.3.3 Positron Emission Tomography (PET).....	11
2.3.4 MRI Biomarkers of AD.....	11
2.4 METHODOLOGY OF CLASSIFICATION OF AD	12

2.4.1 Data Collection.....	12
2.4.2 Pre-Processing.....	13
2.4.3 Feature Extraction	13
2.4.4 Feature Selection	14
2.4.5 Classification.....	15
2.5 ML ALGORITHMS FOR HEALTH DISEASE	15
2.5.1 Concept of ML	15
2.5.2 ML Based-Medical fields.....	17
2.6 DATASETS	17
2.6.1 ADNI.....	18
2.6.2 OASIS	19
2.7 RISK AND PROTECTIVE FACTORS IN THE AD DEVELOPMENT	20
2.7.1 Psychological Factors.....	21
2.7.2 Pre-Existing Disease	22
2.7.3 Lifestyles	24
2.7.4 Other Factors	24
2.8 PERFORMANCE EVALUATION METRICS.....	24
2.9 LITERATURE REVIEW.....	27
2.9.1 Article Selection.....	27
2.9.2 Literature Evaluation.....	29
2.10 SUMMARY	35
3. METHODS OF THE THESIS.....	36
3.1 INTRODUCTION.....	36
3.2 NAIVE BAYES	36
3.3 K-NEAREST NEIGHBOUR.....	37
3.4 MULTI-LAYER PERCEPTRON.....	38
4. RESULTS AND DISCUSSION	41

4.1	INTRODUCTION.....	41
4.2	MODELING AND SCENARIOS.....	41
4.2.1	Data Collection.....	41
4.2.2	Naive Bayes.....	41
4.2.3	K-Nearest Neighbour	42
4.2.4	Multi-Layer Perceptron	43
4.3	PERFORMANCE EVALUATION	43
4.3.1	Accuracy.....	43
4.3.2	Recall and F-Measure.....	44
4.3.3	True Positive Rate and False Positive Rate.....	45
4.4	VERIFICATION.....	46
4.5	SUMMARY	48
5.	CONCLUSION AND RECOMMENDATIONS.....	49
5.1	CONCLUSION	49
5.2	RECOMMENDATION	49
	REFERENCES.....	51

LIST OF TABLES

	<u>Pages</u>
Table 2.1: A summary of the sources of the considered papers of Section 2-9.....	28
Table 2.2: A summary of the considered papers of Section 2-9.....	33
Table 3.1: The description of equation (3-7).	39
Table 4.1: Main findings of NB model.....	42
Table 4.2: Main findings of the KNN model.....	42
Table 4.3: Main findings of MLP model.	43
Table 4.4: Comparison of the achieved accuracy of the algorithms.....	44
Table 4.5: Comparison of the achieved Recall and F-measure of the algorithms.	45
Table 4.6: TPR and FPR of the algorithms.....	46
Table 4.7: The achieved accuracy of the models in.....	47
Table 4.8: Comparison of our stud's best model and the best two models in	46

LIST OF FIGURES

	<u>Pages</u>
Figure 1.1: The estimation of the AD in 2050 [5].	1
Figure 2.1: Distribution of considered papers (2019–2022).	6
Figure 2.2: Publishers of the considered papers in this chapter.	6
Figure 2.3: The structure of the chapter.	8
Figure 2.4: Brain progress from a healthy to AD patient [15].	9
Figure 2.5: Example of sMRI [15].	10
Figure 2.6: Example of fMRI [20].	11
Figure 2.7: PET scan of a brain [15].	11
Figure 2.8: Common methodology of AD classification.	12
Figure 2.9: Feature extraction methods.	14
Figure 2.10: Feature extraction methods.	15
Figure 2.11: ML algorithms classification-based learning approaches.	17
Figure 2.12: Number of papers in the ranked scientific databases according to AD datasets from 2020 to 2022.	18
Figure 2.13: Summary of ADNI dataset classifications [22].	19
Figure 2.14: Summary of OASIS dataset classifications.	20
Figure 2.15: Attributes of OASIS datasets.	20
Figure 2.16: Risk Factors of AD.	21
Figure 2.17: Protective Factors for AD Prevention and Slowing its Progress.	21

Figure 2.18: Most widely used evaluation metrics of AD models.	25
Figure 2.19: Percentage Distribution of The Selected Papers of Section 2-9.....	29
Figure 3.1: The Structure of MLP.....	39
Figure 4.1: The detection accuracy of the models.	44
Figure 4.2: Achieved Recall and F-Measure of the models.....	45
Figure 4.3: TPR and FPR of the models.	46
Figure 4.4: Comparison between our study's best model and the two best models in [92].	47

ABBREVIATIONS

AD	: Alzheimer's Disease
ADNI	: Alzheimer's Disease Neuroimaging Initiative
aMCI	: amnestic MCI
AUC	: Area Under the ROC Curve
c-MCI	: MCI converted to AD
CN	: Cognitively Normal
CNN	: Convolutional Neural Network
DWI	: Diffusion weighted imaging
EEG	: Electroencephalography
eMCI	: Early MCI
ENLR	: Aggregation of: Elastic net linear regression
fMRI	: functional Magnetic Resonance Imaging
HC	: Healthy Control
lMCI	: Late MCI
LR	: Logistic Regression
MAP	: Rush Memory and Aging Project
MCI	: Mild Cognitive Impairment
MRI	: Magnetic Resonance Imaging
NACC	: National Alzheimer's Coordinating Center

NFT	: Neurofibrillary tangles
NHIS-IH	: National Health Insurance Service-Ilsan Hospital
NTUH	: National Taiwan University Hospital
OASIS	: Online Aerospace Supplier Information System
pMCI = MCIC	: Progressive MCI (MCI patients who converted to AD)
RAVLT	: Rey's Auditory Verbal Learning Test
RF	: Random Forest
RNN	: Recurrent Neural Network
ROC	: Receiver Operating Curve
RVR	: Relevance Vector Regression
SMC	: Subjective Memory Complaints
sMCI	: Structural MCI
s-MCI = MCInc	: stable MCI (MCI patients who have not converted to AD)
sMRI	: structural Magnetic Resonance Imaging
SVM	: Support Vector Machine
TCIA	: The Cancer Imaging Archive
XNAT	: Extensible Neuroimaging Archive Toolkit

1. INTRODUCTION

1.1 INTRODUCTION

Alzheimer's disease is a clinical condition marked by increasing cognitive and memory deterioration. It is a fairly prevalent disorder among the elderly, accounting for 60–80% of all kinds of dementia. AD has a high incidence rate; however, there is currently no treatment. From the beginning of AD until the final diagnosis, there is a lengthy period. Mild cognitive impairment (MIC) describes patients in the early stages of AD. It is worth mentioning that only 30–40% of MCI may convert to AD [1].

AD is a progressive and eventually deadly illness. According to the World Health Organization (WHO) report in 2020, More than 50 million people globally live with AD and other dementia [2], and it is anticipated to be 66 million by the end of 2029 [2] and 150 million by 2050 [3]. AD patients in the USA in 2020 reached five million [4], where 200,000 persons are less than 65 years old [5]. Furthermore, AD patients are expected to be 14 million by 2050 (see Figure 1.1) [5].

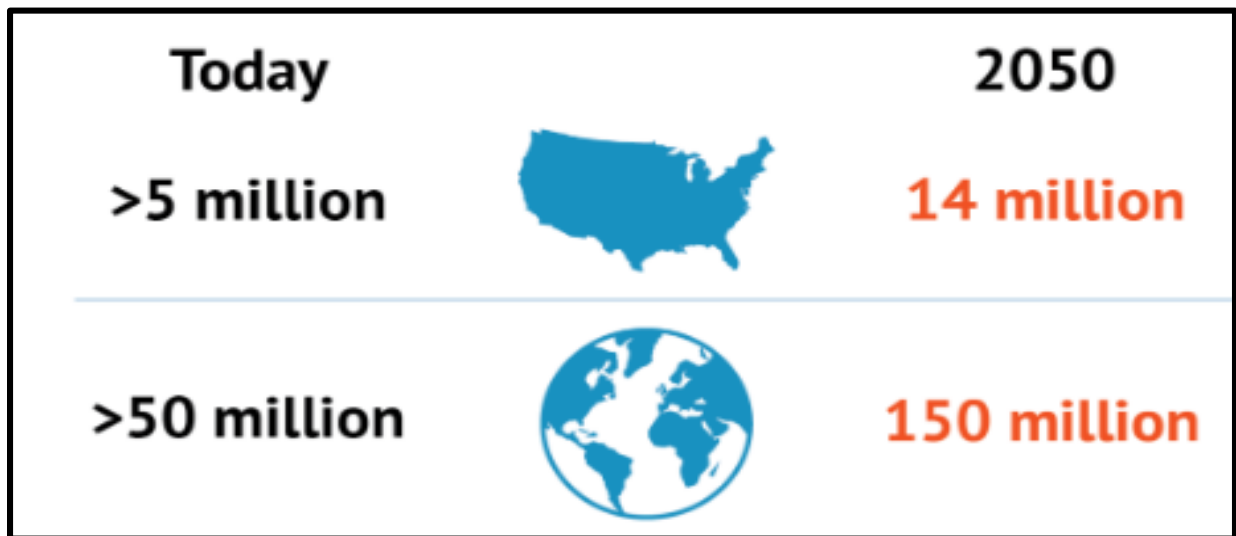


Figure 1.1: The estimation of the AD in 2050 [5].

In exhaustive mental health studies, translational uses of computational neuroscientific techniques have shown to be very useful [6]. This multidisciplinary area of research may assist in

understanding the biological mechanisms regulating the healthy and pathological states of the human brain and translate these processes into clinically observable manifestations. We have seen fast development in high-volume biomedical datasets in the last ten years. Additionally, machine learning (ML) advancements have created new opportunities for diagnosing and anticipating neurodegenerative and neuropsychiatric diseases [7]. This recent innovation has led to the creation of tools that combine several patient-specific data into forecasts and enhance patients' therapeutic findings with such conditions [8] [9]. The ultimate goal of these neuroscientific techniques is to identify and expect the first exposure and provide plans to treat those at high risk for AD and cognitive impairment associated with AD [10].

The rest of this chapter is structured as follows. First, the research motivation is presented in Section 1.2. In the following, we introduce the research problems in Section 1.3. In Section 1.4, the aim and main objectives of this study are outlined. Our methodology is explained in Section 1.5. Finally, the structure of the chapter is outlined in Section 1.6.

1.2 RESEARCH MOTIVATION

The classification of AD using brain imaging has shown promising, less time-consuming results. Numerous researchers have attempted to create a classification system for brain images with fewer research problems. Researchers have achieved encouraging findings in AD classification by machine learning (ML) algorithms. For AD classification, several ML algorithms need to be verified. This idea has motivated us to perform this research.

1.3 PROBLEM STATEMENT

AI can facilitate mobilization and save medical, logistic, and human resources and time. It can be noted that ML algorithms are widely used in many medical systems for identifying patterns in data samples, especially for early diagnosing of AD. Relevant studies (analyzed in depth in Chapter 2) demonstrated that several ML and DL algorithms contribute to classifying AD. This research problem is to classify AD using some unutilized ML algorithms to answer the following questions:

- a. What algorithms have not been utilized in AD classification yet?

- b. What would be their performance?
- c. Will their verification be promising to use them implemented in the future?

1.4 AIM AND OBJECTIVES

1.4.1 Aim

This work aims to improve AD classification based on the OASIS dataset (explained in chapter two). It utilizes ML algorithms to obtain further accurate infection detection and distinguish AD from MIC and Cognitively Normal (CN) cases.

1.4.2 Objectives

To achieve our goal mentioned in section 1.3., we summarize the objectives of this work as follows:

- a. Perform a literature review on the relevant studies published last three years.
- b. Compare and evaluate the performance results of the selected papers.
- c. Conduct a systematic review of the performance of ML algorithms in distinguishing AD from MIC and CN cases.
- d. Build AD classifier models-based machine learning algorithms: Naïve Bayes (NB), K-Nearest Neighbour (KNN), and multi-layer perception (MLP).
- e. Train and test the models with a particular dataset.
- f. Compare the performance of the models.
- g. Verify the models with counterparts.

1.5 RESEARCH METHODOLOGY

To perform this research, a quantitative methodology is adopted. This methodology enables the researchers to follow several steps, including the definition outline, implementation, processing, and evaluation of the outcomes. The datasets are used in the training and measuring models'

performance. Furthermore, the article reviewers' feedback is considered to steer this research. Accordingly, the following are the main phases of our methodology.

- a. Highlight the context of AD.
- b. Present the important techniques utilized for brain imaging.
- c. Focus on the main datasets used to examine AD.
- d. Highlight the AD risk and protective factors.
- e. Analyze some important AD-based ML classifiers published in supreme articles in the last three years.
- f. Conduct a systematic review paper.
- g. Publish the paper in a highly-ranked journal indexed in Clarivate.
- h. Build AD classifier models based on NB, KNN, and MLP.
- i. Train and test the models with a particular dataset.
- j. Compare the performance of the models.
- k. Verify the models with counterparts.
- l. Based on the models' performance, conduct the paper in a highly-ranked journal indexed in Clarivate.

1.6 RESEARCH ORGANIZATION

We present a brief overview of the organization of the thesis.

- a. Chapter One: In this chapter, we briefly introduce the research topic, the motivation and the problem statement. Then, we present the aims and objectives of our research. After that, the chapter describes the research's adopted methodology. Finally, the chapter outlines the organization of the research.

- b. Chapter Two: This chapter provides the necessary background information about AD. After that, it describes the ML algorithms adopted in the literature. The chapter briefly summarizes and records the performances of some supreme selected journal papers.
- c. Chapter Three: In this chapter, we introduce the concept of the models that we select. Additionally, we show the procedure of training and testing the models.
- d. Chapter Four: Presents our performance evaluation scenarios. Additionally, verify the models with counterparts.
- e. Chapter Five: Concludes the thesis by summarizing the main findings of the research. Additionally, some valuable recommendations for AD classification are drawn.

2. BACKGROUND AND LITERATURE REVIEW

2.1 INTRODUCTION

This study enhances our knowledge of AD literature by evaluating and analyzing prior studies on the topic. Recent research has focused on developing effective techniques that employ ML systems to improve AD assessment. This article evaluates 85 publications in the AD field to provide a comprehensive understanding of the existing investigations. The data within the scope of this survey are extracted from articles published between 2019 and 2022 (see Figure 2-1). Figure 2-2 shows the publishers of the considered scientific, where supreme papers are taken.

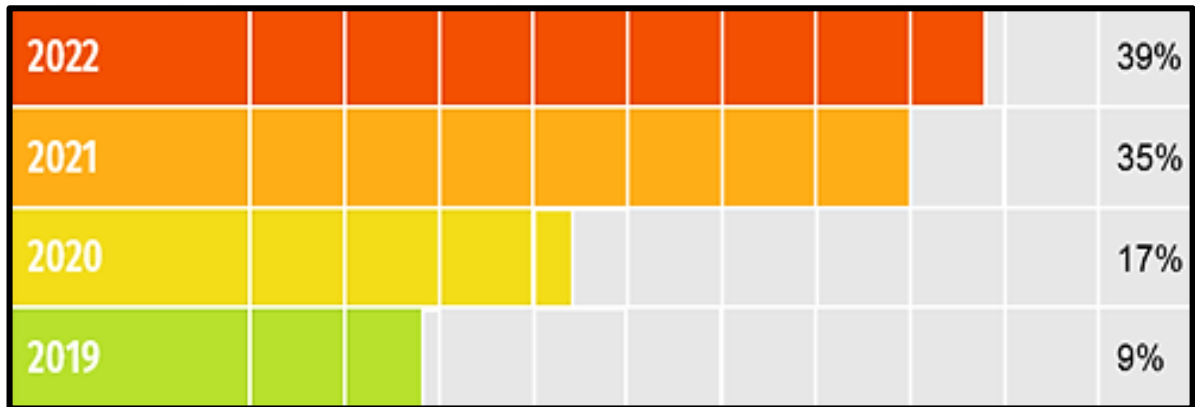


Figure 2.1: Distribution of considered papers (2019–2022).

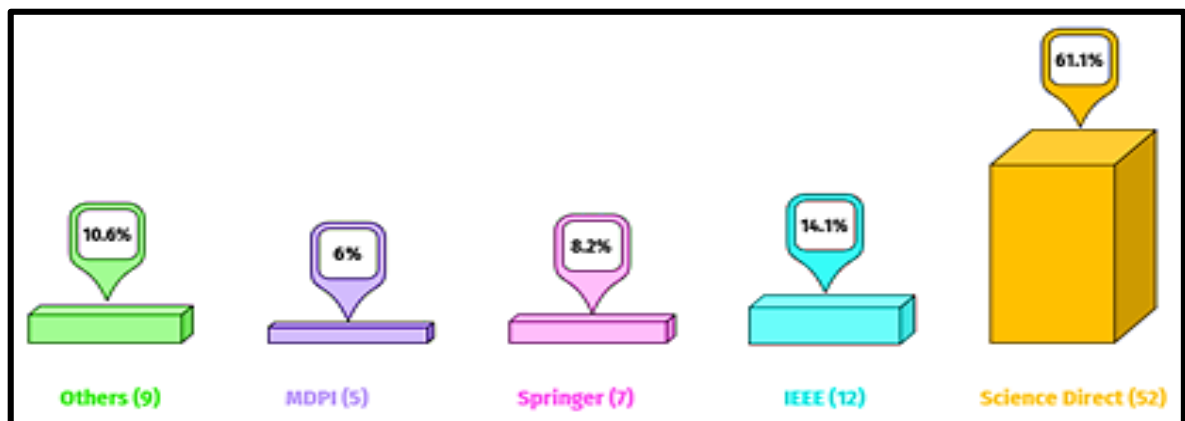


Figure 2.2: Publishers of the considered papers in this chapter.

The following are the research's contributions:

- Highlighting the context of AD and some related disorders.

- b. Presenting the important techniques utilized for brain imaging.
- c. Introducing the approaches of ML algorithms.
- d. Focusing on the main datasets used to examine AD.
- e. Highlighting the AD risk factors (Psychological, Pre-existing disease, lifestyles and other factors).
- f. Present the most widely used metrics used to evaluate the AD-based ML classifiers.
- g. Systematically reviewing some previous studies published in highly ranked journals between 2019 and 2022 were considered.

This chapter is structured as follows. Section 2 introduces the reader to AD and provides a short overview of its discovery. Brain imaging techniques utilized in AD diagnosis and prognosis are presented in Section 3. Section 4 explains the methodology of classification of AD using brain images. Section 5 introduces ML algorithms and approaches in disease prediction. Section 6 highlights the main datasets of AD. Section 7 discusses the psychological, pre-existing disease, lifestyle risk and protective factors in AD development. The most widely used metrics used to evaluate the AD-based ML classifiers are explained in Section 8. Section 9 systematically reviews the 20 supreme journal papers that proposed ML algorithms to classify AD, MCI and CN cases. Finally, the summary is drawn in Section 10. Figure 2-3 shows the road map of this chapter.

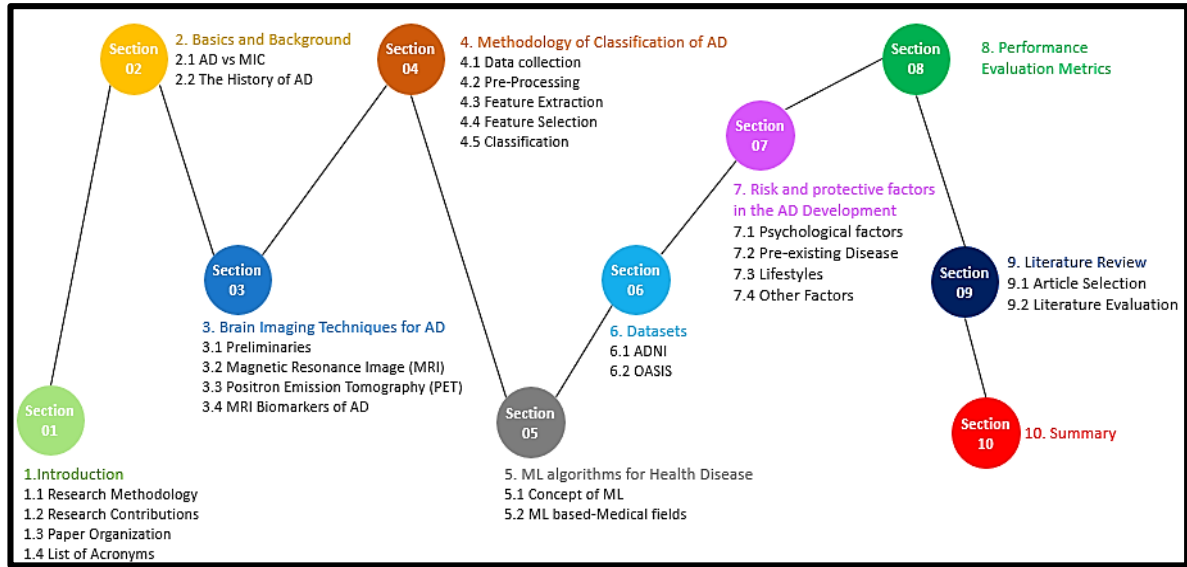


Figure 2.3: The structure of the chapter.

2.2 BASICS AND BACKGROUND

2.2.1 AD vs. MIC

As mentioned earlier, AD is a neurological illness that primarily affects the human brain's memory cells. Confusion, visual changes, and memory loss are the main symptoms of AD patients [11]. AD gradually reduces memory and cognitive abilities, destroying the ability to do simple tasks. The investigations revealed that AD symptoms might be noticed as early as the early sixties [12].

On the other hand, MCI is a stage of dementia in which patients show more cognitive decline than Cognitively Normal (CN) persons [13]. MCI is thus considered to be an early stage of AD. Problems in thinking skills, memories, and even language are the main symptoms of MCI patients. Stable MCI (SMCI) and Progressive MCI (PMCI) are the stages of MCI cases. While PMCI patients gradually develop few AD symptoms, SMCI cases remain stable [12]. According to the study [14], eight out of ten persons with MCI get AD after seven years, but only three out of ten people with CN will develop AD. Figure 2-4 compares a healthy brain to a brain damaged by AD [15].

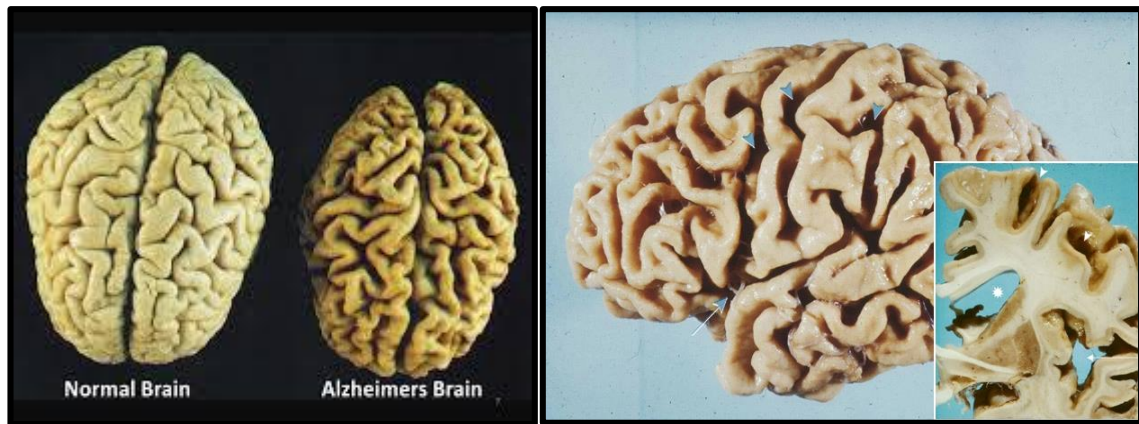


Figure 2.4: Brain progress from a healthy to AD patient [15].

2.2.2 The History of the AD

In 1906, Alois Alzheimer, a German psychiatrist, introduced the first case of AD [15]. Then, Kraepelin coined the conditions of Alzheimer's disease early last century. He discussed, in 1910, in "Clinical Psychiatry: A Text-book for Students and Physicians" a certain group of patients with serious cell transformations. The transformations involve too many plaques, the death of about 1-3 of the cerebral cortex, altering them with particular bursts of colored neurofibrils and representing the most severe form of malnutrition. Therefore, Kraepelin described the disease when it was unclear. [16].

In 1997, Dr. Gerber and his group tested histological cuts of a patient with brain tissues that were well preserved for over 90 years [16]. Many amyloid plaques were revealed by an evaluation of the cuts. The work has been considered the second study in AD, where the mutational analysis of preserved brain tissue is applicable. Therefore, the findings of Alois Alzheimer became credible in his 100th-anniversary discovery.

2.3 BRAIN IMAGING TECHNIQUES FOR AD

2.3.1 Preliminaries

Brain imaging methods may be used to view the brain's function, structure or pharmacology in a non-invasive manner. Generally, functional imaging and structural imaging are the categories of imaging techniques [17]. The information on brain activities is provided by Functional imaging (such as thinking, remembering, and working). In contrast, structural imaging can identify the information on the brain's structure (such as neurons, synapses, and

glial cells, synapses [18]. The following are the most common neuroimaging techniques for AD.

2.3.2 Magnetic Resonance Image (MRI)

In this type, magnetic fields and radio waves are utilized to produce high-resolution two-dimension (2D) and three-dimension (3D) images of brain structures. No harmful radiations are generated from radioactive tracers or X-rays. Structural MRI (sMRI) is often used MRI for Ad patients. It detects brain atrophy by measuring brain volumes in vivo (such as neurons, cells, and tissue loss) [19]. Figure 2-5 illustrates an example of an sMRI to detect brain degeneration [15].

On the other hand, to obtain the human primary visual cortex and detect brain topography, functional MRI (fMRI) has been proposed [20]. fMRI gives useful data and information regarding the functions (activities) of the human brain (see Figure 2-6). Examples of fMRI methods are brain imaging based on spin-labeling and Blood Oxygenation Level Dependent. The methods are sensitive to the brain metabolic rate of cerebral blood flow and oxygen consumption [21].

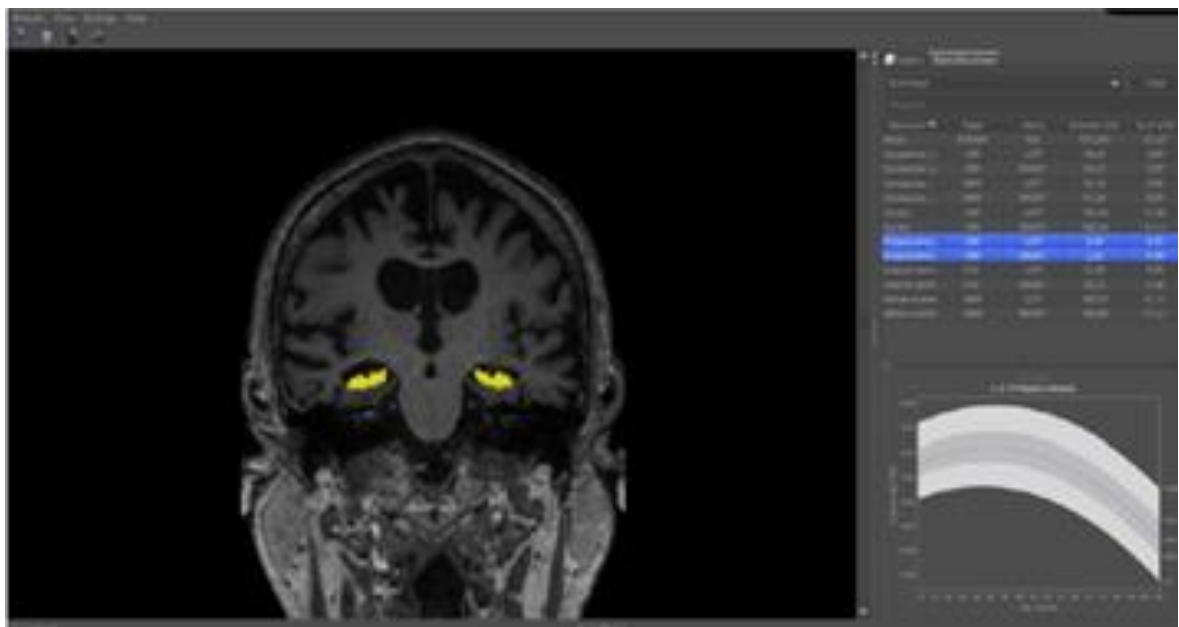


Figure 2.5: Example of sMRI [15].

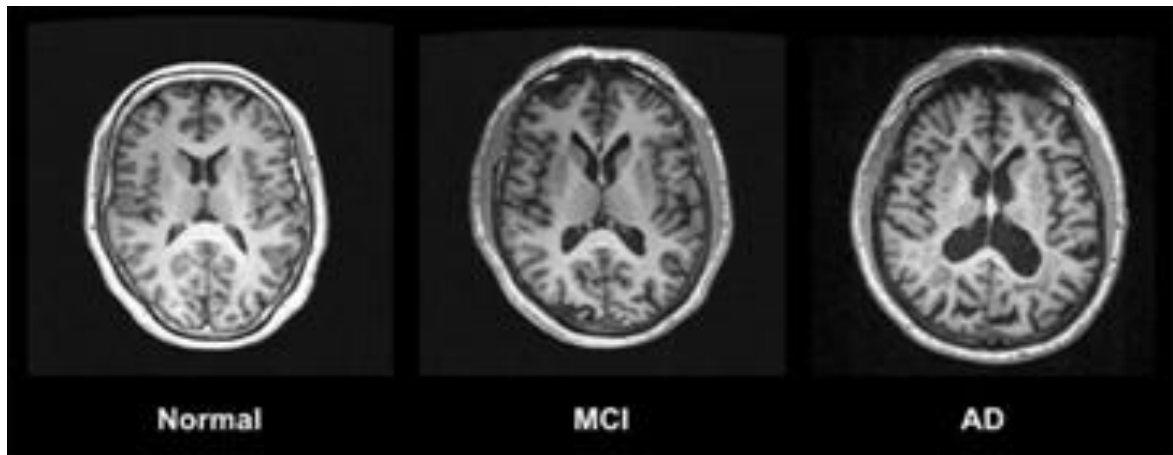


Figure 2.6: Example of fMRI [20].

2.3.3 Positron Emission Tomography (PET)

PET uses radiotracers to analyze the activities of the brain as radioactive spheres. Figure 2-7 illustrates the most commonly used tracers for AD diagnosis, where amyloid and fluorodeoxyglucose are used. Working, remembering, thinking, listening and looking were specific actions [15].

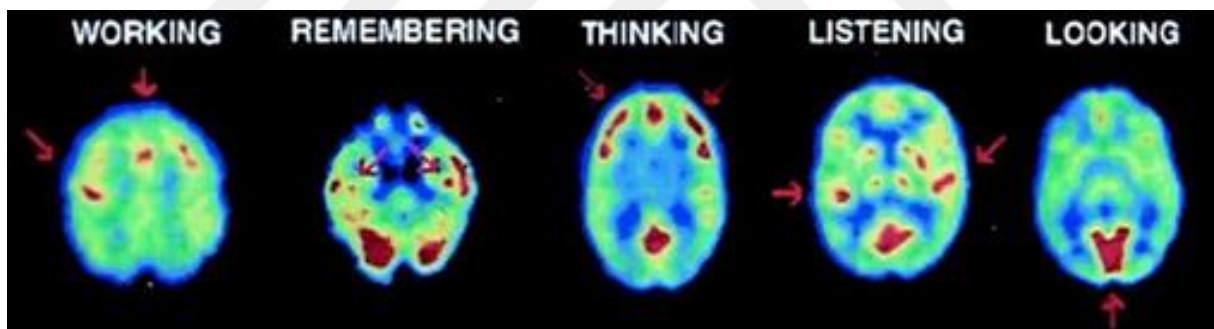


Figure 2.7: PET scan of a brain [15].

2.3.4 MRI Biomarkers of AD

Identifying extremely sensitive and specific biomarkers in the AD research field is crucial. The biological monitoring material must be able to identify the characteristics and pathological changes of the nervous system [1]. AD biomarkers should contain the following characteristics:

- a. Inexpensive, easy to implement, non-invasive, and reliable

- b. Able to distinguish the forms of dementias (especially AD).
- c. Efficient and capable of determining initial AD.
- d. Able to certify neuropathologically confirmed AD cases.
- e. Able to determine neuropathology characteristics of AD cases.
- f. Genetic, biochemical, and neuroimaging biomarkers contribute to better characterizing AD. MRI biomarkers are considered in the current study due to their vast potential for detecting AD [15].

2.4 METHODOLOGY OF CLASSIFICATION OF AD

Numerous processes are required for the successful categorization of any image. After collecting the samples, pre-processing is the next step for classification. Pre-processing deals with removing noise and other effects that impact image quality. Next, effective feature extraction is implemented to determine related features. After that, for appropriate classification, distinct features are chosen. Lastly, the classification is trained and tested based on the selected features. The methodology of AD classification is depicted in Figure 2-8.

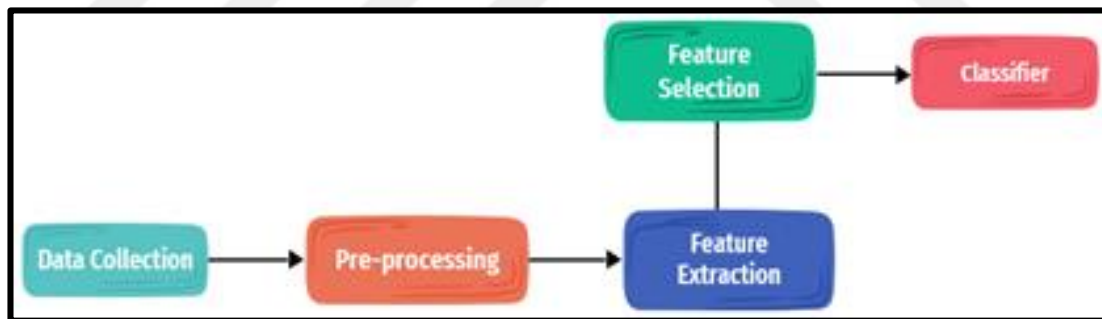


Figure 2.8: Common methodology of AD classification.

2.4.1 Data Collection

The first step in classification is collecting data, which refers to obtaining sufficient brain images of CN, MCI, and AD patients. PET, sMRI, and T2Weighted are common brain images used in the studies. Alzheimer’s Disease Neuroimaging Initiative (ADNI) [22], Open Access Series of Imaging Studies (OASIS) [23], National Alzheimer’s Coordinating Center (NACC) [24], National Health Insurance Service-Ilsan Hospital (NHIS-IH) [25], Extensible

Neuroimaging Archive Toolkit (XNAT) [26], and The Cancer Imaging Archive (TICA) [27] are the often-utilized data sources for AD patients. For the reader's convenience, Section 6 is dedicated to introducing ADNI and OASIS datasets as they are the most publicly available online data sources.

2.4.2 Pre-Processing

Before processing to further computational process, pre-processing deals are the operations to extract relevant information. For AD classification, pre-processing is crucial to achieving an accurate classification outcome. Morphological operations, skull stripping, noise filtering, and image resizing are commonly pre-processing steps [28]. Among them, skull stripping is the most utilized type because some unwanted pixels can be captured by the brain imaging mechanisms in the form of the skull [12].

2.4.3 Feature Extraction

It is a process of generating new features from existing and extracting the most relevant characteristics for classifying an item. The newly compacted features may summarize the maximum amount of data included in the original collection of features [29]. Feature extraction techniques' main benefits are reducing time complexity, better training, and improving accuracy [12]. These techniques are mathematical models based on different image properties [28]. Figure 2-9 shows several feature extraction techniques: texture, voxel morphometry, graph/network, scale-invariant feature transforms, eigenvector, wavelet transform, harmonic function, and artificial neural network [12].

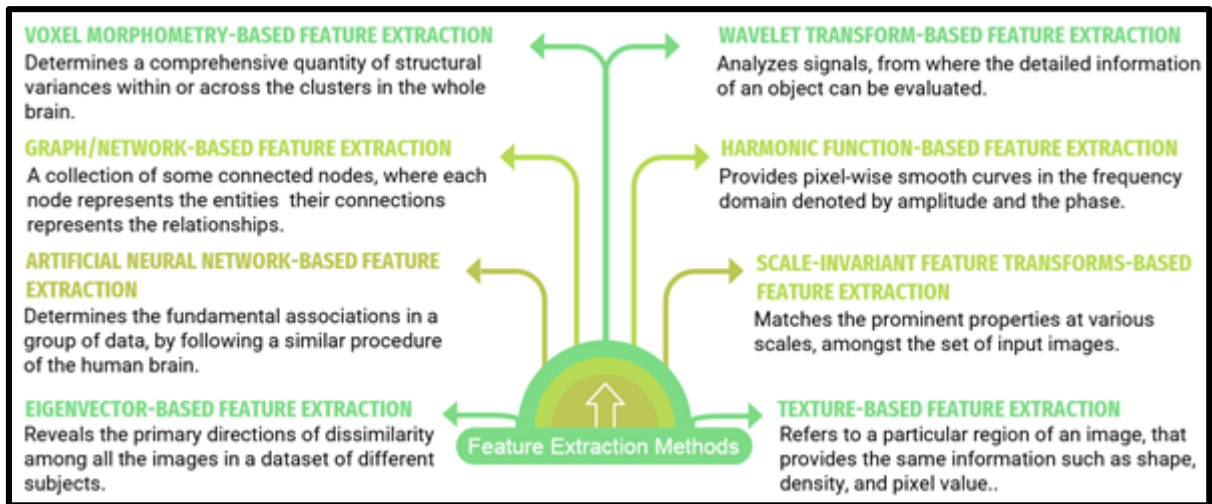


Figure 2.9: Feature extraction methods.

2.4.4 Feature Selection

Feature Selection is crucial in reducing the dimensionality of the data and improving the performance of any proposed framework [30]. Some less relevant features can sometimes be extracted in the feature extraction step. It makes the model learn falsely; consequently, classification accuracy may affect adversely. Following a specific paradigm for classification, feature selection is selecting just the most features by removing the unneeded ones. The main pros of using a proper feature selection approach are improving the model's accuracy, decreasing the complexity and over-fitting issues, and faster training of the classifier [12]. As illustrated in Figure 2-10, feature selection methods are classified into: Filter methods, Wrapper methods, Embedded methods, and Hybrid methods [31].

01	Filter Methods	Univariate Selection (ANOVA) Chi Square Based on correlation
02	Wrapper Methods	Forward Selection Backward Selection Exhaustive Search
03	Embedded Methods	Lasso/Ridge (using Elastic Net) Tree-based Selection Regression Coefficients
04	Hybrid Methods	Feature shuffling Recursive Feature Elimination Recursive Feature Addition

Figure 2.10: Feature extraction methods.

2.4.5 Classification

It is a method for categorizing a collection of pixels using spectral or textural characteristics based on a set of protocols. This procedure is performed by one, or multiple machine learning and/or deep learning techniques perform this procedure. For the reader's convenience, we assigned the following section to review to present the fundamental technological pillars of machine learning algorithms.

2.5 ML ALGORITHMS FOR HEALTH DISEASE

As humans are imperfect, it is not unexpected that a patient may be over-diagnosed more often. If overdiagnosis occurs, issues such as unneeded treatment may develop, hurting the health and economics of people [7]. This section briefly introduces the reader to the machine learning concept and its medical applications.

2.5.1 Concept of ML

Machine learning is a technique that uses mathematical and statistical methods to draw inferences from data samples, enabling computers to learn without being explicitly programmed. In 1959, Arthur Samuel firstly introduced ML in pattern recognition and game algorithms to learn from their experience. Thus, ML was first recognized, and its significant achievement was acknowledged. Learning from data to predict or make judgments, depending

on the given job, is the core principle of machine learning [21]. Due to ML technology, many formerly worked tasks may now be accomplished quickly and with little effort. With the rapidly increasing data storage and computer power, it becomes easier to train data-driven ML models to anticipate findings with excellent accuracy. Multiple publications provide different ML techniques.

Supervised, Semi-supervised and Unsupervised are the main categories of ML algorithms [18]. However, machine learning algorithms may be classified into subgroups depending on their respective learning strategies [7]:

a. Learning Problems.

- i. Supervised learning.
- ii. Unsupervised learning.
- iii. Reinforcement learning.

b. Learning Techniques.

- i. Online learning.
- ii. Transfer learning.
- iii. Ensemble learning.

c. Active Learning.

- i. Multi-task learning.
- ii. Hybrid learning.
- iii. Semi-supervised learning.
- iv. Self-supervised learning.
- v. Multi-instance learning.

d. Statistical Inferences.

- i. Inductive learning.
- ii. Deductive learning.
- iii. Transductive learning.

Figure 2-11 summarizes the approaches mentioned above and gives an example of each type [3] [7] [8] [12] [18] [20].

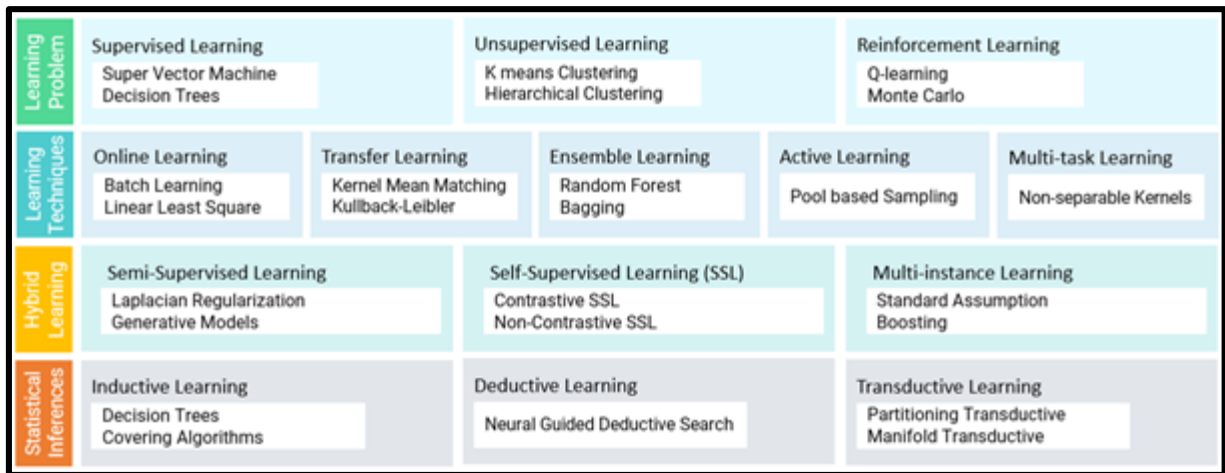


Figure 2.11: ML algorithms classification-based learning approaches.

2.5.2 ML based-Medical fields

The rise of machine learning algorithms in disorders diagnostic domains demonstrates the applicability of the technology in medical disciplines.

- a. Alzheimer's disease [1].
- b. Heart failure [32].
- c. Kidney disease [33].
- d. Breast cancer [34].
- e. Diabetes [35].
- f. pneumonia [36]

These are just a few diseases that ML may identify [37].

2.6 DATASETS

Although detecting Alzheimer's disease is challenging, scholars do not require to work alone and may use many online datasets and software packages for assistance. The depth model may be implemented via Torch, Tensorflow, Keras, Matlab and other software packages. ADNI, OASIS, and other datasets [1]. The datasets usually include brain MRI scans of three different groups of patients: CN, MCI, and AD. The primary objective of the studies was to determine if serial MRI, PET, and other biological markers, as well as clinical and neuropsychological evaluation, can be used to evaluate the development of MCI and early AD.

As mentioned earlier, for AD classification, ADNI and OASIS are the most used publicly available online data sources. Therefore, during 2020-2022, we searched the papers that utilized these two datasets. Two campaigns after defining essential keywords have performed, firstly: (“Alzheimer’s disease” OR “AD”) AND (“Alzheimer’s Disease Neuroimaging Initiative” OR “ADNI”). Secondly: (“Alzheimer’s disease” OR “AD”) AND (“Open Access Series of Imaging Studies” OR “OASIS”). As shown in Figure 2-12, the search has been conducted on three highly ranked scientific databases: IEEE, Science Direct, and Springer. Both datasets have been highly utilized. However, the rate of ADNI to OASIS is 3:1. Therefore, we dedicated this section to explaining these two datasets.

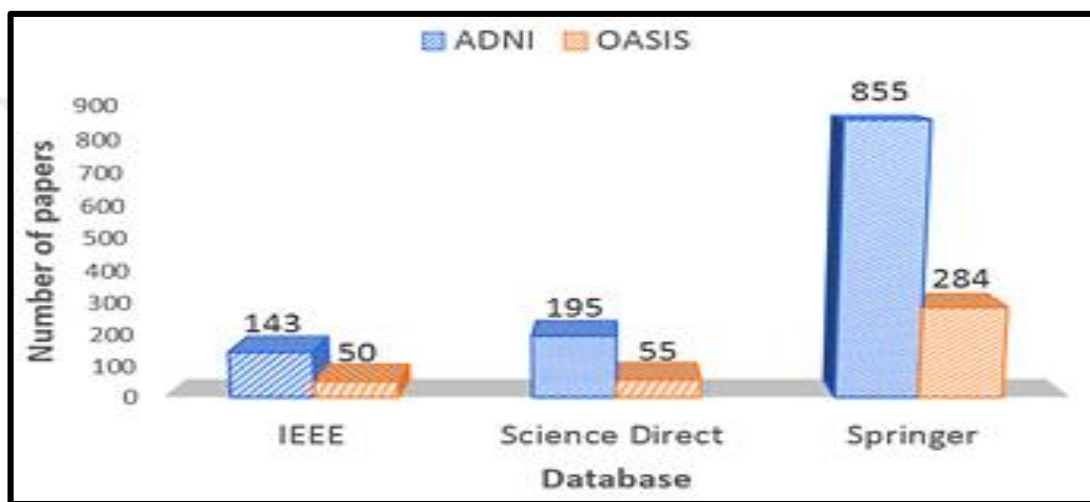


Figure 2.12: Number of papers in the ranked scientific databases according to AD datasets from 2020 to 2022.

2.6.1 ADNI

In 2004, the ADNI was established as a public-private collaboration under the direction of MD Principal Investigator Michael W. Weiner. ADNI development aims to determine if serial MRI, PET, and other biological markers, as well as clinical and neuropsychological evaluation, may be integrated to monitor the development of MCI and early AD. Currently, ADNI is categorized into four stages:

- a. ADNI-1.
- b. ADNI-GO.
- c. ADNI-2.
- d. ADNI-3.

DNI-1 and ADNI-GO are baseline data, whereas ADNI-2 and ADNI-3 mainly consist of newly added modal data. Figure 2-13 summarizes the ADNI dataset categories (for up-to-date information, see [22]).

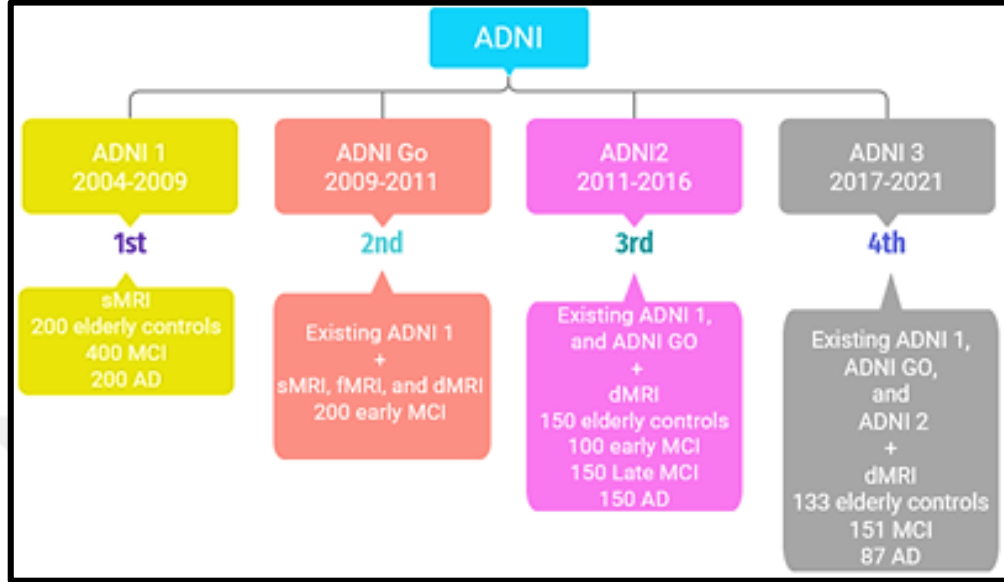


Figure 2.13: Summary of ADNI dataset classifications [22].

2.6.2 OASIS

By offering the scientific community open neuroimaging datasets, OASIS aims to facilitate future discoveries in AD. OASIS dataset is classified into five stages:

- a. OASIS 1.
- b. OASIS 2.
- c. OASIS-3.
- d. OASIS-3 TAU.
- e. OASIS-4.

A summarized description of these datasets is shown in Figure 2-14. Classification attributes (of the participant) in the OASIS datasets used in the experiments are shown in Figure 2-15. It is worth mentioning that some attributes may have different settings in OASIS phases. For example, EDUC refers to the education level of the participant. In OASIS 1, the level varies from 1 to 5, where one is education below the academic school and five is after higher education). However, OASIS 2 and beyond indicates the years of education. For up-to-date information, see [23].

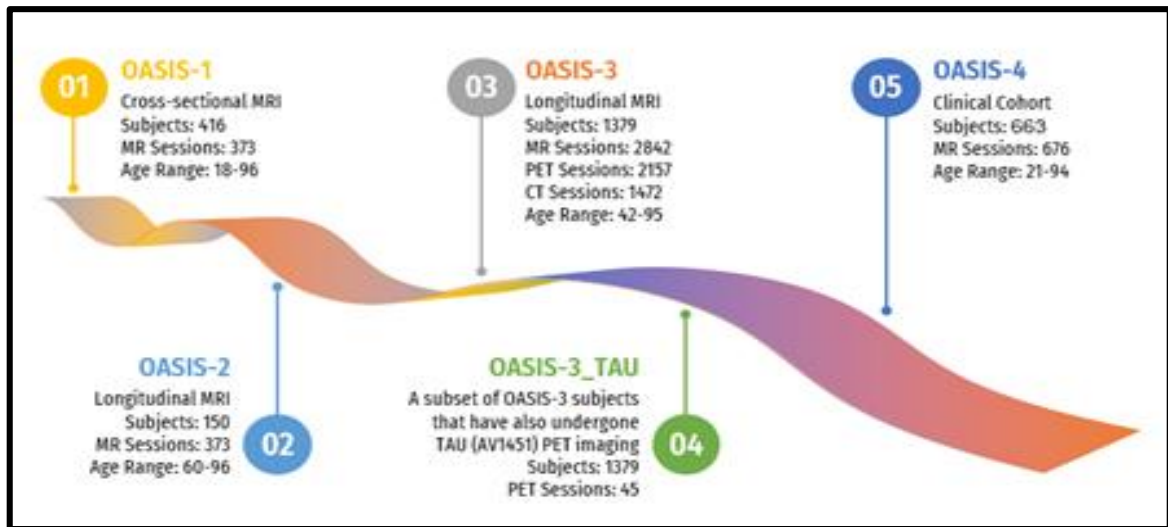


Figure 2.14: Summary of OASIS dataset classifications.

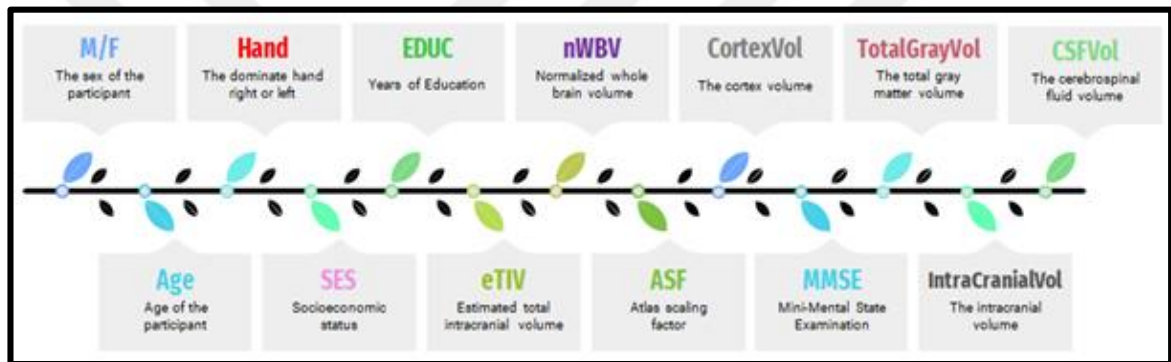


Figure 2.15: Attributes of OASIS datasets.

2.7 RISK AND PROTECTIVE FACTORS IN THE AD DEVELOPMENT

As previously said, AD is a complex and multifaceted condition caused by the combination of genetic vulnerability and environmental variables throughout the life cycle [38]. AD development is not influenced by gender differences only [39] [40]. Epidemiological studies have found possibly modifiable AD risk and protective variables [41]. Additionally, AD is believed to begin decades before clinical symptoms appear. Thus, treatments addressing a number of risk factors in non-demented older individuals, including the population of middle age, may prevent or postpone AD development [42].

In this section, we review recent epidemiological developments about AD risk variables that may be modified, emphasizing the concept of early prevention. As illustrated in Figure 2-16,

studies have demonstrated that several risk factors impact AD development. Figure 2-17 shows the protective factors for AD prevention [43].

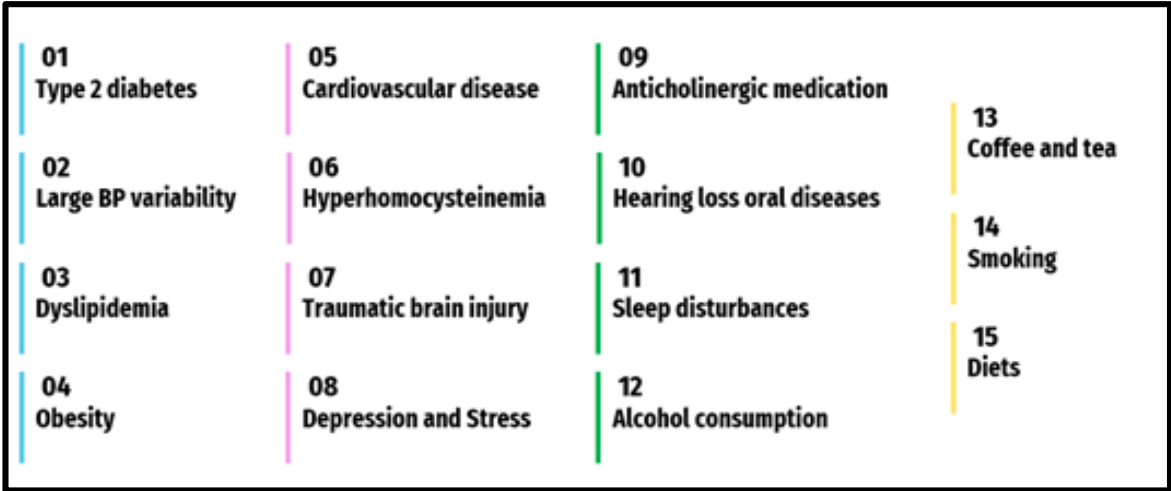


Figure 2.16: Risk Factors of AD.

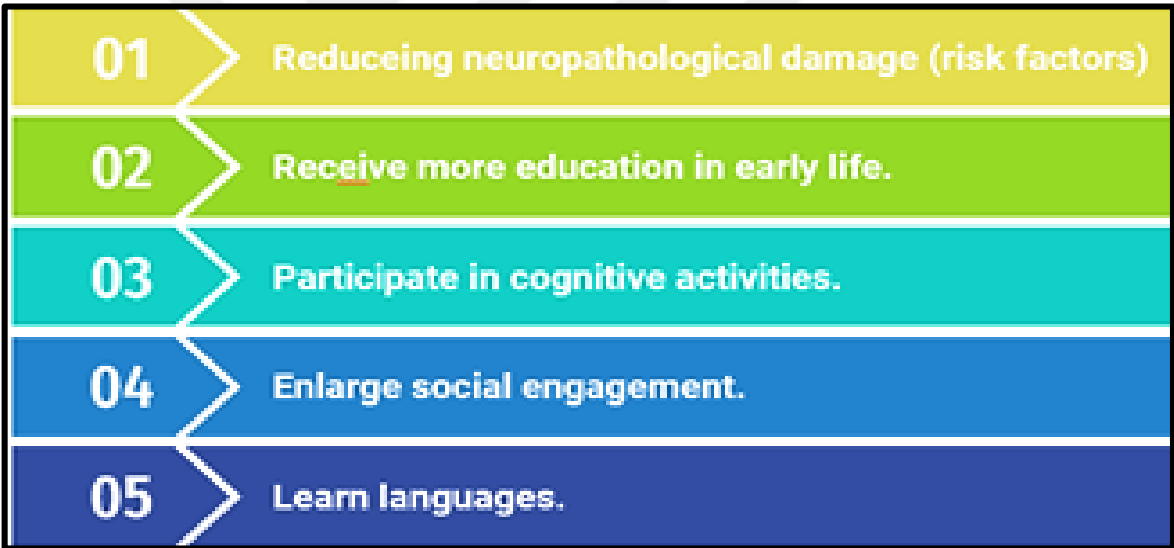


Figure 2.17: Protective Factors for AD Prevention and Slowing its Progress.

2.7.1 Psychological factors

a. Educational attainment

Completing education might improve cognitive abilities and language processing. Long-term education may also positively affect brain volumes, such as increased cortical thickness and surface area in the prodromal phase of AD [43]. Studies demonstrated that Higher education is one of the necessary protective factors against AD [44].

b. Cognitive activity and bilingualism

To maintain cognitive health, bilingualism and cognitive activity were also helpful. To prevent AD, it is vital to enhance access to education, particularly language, and to stimulate cognitive activity among the general population [45]. Active cognitive activity participation was predicted to reduce AD risk by 46% [43].

c. Social engagement

Due to the early formation of cognitive reserve via frequent healthy social interaction, frequent social contact with friends was associated with a small reduction in dementia risk [43]. Participating in more frequent social activities and cultivating good social interactions is advisable [46].

d. Depression and stress

Depressive symptoms represented a prodrome rather than a causative risk factor for AD. In addition, mendelian randomization research did not demonstrate a causal link between AD and depression [43]. Thus, this relationship needs to be investigated further in depth in the future.

2.7.2 Pre-existing Disease

a. Cardiovascular diseases

Priority one in preventing Alzheimer's disease should be the early detection and treatment of vascular hazards and maintaining a healthy cardiovascular system. Pharmaceuticals such as oral anticoagulants and catheter ablation would dramatically reduce the risk of AD in people with atrial fibrillation [47].

b. Hypertension and dyslipidemia

Blood lipids have important roles in AD development (such as total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) [43]. Regular usage of medications might help patients control these disorders. For more details about the cardiometabolic and genetic impacts, we refer the reader to the review paper [48].

c. Diabetes

Diabetes was associated with an increased chance of developing AD. Those with untreated diabetes showed a greater CSF p-tau level than those on antidiabetic medicines or euglycemic adults. Indicating that tau pathology may be mitigated using antidiabetic drugs. We refer the interested reader to the review paper [49] for more information.

d. Traumatic brain injury

In the scientific literature, participants exposed to traumatic brain injury were shown to have a higher risk of AD [50]. According to their death certificates, athletes with several head injuries over a long time were more likely to die from AD. [43].

e. Obesity

Consistent data suggests that middle-aged individuals with a more significant body mass index have an increased risk of AD (BMI). In contrast, being overweight or obese in old age may provide cognitive protection. According to the research, young persons must maintain or drop weight within a healthy range (18.5-24.9 kg/m²). However, older adults should prevent weight reduction above this range; otherwise, This situation should be the center of the concern. [49].

f. Oral Disease

Oral diseases have significant concerns for cognitive dysfunction (such as chronic periodontitis and tooth loss), possibly mediated by local and systemic inflammatory reactions [51]. Accordingly, to prevent AD in developing countries, dental care should get significant focus.

g. Hearing loss

The listening status could be mitigated by cochlear implants and hearing aids. These may lead to reduce cognitive decline rate. Early detection and treatment of hearing loss may significantly impact AD prevention [52].

2.7.3 Lifestyles

Numerous prospective studies on lifestyle factors associated with the risk of cognitive impairment and AD were discovered as follows [43].

- a. Sleep disturbances [53].
- b. Physical activity [54].
- c. Diets (such as Mediterranean diet [55], Ketogenic Diet [56], and Western diet [57].
- d. Tea [58] and Coffee [59].
- e. Omega-3 fatty acids [60]
- f. Alcohol [61].
- g. Smoking [62].

2.7.4 Other Factors

- a. Pollutions [63].
- b. Medications [64].

2.8 PERFORMANCE EVALUATION METRICS

In the ML field, classification issues are often compared based on accuracy, specificity, precision, sensitivity, and area under the curve. These metrics are typically used to evaluate recommendation systems' performance or models' generalization capabilities [28] [65]. For example, AD is categorized as follows:

- a. True positive (T_P).
- b. True negative (T_N).
- c. False positive (F).
- d. False negative (F_N)

While T_P and T_N refer to the person being diagnosed correctly, F_P and F_N mean misdiagnosed. This section briefly defines the evaluation metrics in AD classification [1] [12] (see Figure 2-18).

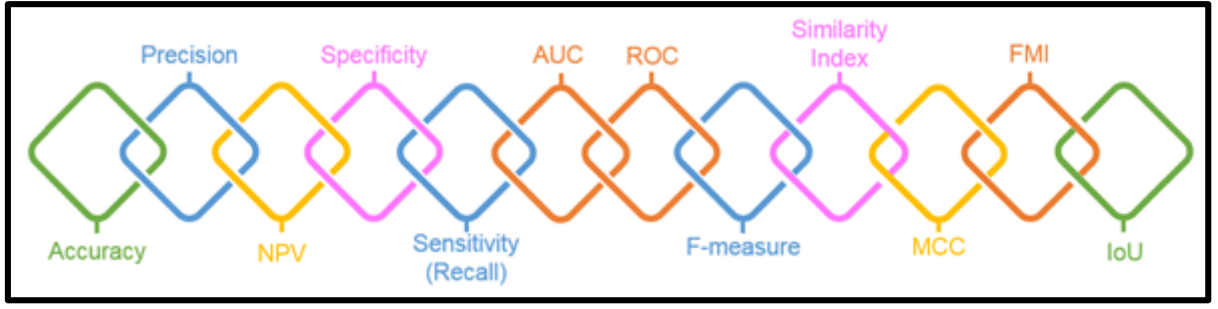


Figure 2.18: Most widely used evaluation metrics of AD models.

Accuracy: It calculates the model's ability to correctly identify all pixels or classes (negative or positive). It answers the following question: How many patients did we correctly label out of all the patients?

$$Accuracy = \frac{T_N + T_P}{T_P + F_P + T_N + F_N} \quad (2-1)$$

Precision: It measures the proportion of T_P (positives) in the cases ($F_P + T_P$) considered to be positive (correctly and incorrectly) (also called positive predictive value (PPV). It answers the following: How many of those who we labeled as AD actually have AD?

$$Precision = \frac{T_P}{F_P + T_P} \quad (2-2)$$

Negative Predictive Value (NPV): It is the opposite of Precision; it measures the proportion of T_N (negatives) among all the cases ($F_P + T_P$) judged to be negative (correctly and incorrectly). It answers the following: How many of those who we labeled as not AD actually have not AD?

$$NPV = \frac{T_N}{T_N + F_N} \quad (2-3)$$

Specificity: It calculates how many (T_N) are appropriately identified from all negatives ($F_P + T_N$) cases. It answers the following question: Of all the healthy people, how many of those did we correctly predict as healthy?

$$Specificity = \frac{T_N}{F_P + T_N} \quad (2-4)$$

Sensitivity (Recall): It calculates how many (T_P) are appropriately identified from all positives ($F_P + T_N$) cases. It answers the following question: How many of those do we correctly predict are really AD patients?

$$Sensitivity = \frac{T_P}{T_P + F_N} \quad (2-5)$$

F-measure (F-score or F1-score): The F-measure score is harmonically the mean of accuracy and recall. The perfect precision and recall score means the highest F-score (i.e., equals 1).

$$F - measure = 2 * \frac{Precision * Recall}{Precision + Recall} \quad (2-6)$$

Receiver operating characteristic (ROC) curve: At a given threshold, it is simple to determine the discriminating power of a classifier on a sample. The ROC curve appropriately represents the connection between the specificity and sensitivity of a specific analytical procedure. It is a comprehensive representation of the accuracy of a diagnostic method. ROC measures the general usefulness of a test at different threshold values. The larger the area, the more valuable the test (ranges from 0% to 100%).

Area under the curve (AUC): It is an area under T_P rate vs. F_P rate. AUC calculates the model's ability to distinguish between classes, and is used as a summary of the receiver characteristics curve.

Matthews correlation coefficient (MCC): It is a more balanced indicator that considers all positives and negatives (T_P, F_P, T_N, F_N).

$$MCC = \frac{(T_N * T_P) - (F_N * F_P)}{\sqrt{(T_N + F_N) * (T_N + F_P) * (F_N + T_P) * (F_P + T_P)}} \quad (2-7)$$

Fowlkes–Mallows index (FMI): It is usually used as a clustering performance indicator by calculating the geometric mean of precision and sensitivity rates. A better clustering result means a large FMI value.

$$FMI = \frac{T_P}{\sqrt{(F_N + T_P)(F_P + T_P)}} \quad (2-8)$$

Similarity index: It refers to the similar identity between the input image and the detected infected brain region.

$$Similarity\ index = \frac{2T_P}{F_N + F_P + 2T_P} \quad (2-9)$$

Intersection over union (IoU): It calculates the between the prediction output of the model and the annotated ground truth mask. It is also called the Jaccard index (JI).

$$IoU = \frac{T_P}{F_N + F_P + T_P} \quad (2-10)$$

2.9 LITERATURE REVIEW

2.9.1 Article Selection

The search was carried out as follows: ‘Alzheimer’s Disease’ AND (‘AD’ OR ‘Prediction’ OR ‘Classification’ OR ‘Classifier’ OR ‘Machine learning’ OR ‘Deep learning’ OR ‘SVM’ OR ‘Logistic Regression’ OR ‘Random Forest’ OR ‘KNN’ OR ‘Decision Tree’ OR ‘neural networks’ OR ‘ANN’, ‘RNN’ OR ‘CNN’ OR ‘DNN’ OR ‘XGB’ OR ‘Dataset’ OR ‘ADNI’ OR ‘OASIS’ OR ‘Feature extraction’ OR ‘Feature selection’). To simplify the analysis, 20 papers were analyzed to understand the existing studies. Relevant data were taken from papers published during the period 2019–2022. Table 2-1 and Figure 2-19 show the considered scientific papers within the scope of this section.

Table 2.1: A summary of the sources of the considered papers of Section 2-9.

Study	Year	Publication	Publisher
[66]	2019	IEEE Access	IEEE
[67]	2019	Magnetic Resonance Imaging	ScienceDirect
[68]	2019	Alzheimer's and Dementia	ScienceDirect
[69]	2019	NeuroImage: Clinical	ScienceDirect
[70]	2019	NeuroImage: Clinical	ScienceDirect
[71]	2019	NeuroImage: Clinical	ScienceDirect
[72]	2019	Procedia Computer Science	ScienceDirect
[73]	2020	Neuroinform	Springer
[74]	2020	Sensors	MDPI
[75]	2020	Journal of Prevention of Alzheimer's Disease	Springer
[76]	2020	Applied Science	MDPI
[77]	2020	Informatics in Medicine Unlocked	ScienceDirect
[78]	2020	NeuroImage	ScienceDirect
[79]	2021	IEEE Journal of Biomedical and Health Informatics	IEEE
[80]	2021	IEEE Access	IEEE
[81]	2021	IEEE Access	IEEE
[82]	2021	IEEE Transactions on Neural Systems and Rehabilitation Engineering	IEEE
[83]	2021	NeuroImage	ScienceDirect
[84]	2022	NeuroImage: Clinical	ScienceDirect
[85]	2022	Journal of King Saud University-Computer and Information Sciences	ScienceDirect

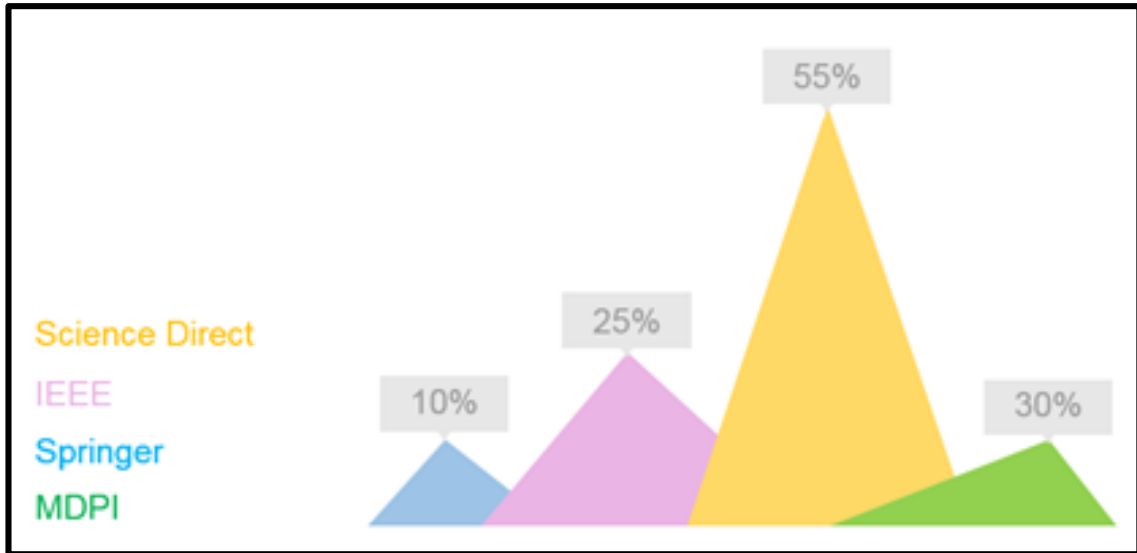


Figure 2.19: Percentage Distribution of The Selected Papers of Section 2-9.

2.9.2 Literature Evaluation

The authors in [66] suggested voxel-based hierarchical feature extraction (VHFE) method for early AD identification. Firstly, the brain is divided into 90 areas of interest using the automated anatomical labeling (AAL) template (ROIs). Then, to separate the non-informative data, they chose the informative voxels in each ROI with a baseline of their values and vectorized them. By utilizing the ADNI dataset, the model achieved excellent accuracy (AD vs. NC = 99.70%, AD vs MCI = 97.80%, and NC vs MCI = 98.90%). However, the suggested hierarchical feature extraction technique is not limited to capturing the local characteristics in each ROI extracted by the first-stage feature extraction method. Furthermore, the universality of the approach didn't approve. In [67], the authors implemented Siamese networks to distinguish controls vs. symptomatic AD cases. They used the suggested kernel-normalized whole-brain anatomical volumetric asymmetry-encoding features. The model achieved 94.36% (92.20%) accuracy using ADNI (ADNI and BIOCARD). Nevertheless, the algorithm must be applied to different asymmetric features, such as shapes, cortical thickness, and voxel intensities.

The authors in [68] extracted two hundred and thirty-two variables from the last MRI before death using FreeSurfer. Nonparametric correlation analysis and multivariable SVM classification were performed to provide a predictive model of Braak NFT (neurofibrillary tangles) staging. The model has been designed by multivariable SVM and trained using three

datasets (ADNI, NACC, and MAP). Although the method showed promising results, the model Can be predicted to some extent from in vivo cross-sectional MRI metrics using automatic brain segmentation and classification-based machine-learning techniques. On the basis of a single cross-sectional brain structural MRI scan, a deep learning algorithm was designed in [69] to predict the individual diagnosis of AD and MCI who would convert to AD (c-MCI). The model achieved an accuracy of 99% (ADNI) and 98% (ADNI + Institute of Experimental Neurology (Italy)). However, the model cannot exclude the presence of future c-MCI among s-MCI patients.

Progressive Learning Algorithm utilized in [70] to examine the diagnosis of MCI patients after two and five years of follow-up. The authors analyzed its effect on the predictive ability of baseline volumetric MRI parameters mostly engaged in AD. In a trial sample of 248 MCI patients followed up over five years, predictive power was evaluated regarding the area under the ROC curve (AUC), specificity, and sensitivity. They further compared the sensitivity in those MCI that converted before two years and those that converted after two years. However, the findings have implications on the novel ML algorithms that learn discriminative patterns from a sample of s-MCI and pMCI over a short follow-up time

As a diagnostic tool for AD, the authors in [71] examined the multimodal MRI utility (T1-weighted structure and diffusion MRI) combined with high-throughput brain phenotyping-morphometry, structural connectomics, and ML algorithm. The model has developed three algorithms: Random Forest, Logistic Regression (LR), and (SVM) with a linear kernel. The authors calculated SMC to AD, SMC to MCI, and MCI to AD, based on samples taken from (National Health Insurance Service-Ilsan Hospital (NHIS-IH) and ADNI-2. Using NHIS-IH (ADNI-2) the accuracy reached 97% (96%), 83% (70%), and 97% (75%), respectively. However, there are limitations related to the NHIS-IH data. Firstly, lack of healthy controls in the cohorts. Secondly, the AD group had significantly greater age than the MCI or SMC groups.

Automatic classification of brain tumors and AD in MRI was proposed in [72]. The proposed algorithm encompasses four stages: MRI image acquisition, pre-processing, feature extraction, and classification. In the article, the bag features modules have been used to classify the brain with tumor and MRI of the brain of AD from normal brain MRI. The model was designed by SVM and trained and tested with images from the Cancer Imaging Archive

(TCIA), XNAT, Oasis and a few Google searches. Although the accuracy reached 97%, it can be reduced as the grid size is reduced.

3D-Deep learning-based automatic diagnosis of AD with joint MMSE (Mini-Mental State Examination) prediction using Resting-state fMRI developed in [73]. The authors evaluated a deep learning method for diagnosing AD and jointly predicted the MMSE scores of South Korean patients with AD. Three hundred thirty-one individuals were scanned using resting-state functional Magnetic Resonance Imaging (rs-fMRI) to generate functional 3D independent component spatial maps for use as features in classification and regression tasks. The model was developed using CNN and SVM-based recursive feature elimination and achieved an accuracy of 85.27% AD vs. NC. Nevertheless, the work needs to be validated with larger imaging data sets. The authors in [74] used SVM to emphasize learning and feature repetition in width instead of length to improve AD classification performance. The classifier achieved an accuracy of 98.81% AD vs. NC, 81.61% MCI vs. NC, and 81.40% AD vs. MCI. However, the proposed structure used to form the feature sets in this experiment is not optimal for other datasets.

In [75], the authors developed a machine learning framework using linear regression (LR) and improved the performance of feature selection by Genetic Algorithm (GA). The framework tested with ADNI dataset samples and achieved an accuracy (AUC) of 91.87% to 98.45% (89.80% to 95.35%). However, GAs do not scale well with complexity. The performance of three state-of-the-art classification models, namely SVM, RF and ANNs, were compared in [76]. The results confirmed that the whole brain structural communicability alterations due to AD are valuable biomarkers for the characterization and investigation of pathological conditions. The authors calculated each algorithm's accuracy, sensitivity, specificity, and AUC using the ADNI dataset. The authors in [77] utilized Non-linear SVM using a radial basis function kernel to measure the regional cortical thickness of both left and right hemispheres (68 features) using FreeSurfer analysis for each individual. Using the ADNI dataset, the classifier in all four groups (AD, IMCI, eMCI, and Control) achieved good results. However, the performance of the model is useful for clinical diagnosis.

Electroencephalography (EEG) can potentially address AD development due to its low cost and portability. In [78], The authors gathered EEG, sMRI, and neuropsychological data from 55-year-olds with Alzheimer's disease (AD), amnesic mild cognitive impairment (aMCI), and

healthy controls (HCs) (about 60 per group). They evaluated a range of candidate EEG markers (i.e., functional connectivity and frequency band power) for AD and aMCI classification and compared their performance with sMRI. They also tested a combined EEG and cognitive classification model using MMSE. The result showed a sensitivity of over 70%, and sMRI outperformed resting state EEG at classifying AD.

For early AD detection, the authors in [79] developed a method using SVM to identify potential blood-based non-amyloid biomarkers. Specifically, they identified five novel panels of non-amyloid proteins with the potential to serve as biomarkers of early AD. Although achieving Sensitivity (Specificity) was over 80% (70%), the model suffers from several issues. Firstly, the dataset is small, which limits the effect of training and classification. Secondly, their findings may not generalize well to other cohorts. Thirdly, the accuracy of the model didn't calculate. The authors in [80] proposed an aggregated approach of Hough-CNN, CNN and DNN models to diagnose AD based on volumetric features from sMRI data. The dataset was utilized from National Research Center for Dementia (NRCD), South Korea, and the accuracy reached 94% (94.82%) in the right (left) hippocampi. However, the algorithm must be verified with large open-source datasets and other modalities' data.

The authors in [81] proposed a new method using Latent space in deep learning to model the longitudinal progression of brain MR images using personalized memory. The authors used the ADNI dataset to achieve a Similarity Index Measure (SIM) of 95%. However, the evaluation of anticipated pictures is restricted to the use of image quality measurements. Potential models were developed in [82] and identified five novel candidate non-amyloid biomarkers for early AD detection utilizing a new approach. Takagi-Sugeno-Kang (TSK) fuzzy model has been used and tested using samples from Tangshan Gongren hospital in China. Although the model achieved an accuracy of 98%, the dataset was small and didn't include MCI subjects. The Bayesian classifier has been used by [83] to develop a robust parametric model of AD progression based on alternating M-estimation using the logistic loss to address potential curve-fitting problems such as outliers. The model was trained and tested using two datasets, ADNI and NACC and achieved 0.929 ± 0.012 , and 0.928 ± 0.016 , respectively. The authors in [84] employed a deep learning longitudinal model, graph convolutional and recurrent neural network (graph-CNN-RNN), on a series of brain structural MRI scans for AD prognosis. The authors used datasets OASIS and ADNI to demonstrate

their design. However, the performance and robustness of the proposed model should be further tested on longitudinal datasets with larger samples. Recently, the authors in [85] built a cognitive-based 3-tiered ML algorithm employing baseline characteristics to predict AD or MCI to construct psychometric test results. The model was built using XGB, RF, and SVM and achieved an accuracy of 95% in classifying AD, MCI, and CN. However, Due to the small number of participants investigated, the ADNI dataset's final CN, MCI, and AD subject prediction may have been impacted. Finally, Table 2-2 summarizes the papers mentioned above.

Table 2.2: A summary of the considered papers of Section 2-9.

Ref.	Algorithm	Dataset	Results
[66]	CNN	ADNI	Accuracy: AD vs MCI = 97.80%, AD vs NC = 99.70%, and NC vs MCI = 98.90%
[67]	SNN	ADNI, and BIOCARD	Accuracy: 94.36% (ADNI), and 92.20% (ADNI + BIOCARD)
[68]	Multivariable SVM	ADNI, NACC, and MAP	Accuracy: 62.4% correct classification rate for discrimination between transentorhinal, limbic, and isocortical groups
[69]	CNN	ADNI and the Institute of Experimental Neurology	Accuracy: 99% (ADNI), and 98% (ADNI + Institute of Experimental Neurology)
[70]	Progressive Learning Algorithm	ADNI	AUC: (2 vs 5 years) = (73% vs 85%), Specificity: (2 vs 5 years) = (56% vs 71%), and Sensitivity: (2 vs 5 years) = (81% vs 78%),
[71]	RF, LR, and SVM with a linear kernel	NHIS-IH and ADNI-2	Accuracy: NHIS-IH: (SMC to AD: 97%), (SMC to MCI: 83%), and (MCI to AD: 97%). ADNI-2: (HC to AD: 96%), (HC to MCI: 70%), and (MCI to AD: 75%).
[72]	SVM	TCIA, XNAT, OASIS, and Google search	Accuracy: 97%
[73]	CNN and SVM-based recursive feature elimination	Gwangju (South Korea)	Accuracy: 85.27%

Table 2.2: A summary of the considered papers of Section 2-9 ‘Table Contied’.

[74]	SVM	ADNI	Accuracy: 98.81% AD vs NC, 81.61% MCI vs NC, and 81.40% AD vs MCI
[75]	LR	NACC	Accuracy: 91.87% to 98.45% AUC: 89.80% to 95.35%,
[76]	ANNs, SVM, and RF	ADNI	Accuracy: ANNs: 75%, SVM: 72%, RF: 74% AUC: ANNs: 83%, SVM: 81%, RF: 82%. Sensitivity: ANNs: 79%, SVM: 68%, RF: 72%. Specificity: ANNs: 76%, SVM: 75%, RF: 77%.
[77]	Non-linear SVM using a radial basis function kernel	ADNI	Accuracy: 75% in classifying all four groups (AD, IMCI, eMCI, and Control)
[78]	Penalized Logistic Regression	Outpatient memory clinic of the Department of Neurology	Sensitivity: > 70%. AUC: sMRI 1.00 vs 0.76,
[79]	SVM	ADNI	Sensitivity: > 80%, and Specificity > 70%
[80]	Hough-CNN, CNN, and DNN	NRCD (South Korea)	Accuracy: 94% Right hippocampi. 94.82% Left hippocampi.
[81]	Latent space in deep learning	ADNI	SIM: 95.3±1.5
[82]	TSK fuzzy model	Tangshan Gongren hospital	Accuracy: 98.1%
[83]	Bayesian	ADNI and NACC	AUC: ADNI: 0.929 ± 0.012, NACC: 0.928 ± 0.016
[84]	Graph-CNN-RNN	ADNI and OASIS	Accuracy: 80%
[85]	XGB, RF, and SVM	ADNI	Accuracy: 95.12% among (AD/MCI/CN)

2.10 SUMMARY

Alzheimer's disease is one of the world's most famous neurological diseases that cause death, and the number of patients has risen dramatically. Manual diagnosis of AD by a neurologist is time-consuming and may not always provide reliable findings. The classification of AD using brain imaging has shown promising, less time-consuming results. Numerous researchers have attempted to create a classification system for brain images with fewer research problems.

Although researchers have achieved encouraging findings in AD classification using brain imaging, there are still several obstacles to overcome in this study area. Obtaining enough data for the research is one of the primary obstacles. Most academics get data from just two internet databases, OASIS and ADNI. Consider the gender and age distribution, which may significantly influence AD distinction from other subject groups. In such a scenario, the data may not adequately train an ML model correctly.

Identifying the correct biomarkers for Alzheimer's disease is a further crucial challenge. Sometimes, comparable brain structure changes might develop due to other neurological disorders, and training or testing should consider these facts. Sets may yield an incorrect result despite the model's complete correctness.

3. METHODS OF THE THESIS

3.1 INTRODUCTION

As shown in the preceding chapter, there are sophisticated and reliable techniques for forecasting future trends using historical information. AI models can learn from data and make accurate predictions based on existing data. As far as we know, this is the first study to assess three different AD classification models using three ML algorithms: Naïve Bayes, K-Nearest Neighbour (KNN), and Multi-layer Perceptron (MLP).

The organization of this chapter is as follows. Section 3.2 briefly discusses the Naïve Bayes model. In the following, we introduce the KNN model in Section 3.3. In Section 3.4, the MLP model is presented. Finally, the summary of the chapter is outlined in Section 3.5.

3.2 NAIVE BAYES

NB is also known as a Simple Bayesian Classifier. It is a supervised learning technique that solves classification issues based on the Bayes theorem. It is an easy probabilistic method in the classification approach that derives its probability value from the related collection's frequency and value combinations. Therefore, NB is quite efficient and simple to implement on many datasets [86].

Let the feature vector is defined as $\vec{x} = (x_1, x_2, \dots, x_m)$. All possible categories that $\vec{x}$ belong is denoted as $S = (s_1, s_2, \dots, s_n)$. The fundamental of the Naïve Bayes model is to calculate the probabilities $\vec{x}$ written as $p_1, p_2, \dots, p_m$. For example, the probability that $\vec{x}$ belongs to category s_i is p_i .

Category $\vec{x}$ belongs to will be known when the $\max(p_1, p_2, \dots, p_m)$ are determined. Accordingly, determining the maximum value of equation (3-1) is considered a Naïve Bayes classification problem.

$$P(s_i|x_1, x_2, \dots, x_m) = \frac{P(x_1, x_2, \dots, x_m|s_i)P(s_i)}{P(s_1, s_2, \dots, s_m)} \quad (3-1)$$

where, $P(x_1, x_2, \dots, x_m|s_i)$ is the probability that the category s_i consists $\vec{x}$, if the training sample is in s_i is known. The probability $P(s_i)$ defines the probability that a random sample belongs to the category s_i . The joint probability of all possible categories is defined by $P(s_1, s_2, \dots, s_m)$.

$P(s_1, s_2, \dots, s_m)$ is constant for all categories; therefore, the above formula can be written as follows:

$$s_{Naïve Bayes} = arg \max_{s_i \in S} P(x_1, x_2, \dots, x_m|s_i)P(s_i) \quad (3-2)$$

The term in $\vec{x}$ are identically distributed according to NB assumption. Consequently, their joint probability distribution can be written in product terms.

$$P(x_1, x_2, \dots, x_m|s_i) = \prod_{j=1}^m P(x_j|s_i) \quad (3-3)$$

Therefore, the goal is to find the following.

$$s_{Naïve Bayes} = arg \max_{s_i \in S} P(s_i) \prod_{j=1}^m P(x_j|s_i) \quad (3-5)$$

The assumption underlying the use of the NB algorithm is the independence of feature vectors. There are always several dependent vectors provided in the training set.

The equation (3-5) shows that all probabilities $P(x_j|s_i)$ should be independent of each other; otherwise, incorrect classification outcomes will the algorithm produce. It is crucial to establish a system that eliminates feature vector dependencies as much as feasible [87].

3.3 K-NEAREST NEIGHBOUR

KNN is a non-parametric classification method. Since 1970, KNN algorithms have been used in several applications, such as statistical estimation and pattern recognition. It is known that the

examination of learning and prediction is conducted depending on the provided issue or dataset. Predictions in the KNN method are based only on neighbor data values, with no assumptions made about the dataset. K denotes the number of nearest neighbour data values in KNN. The algorithm decision is made to classify the given dataset according to K [88].

The KNN model classifies the training dataset directly. It indicates that a new instance is predicted by seeking K neighbor examples in the complete training set and categorizing them based on the class of instances with the most significant frequency. Using the Euclidean distance formula, related instances are identified.

The square root of the sum of squared differences between the new instance (x_i) and the old instance (y_j) is the Euclidean distance [89].

$$Euclidean_{i,j} = \sqrt{\sum_{p=1}^m (x_{ip} - y_{jp})^2} \quad (3-6)$$

3.4 MULTI-LAYER PERCEPTRON

MLP is a form of neural network that uses the back-propagation approach for supervised learning. Figure 3.1 shows the structure of MLP consists of a three-layer layout: 1) input layer, 2) hidden layer(s), and 3) output layer(s). Each neuron is linked to all neurons in the following layer. MLP is widely stated to play an essential role in non-linear issues [90].

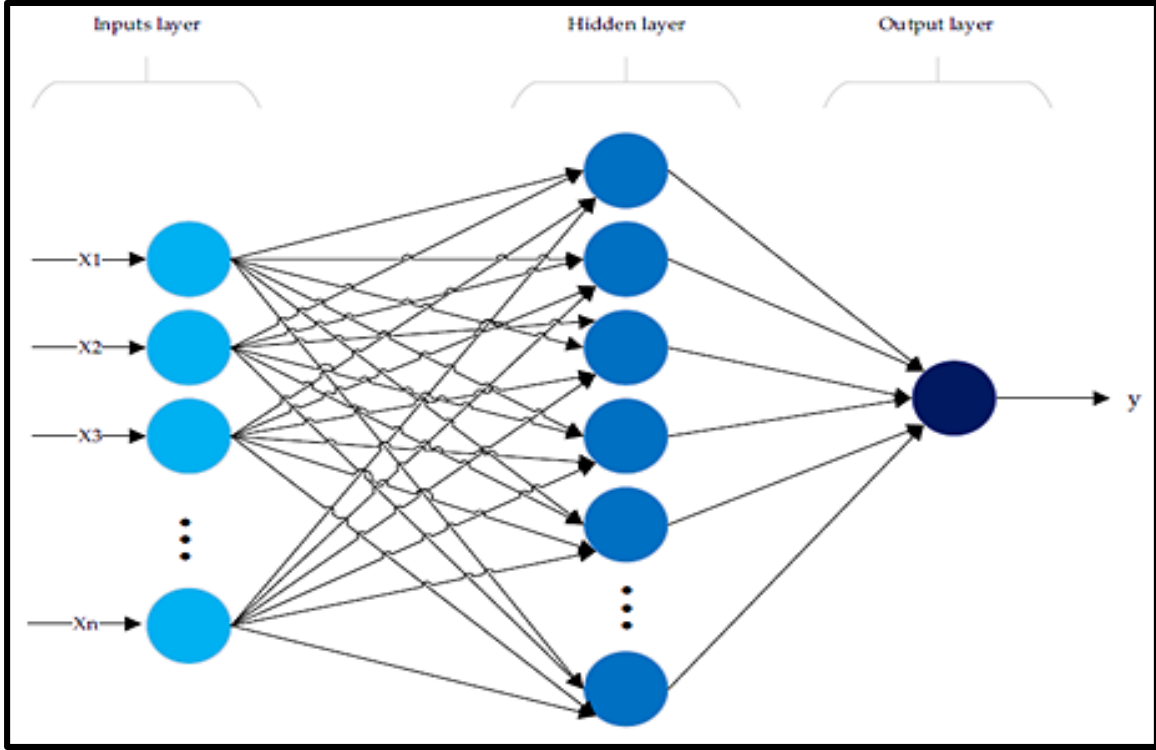


Figure 3.1: The Structure of MLP.

The input values, bias values, and the output of input variables are determined as follows:

$$S_i = \sum_{i=1}^m w_{ij} I_i + \beta_i \quad (3-7)$$

Table (3-1) list the representation of each symbol.

Table 3.1: The description of equation (3-7).

Symbol	Description
I	The input layer
I_i	the input variable i
m	the total number of inputs
w_{ij}	weight of connections in j level
S	the activation function

The sigmoid function is mainly used as the activation function in MLP and is written as follows:

$$f_i = \frac{1}{1+e^{-s_i}} \quad (3-8)$$

Therefore, equation (3-9) is used to measure the ultimate output neuron j :

$$y_i = f_i \sum_{i=1}^m w_{ij} I_i + \beta_i f_i \quad (3-9)$$

Where y_i is the output value of MLP. This must be compared to the goal values to calculate the model's performance. [91].

4. RESULTS AND DISCUSSION

4.1 INTRODUCTION

This chapter is dedicated to evaluating the performance of our models: NB, KNN, and MLP, on classifying AD patients for HC cases. We compare our findings with a counterpart to demonstrate the superiority of our models. To achieve our goal, we developed our experiments with Python, which is an interpreted, object-oriented, high-level programming language with dynamic semantics.

This chapter is structured as follows. Section 2 presents the modeling and the scenarios of our model. Section 3 evaluates and discusses the main findings of the proposed models. Section 4 provides a summary of this chapter.

4.2 MODELING AND SCENARIOS

4.2.1 Data Collection

Before delving into building our classifiers, we select the OASIS dataset for training and testing. For further information about OASIS, see chapter 2. We selected OASIS dataset because we verified our classifiers with the models published in [92], which were developed by the OASIS dataset. In the beginning, the dataset was divided into two parts for training and examination based on the theory of data division for the purpose of study, 70% for training and 30% for examination. Since the number of instances in OASIS is 373, the number of instances in training (testing) is 261 (112).

4.2.2 Naive Bayes

The first scenario was the application of the Naive Bayes algorithm on the training data to build a test model of the algorithm on the data. After preparing the model, the model is applied to the examination data to reach a test of accuracy and efficiency of the model test in identifying and diagnosing people with AD. Table (4-1) shows the main findings of the NB model.

Table 4.1: Main findings of NB model.

Item	Training	Testing
Correctly classified instances	238	100
Incorrectly classified instances	23	12
Total number of instances	261	112
Accuracy	91.18%	89.28%
Recall	0.912	0.893
F-measure	0.902	0.882
TPR	0.912	0.893
FPR	0.061	0.071

4.2.3 K-Nearest Neighbour

In the second scenario, we applied the KNN algorithm to study the model's effect in testing the data related to the detection of AD by reading the data, based on building an accuracy test model and applying the near-neighbor algorithm to the training and examination data. Table (4-2) lists the main findings of the KNN model.

Table 4.2: Main findings of the KNN model.

Item	Training	Testing
Correctly classified instances	219	92
Incorrectly classified instances	42	20
Total number of instances	261	112
Accuracy	83.91%	82.14%
Recall	0.839	0.821
F-measure	0.832	0.815
TPR	0.839	0.821
FPR	0.147	0.132

4.2.4 Multi-Layer Perceptron

In the third scenario, we applied the neural network algorithm that works in the form of multiple layers to build a case study model. In this scenario, the algorithm was applied to build an AD test model on a data set divided into training and examination. The test model was built through the training set and then applied to the examination group to study the results that indicate the efficiency and accuracy of sample selection by applying the algorithm in detecting AD.

Table 4.3: Main findings of MLP model.

Item	Training	Testing
Correctly classified instances	245	102
Incorrectly classified instances	16	10
Total number of instances	261	112
Accuracy	93.87%	91.07%
Recall	0.939	0.911
F-measure	0.928	0.898
TPR	0.939	0.911
FPR	0.053	0.064

4.3 PERFORMANCE EVALUATION

Based on the achieved results in pervious sub-sections, we compare them to show the best model among the models: NB, KNN, and MLP.

4.3.1 Accuracy

Table 4-4 and Figure 4-1 illustrate the accuracy of detection of the models is promising in both training and testing. However, the MLP model achieved the best results, which reached 93.87% (91.07%) in the training (testing) phase.

Table 4.4: Comparison of the achieved accuracy of the algorithms.

Model	Training	Testing
MLP	93.87%	91.07%
KNN	83.91%	82.14%
NB	91.18%	89.28%

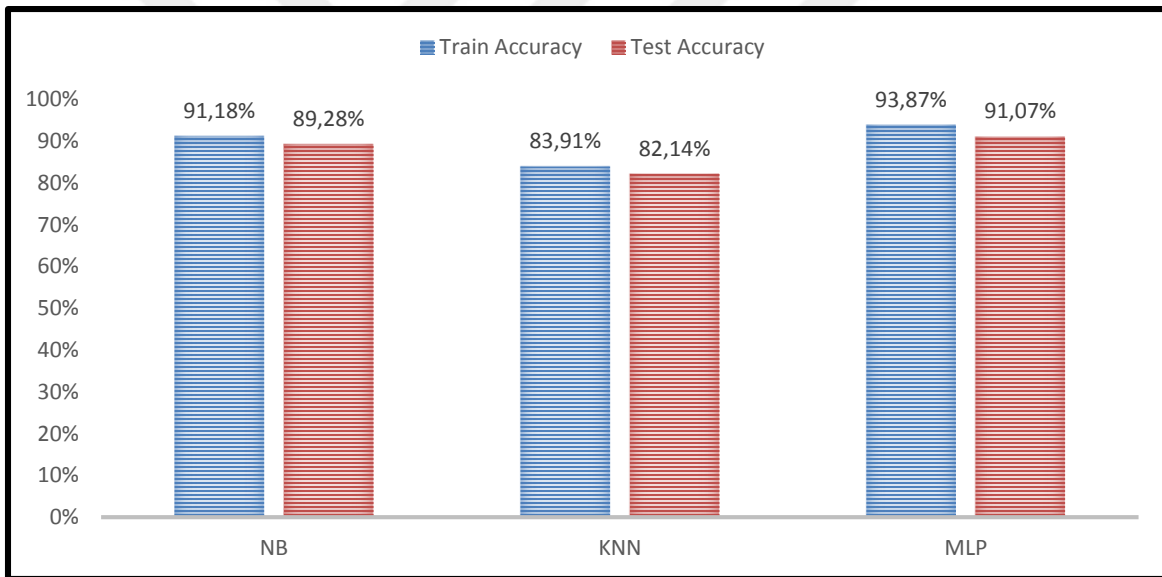


Figure 4.1: The detection accuracy of the models.

4.3.2 Recall and F-Measure

Similar to the above, we compared the models' findings for recall and F-measure to determine the best model. As illustrated in Table 4-5 and Figure 4-2, again, MLP achieved the best results where the recall and F-measure reached 0.939 and 0.928 (0.911 and 0.898) in the training (testing) phase.

Table 4.5: Comparison of the achieved Recall and F-measure of the algorithms.

Model	Training		Testing	
	Recall	F-measure	Recall	F-measure
MLP	0.939	0.928	0.911	0.898
KNN	0.839	0.832	0.821	0.815
NB	0.912	0.902	0.893	0.882

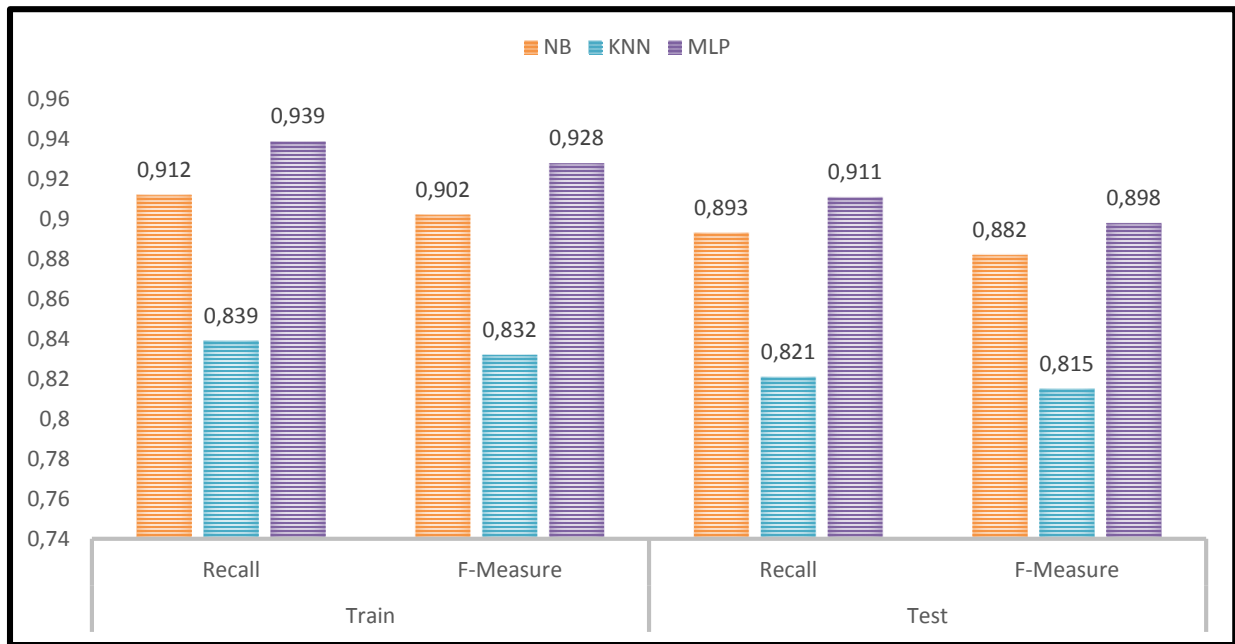


Figure 4.2: Achieved Recall and F-Measure of the models.

4.3.3 True Positive Rate and False Positive Rate

Table 4-6 and Figure 4-3 illustrate the TPR and FPR of the models are promising in both training and testing. Specifically, the MLP model achieved the best results among the models, which reached 0.939 and 0.053 (0.911 and 0.064) in the training (testing) phase.

Table 4.6: TPR and FPR of the algorithms.

Model	Training		Testing	
	Recall	F-measure	Recall	F-measure
MLP	0.939	0.053	0.911	0.064
KNN	0.839	0.147	0.821	0.132
NB	0.912	0.061	0.893	0.071

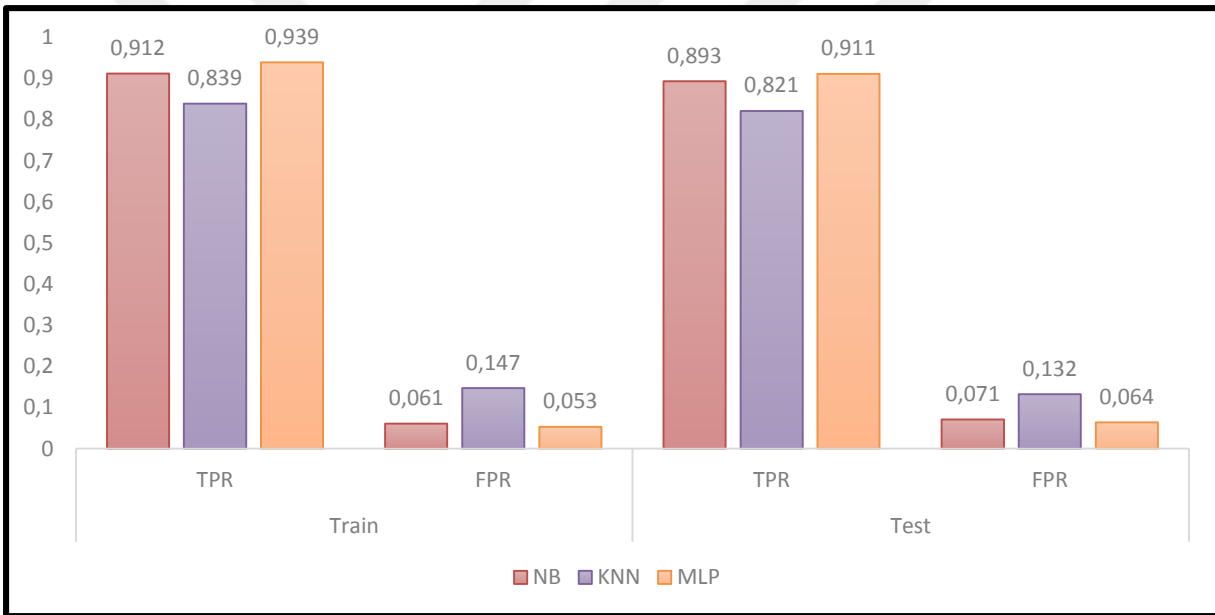


Figure 4.3: TPR and FPR of the models.

4.4 VERIFICATION

To verify our models, in this subsection, we compare the achieved accuracy of our models with counterparts. The comparisons were made with the models of [92]: Logistic Regression, SVM, Decision Tree, Random Forest, and AdaBoost. The author utilized the OASIS dataset for training the models to identify patients with AD or not. This is why we trained and tested our models via the OASIS dataset. Table 4-6 shows the achieved accuracy and Recall of the models. It is clear

Random Forest and AdaBoost models showed the best outcomes in terms of accuracy (84.21%). However, Random Forest model achieved better Recall (0.800).

Table 4.7: The achieved accuracy of the models in [92].

Model	Accuracy	Recall
Random Forest	84.21%	0.809
AdaBoost	84.21%	0.659
SVM	81.57%	0.700
Decision Tree	81.57%	0.650
Logistic Regression	78.94%	0.750

Accordingly, we compared the outcomes of Random Forest and AdaBoost in [92] with the present study's best model (MLP). Table 4-7 and Figures 4-4 demonstrate the superiority of MLP over the best models of [92] in terms of accuracy and recall.

Table 4.8: Comparison of our study's best model and the best two models in [92].

Model	Accuracy	Recall
MLP (present study)	91.07%	0.911
Random Forest	84.21%	0.809
AdaBoost	84.21%	0.659

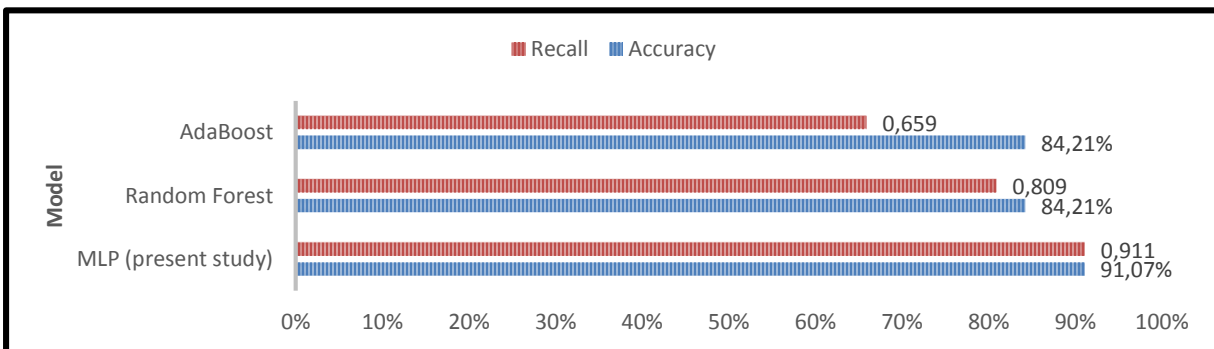


Figure 4.4: Comparison between our study's best model and the two best models in [92].

4.5 SUMMARY

In this chapter, we developed the models of the research: MLP, KNN, and NB. The models have been trained and tested using the OASIS dataset. The evaluations were conducted regarding the accuracy, recall, F-measure, TPR, and FPR. The comparisons revealed that MLP achieved the best outcomes. Furthermore, we verified with the counterpart's models. The verification demonstrated that MLP (of this study) outperformed its counterpart's models.



5. CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

Alzheimer's disease is one of the most notable neurodegenerative diseases that cause mortality worldwide. Globally, the number of AD patients is growing dramatically. The neurologist's manual technique for diagnosing AD is time-consuming and may not always provide reliable findings. The categorization of AD using brain imaging has shown promising, less time-consuming results. Numerous researchers have attempted to create a classification system based on brain images with fewer research problems. Nevertheless, the structure of the human brain is very complicated, and it holds a vast amount of information. Scalability is one of the most significant obstacles in extracting characteristics from brain imaging.

This has two main contributions: a) Conduct the state-of-the-art of AD, and b) Develop three models for classifying AD cases using ML algorithms.

In the first part, we presented background about AD history, brain imaging techniques for AD, and AD classification methods. Then, ML approaches in health diseases were introduced. According to the literature, for AD classification, ADNI and OASIS are the most used publicly available online data sources. Therefore, we searched how many these two datasets have been utilized during 2020-2022 on three highly ranked scientific databases: IEEE, Science Direct, and Springer. Next, we studied the main substantial risk (protective) factors influencing AD's deterioration (improvement). Lastly, we analyzed in depth 20 articles published recently.

We developed our study models in the second part: MLP, KNN and NB. The models have been trained and tested using the OASIS dataset. The evaluations were conducted regarding the accuracy, recall, F-measure, TPR, and FPR. The comparisons revealed that MLP achieved the best outcomes. Furthermore, we verified with the counterpart's models. The verification demonstrated that MLP (of this study) outperformed its counterpart's models.

5.2 RECOMMENDATION

Before completing this thesis, we recommend the following:

- a. Develop more powerful models that can achieve better results.
- b. Improve our study by taking both OASIS and ADNI datasets in training and testing the models.
- c. Use feature selection methods to improve the performance of the models.
- d. Use more than one model to achieve better results.



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