



Article Discrimination of the Cognitive Function of Community Subjects Using the Arterial Pulse Spectrum and Machine-Learning Analysis

Hsin Hsiu ^{1,2,*}, Shun-Ku Lin ^{3,4,5}, Wan-Ling Weng ¹, Chaw-Mew Hung ⁶, Che-Kai Chang ¹, Chia-Chien Lee ¹ and Chao-Tsung Chen ^{4,5,7}

- ¹ Graduate Institute of Biomedical Engineering, National Taiwan University of Science and Technology, Taipei 106, Taiwan; a0931355907@gmail.com (W.-L.W.); f68528@gmail.com (C.-K.C.); b0926184483@gmail.com (C.-C.L.)
- ² Biomedical Engineering Research Center, National Defense Medical Center, Taipei 114, Taiwan
- ³ Institute of Public Health, National Yang Ming Chiao Tung University, Taipei 112, Taiwan; gigilaskl@gmail.com
- ⁴ Department of Chinese Medicine, Taipei City Hospital, Renai Branch, Taipei 106, Taiwan; DAI44@tpech.gov.tw
- ⁵ General Education Center, University of Taipei, Taipei 100, Taiwan
- ⁶ Department of Healthcare, Taipei Veterans Home, New Taipei City 110, Taiwan; ivlwh1128@gmail.com
- ⁷ Institute of Traditional Medicine, National Yang Ming Chiao Tung University, Taipei 112, Taiwan
 - Correspondence: hhsiu@mail.ntust.edu.tw; Tel.: +886-22730-3730

check for updates Citation: Hsiu, H.; Lin, S.-K.; Weng, W.-L.; Hung, C.-M.; Chang, C.-K.; Lee, C.-C.; Chen, C.-T. Discrimination of the Cognitive Function of Community Subjects Using the Arterial Pulse Spectrum and Machine-Learning Analysis. *Sensors* 2022, 22, 806. https://doi.org/ 10.3390/s22030806

Academic Editors: Javad Rezazadeh, Omid Ameri Sianaki and Reza Farahbakhsh

Received: 5 December 2021 Accepted: 14 January 2022 Published: 21 January 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). **Abstract:** Early identification of cognitive impairment would allow affected patients to receive care at earlier stage. Changes in the arterial stiffness have been identified as a prominent pathological feature of dementia. This study aimed to verify if applying machine-learning analysis to spectral indices of the arterial pulse waveform can be used to discriminate different cognitive conditions of community subjects. 3-min Radial arterial blood pressure waveform (BPW) signals were measured noninvasively in 123 subjects. Eight machine-learning algorithms were used to evaluate the following 4 pulse indices for 10 harmonics (total 40 BPW spectral indices): amplitude proportion and its coefficient of variation; phase angle and its standard deviation. Significant differences were noted in the spectral pulse indices between Alzheimer's-disease patients and control subjects. Using them as training data (AUC = 70.32% by threefold cross-validation), a significant correlation ($R^2 = 0.36$) was found between the prediction probability of the test data (comprising community subjects at two sites) and the Mini-Mental-State-Examination score. This finding illustrates possible physiological connection between arterial pulse transmission and cognitive function. The present findings from pulse-wave and machine-learning analyses may be useful for discriminating cognitive condition, and hence in the development of a user-friendly, noninvasive, and rapid method for the early screening of dementia.

Keywords: dementia; pulse; spectral analysis; machine learning; community subjects; Mini-Mental State Examination

1. Introduction

Dementia encompasses neurodegenerative disorders that are characterized by the progressive loss of cognitive function and the ability to perform activities of daily living [1]. It gradually becomes a burdensome disease not only for affected individuals but also their families [2].

The standard diagnostic assessment of dementia includes history-taking, clinical examinations (e.g., neurological, mental state, and cognitive examinations), and an interview with a relative other than the informant. Recent guidelines also recommend computed tomography or magnetic resonance imaging of the brain to exclude structural causes for the clinical phenotype [1,2]. It has been reported that anywhere from 29% to 76% of patients with dementia or probable dementia are not diagnosed by primary-care clinicians [2]. Early identification of cognitive impairment through screening would allow patients and their families to receive care at an earlier stage in the disease process, potentially allowing discussions regarding health, financial, and legal decision-making while the patient is still legally capable [2].

Screening is designed to identify unrecognized or asymptomatic disease by administering tests that can be applied rapidly without the primary intention of being diagnostic [1–3]. Recent UK health policy has encouraged the opportunistic testing of older people attending primary care [1]. Screening of people with suspected dementia usually involves a brief test of cognitive function, informant questionnaires, or both, with a low score indicating a need for more in-depth assessments [1]. It has also been suggest that structural neuroimaging, genetic testing, and brief structured assessments (mainly using various questionnaires) can be used in dementia screening [2].

Alterations of the cerebral macrovasculature and microvasculature have been found in association with dementia [4]. These vascular changes can reduce cerebral perfusion and impair the ability to supply energy substrates and oxygen to active brain regions, and thus play a role in neuronal dysfunction and damage [5]. The induced atherosclerosis takes place not only in intracranial vessels but also in extracranial arteries such as the carotid, femoral, and coronary arteries [5,6].

Machine-learning techniques are already widely used to analyze various kinds of biological signals. The arterial pulse waveform transmits along the artery, and its characteristics are determined by the interaction between the pumping of blood by the heart and the arterial tree; it can therefore provide information about arterial wall stiffness [7–9]. Changes in the pulse waveform can be detected by noninvasive measurements, and various analysis methods (e.g., pulse-wave-velocity analysis [7] and frequency-domain analysis [10,11]) have been applied to the pulse waveform to evaluate changes induced by aging and various diseases [12–19]. Changes in the pulse waveform are often complex, and machine-learning analysis has the advantage of being able to capture subtle changes induced by physiological and pathological factors [20]. For example, arterial pulse-wave measurements, frequency-domain pulse analysis, and machine-learning analysis were used to distinguish vascular aging [10]. Another study applying similar methods demonstrated that using multilayer-perceptron analysis with frequency-domain pulse indices as features is highly effective at distinguishing between Alzheimer's-disease (AD) patients and control subjects, with an accuracy of >80% and a particularly high specificity of >90% [11].

Based on our previous findings [11], the present study included community-dwelling subjects from two community sites. The Mini Mental State Examination (MMSE) score was used to define the cognitive condition of the subjects, and the aim was to verify if applying machine-learning analysis to spectral indices of the pulse waveform can discriminate between different cognitive conditions. In the machine-learning analysis, threefold cross-validation was performed to evaluate the training of the models. We also attempted to identify a relationship between the MMSE score and the prediction probability from the testing results of the machine-learning model. The present findings on the induced changes in the vascular properties and the pulse waveform indices may be useful for developing a method to aid the early screening of dementia.

2. Materials and Methods

Details of the present experimental setup and the signal processing methods are available elsewhere [10,11,15]. BPW signal was noninvasively measured in the subjects (typical waveforms were shown in Figure 1; analysis procedure was shown in Figure 2). Frequency-domain analysis was applied to derive the 40 harmonic indices from the measured BPW signal (n = 1-10): amplitude proportion (C_n), coefficient of variation of C_n (CV_n), phase angle (P_n), and standard deviation of P_n (P_n_SD) (details of measurement and analysis are listed in Supplemental Materials). The present study used the MMSE

and machine-learning analysis (eight models; models details see Table 1) to investigate whether measured pulse indices are related to the cognitive condition in a sample of 38 AD patients, 38 control subjects, 39 community subjects, and 8 young subjects (see Table 2). The eight machine-learning methods used in the present study included support vector machine (SVM), multilayer perception (MLP), Gaussian Naive Bayes (GNB), decision tree (DT), random forest (RF), logistic regression (LR), linear discriminant analysis (LDA), and K-nearest neighbor classification (KNN). When performing the threefold cross validation of the training stage, we first randomly assigned the subjects into three subgroups, and then the pulse sequence of the subjects within each subgroup were used to train the model. When performing the testing stage, the data sequence of the pulse indices of the subject was input into the trained model to get the classification probability.



Figure 1. Typical measured pulse waveforms. (**a**) AD patient; (**b**) Control; (**c**) Community Site 1; (**d**) Community Site 2; (**e**) Young.

The subjects were recruited from the Ren-Ai Branch of Taipei City Hospital. Informed consent was obtained from the study participants or their legal designates (approved by the Review Board of Taipei City Hospital; approval no. TCHIRB-10810016-E). A neurologist or psychiatrist diagnosed AD, and evaluated the severity of disability in patients with dementia [11]. Community subjects were recruited at two sites: Site A was Taipei Veterans Home, located in the countryside of New Taipei City, and Site B was Hoping LOHAS Daycare Center, located near the educational area of Taipei (near to National Taiwan University and National Taiwan Normal University). Eight graduate students of National Taiwan University of Science and Technology were also recruited as the young group.

The study was approved by the Research Ethics Committee, National Taiwan University (approval no. 202010EM001). Based on MMSE scores, the subjects were categorized into mild dementia (MMSE scores > 16 and \leq 24), moderate dementia (MMSE scores > 10 and \leq 16), and severe dementia (MMSE scores \leq 10). Subjects were excluded if they did not agree to participate in the study or were unable to cooperate with the research steps, such as due to their limbs trembling involuntarily, restlessness, or agitated movements.





Table 1. Parameters of the machine-learning models.

Machine-Learning Methods	Model Parameters
SVM (support vector machine)	C = 1; kernel: rbf; gamma: auto; tol = 0.0001; max_iter = -1; class_weight: none
MLP (multilayer perception)	hidden_layer_sizes = 100; solver: adam; alpha = 0.0001; batch_size: auto; max_iter = 200; learning_rate_int = 0.001
GNB (Gaussian Naive Bayes)	Priors: none
DT (decision tree)	Criterion: gini; Splitter: best; max_depth: none; min_samples_split = 2; min_samples_leaf = 1; min_weight_fraction_leaf = 0; max_features: none; max_leaf_nodes: none; min_impurity_split = 0.0
RF (random forest)	<pre>n_estimators = 100; criterion: gini; max_depth: none; min_samples_split = 2; min_samples_leaf = 1; min_weight_fraction_leaf = 0; max_features: none; max_leaf_nodes: none</pre>
LR (logistic regression)	Penalty: l2; Solver: lbfgs; multi_class: auto; class_weight: none
LDA (linear discriminant analysis)	Solver: svd; Shrinkage: none; Priors: none
KNN (K-nearest neighbor classification)	n_neighbors = 5; weights: uniform; algorithm: auto; n_jobs: none; p: none

			AD p	oatients				
	Mild d 16 < MN	ementia MSE < 24	Moderat 10 < MI	e dementia MSE ≤ 16	Heavy d MMSE	ementia $E \le 10$		
gender	male	female	male	female	male	female		
Subject number	4	6	5	7	6	10		
subject number (male + female)	1	10		12	16			
Total subject number				38				
Age	71.33 ± 6.5	73.86 ± 7.86	67 ± 19	77.42 ± 11.51	74.33 ± 9.29	77.4 ± 7.02		
Age(male + female)	73.1	± 7.21	73.08	± 15.27	76.25	± 7.79		
Age (all)			74.42	\pm 10.44				
HR	68 ± 11.53	70.14 ± 11.86	67 ± 3.53	67.85 ± 16.24	66.4 ± 13.92	67.6 ± 9.64		
HR (male + female)	69.5 ±	± 11.57	67.5	± 12.19	68.87 -	± 11.1		
HR (all)			68.8	± 11.18				
		Com	munity Site A (Taipei Veterans H	ome)			
	MMS	E > 24	Mild c 16 < M	lementia MSE < 24	Moderate 10 < MM	dementia $SE \le 16$		
gender	male	female	male	female	male	female		
Subject number	8	0	7	0	5	0		
subject number (male + female)		8		7	5			
Total subject number				20				
Age	81.09 ± 10.31		$83.43{\pm}9.02$		77.08 ± 5.36	0		
Age(male + female)	$81 \pm$	10.31	83=	± 9.02	86.4 ±	- 7.92		
Age (all)			83.05	5 ± 9.10				
HR	67.25 ± 15.26		68.29 ± 4.72		62.20 ± 5.22			
HR (male + female)	67.25	± 15.26	68.29	0 ± 4.72	62.20 ± 5.22			
HR (all)								
		Communi	ity Site B (Hopin	ng LOHAS Dayca	re Center)			
	MMS	E > 24	Mild c 16 < Mi	lementia MSE \leq 24	Moderate dementia $10 < MMSE \le 16$			
gender	male	female	male	female	male	female		
Subject number	2	8	1	6	2	0		
subject number (male + female)	1	10		7	2			
Total subject number				19				
Age	71.53 ± 0.71	$75.64{\pm}~6.97$	76.23	81.26 ± 4.51	84.46 ± 6.36			
Age(male + female)	74.3	± 6.33	80.71	l±4.61	84.46 =	± 6.36		
Age (all)			78.25	$5\pm\overline{6.88}$				
HR	79.50 ± 12.02	68.38 ± 6.86	61.00	67.00 ± 8.00	65.50 ± 6.36			
HR (male + female)	70.6	70.6 ± 8.64 66.14 ± 7.65 65.5						
HR (all)			68.42	2 ± 8.04				

Table 2. Characteristics of subjects.

	Cor	itrol	Young				
gender	male	female	male	female			
Subject number	11	27	7	1			
Total subject number	3	8	8				
Age	74.24 ± 3.26	72.08 ± 4.94	23.85 ± 1.46	23			
Age (all)	72.71	± 4.58	$23.75 \pm$	1.38			
HR	78.09 ± 9.11	79.88 ± 7.27	66.00 ± 5.94	64.00			
HR (all)	79.36	± 7.76	$65.75 \pm$	5.54			

Table 2. Cont.

3. Results

The characteristics of the study subjects are listed in Table 2. Figure 3 compares the harmonic indices of the BPW signals (p values are listed in Table 3). For the amplitude ratios, C_4 – C_{10} were larger in the AD patients than the control subjects (significantly for C_5 – C_{10}). All C_n indices were larger in Site-A subjects than in Site-B subjects (significantly for C_8 and C_{10}). For phase-angle indices of BPW signals, Group AD had the largest values of all CV_n indices and P_2 – P_9 (compared with Control; p < 0.05 for P_8 and P_9 , $0.05 for <math>P_5$ and P_6).



Figure 3. Comparisons of BPW harmonic indices of AD patients, control, community (Sites A and B), and young subjects: (a) C_n , (b) CV_n , (c) P_n , and (d) P_n_SD . Data are mean and standard-deviation values. C_6-C_{10} values have been multiplied by 10 to make the differences clearer. *p* values are listed in Table 3.

	<u>C1</u>		C2				<u>C3</u>					C4					C5												
\searrow	AD	Control	Site A	Site B	Young	\searrow	AD	Control	Site A	Site B	Young	\searrow	AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young	/	AD	Control	Site A	Site B	Young
AD	/	0.634	< 0.001	0.031	0.017	AD	/	0.175	< 0.001	0.025	0.516	AD	/	0.984	0.025	0.063	< 0.001	AD	/	0.254	0.296	0.849	0.002	AD	/	0.017	0.765	0.160	0.649
Control	\langle		< 0.001	< 0.001	< 0.001	Control	\backslash		< 0.001	< 0.001	0.921	Control			0.012	0.041	< 0.001	Control	\backslash		0.015	0.303	< 0.001	Control		$\overline{}$	0.021	0.755	0.034
Site A	$\overline{}$			0.151	< 0.001	Site A		\sim		0.276	0.014	Site A	$\overline{\ }$			0.492	0.044	Site A	$\overline{\ }$	\sim		0.216	0.043	Site A	$\overline{\ }$	$ \frown $		0.151	0.841
Site B					<0.001	Site B		\sim			0.052	Site B					<0.001	Site B					<0.001	Site B		\sim	\sim		0.133
V.					-0.001	V.		\sim			0.002	V.			$\overline{}$		-0.001	V.					.0.001	V.		\sim			S55
Toung						roung						roung						Toung						Toung					
	4.0	C	V1	Ster D	v		4.0	C	V2	C'to D	V		4.0	C C	V3	Ster D	v		4.0	C	V4	Ste D	¥		4.0	<u>c</u>	V5	C't. D	¥
	AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young
AD	\langle	<0.001	0.061	0.023	0.104	AD		<0.001	0.131	0.017	0.237	AD	$\langle \rangle$	<0.001	0.170	0.002	0.027	AD	$\langle \rangle$	<0.001	0.100	0.003	0.013	AD	$\langle \rangle$	<0.001	0.291	0.011	0.140
Control		\langle	0.097	0.569	0.887	Control	/	$\overline{\ }$	0.008	0.336	0.082	Control	/	\langle	0.001	0.960	0.806	Control	/	/	0.056	0.862	0.602	Control	/	\sim	0.038	0.621	0.883
Site A		\sim		0.408	0.363	Site A		\sim	\sim	0.204	0.791	Site A		\sim		0.013	0.039	Site A				0.078	0.035	Site A		\sim	\sim	0.032	0.206
Site B	$^{\prime}$	/	/	/	0.801	Site B	/		Ϊ	/	0.413	Site B	/	/		/	0.847	Site B	/	Ϊ	/	/	0.392	Site B	/		$\overline{)}$	Ϊ	0.591
Young		\sim		\sim		Young		\sim	\sim			Young		\sim	$\langle \rangle$	\sim		Young		\sim		\sim		Young		\sim	\sim	\sim	
									,						~			_			4								
	AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young		AD	Control	Site A	Site B	Young
AD		0.035	0.241	0.222	0.255	AD		0.126	0.073	0.444	<0.001	AD		0.185	0.015	0.266	<0.001	AD		0.138	0.004	0.012	0.722	AD		0.064	0.023	0.160	0.682
AD C. M. J		0.035	0.000	0.005	0.200	~~~		0.1.20	0.261	0.642	-0.001	~~~		0.105	0.000	0.200	-0.001	а <i>р</i> С. т. 1			0.001	0.012	0.722	an a		0.001	0.025	0.010	0.112
Control		>	0.006	0.005	0.029	Control	\rightarrow	>	0.351	0.643	<0.001	Control		>	0.080	0.946	< 0.001	Control			0.040	0.130	0.610	Control		$ \rightarrow $	0.244	0.918	0.112
Site A	\langle	\geq	\langle	0.980	0.792	Site A	\langle	\geq	\geq	0.308	<0.001	Site A	\backslash	\geq		0.159	<0.001	Site A	$\langle \rangle$	\sum	\backslash	0.603	0.123	Site A	\backslash	\geq	$ \geq $	0.298	0.073
Site B			/	/	0.725	Site B	/		\langle	/	<0.001	Site B	/	\langle		/	< 0.001	Site B	/	/	/		0.135	Site B	/			/	0.053
Young	\sim	\frown			\sim	Young		\frown	\sim		\sim	Young		\sim			\sim	Young				\frown	\sim	Young		\sim	\sim		
		P1	SD					P2	SD					P3	SD					P4	SD					P5	SD		
$^{\prime}$	AD	Control	Site A	Site B	Young	Ζ	AD	Control	Site A	Site B	Young	/	AD	Control	Site A	Site B	Young	Ϊ	AD	Control	Site A	Site B	Young	/	AD	Control	Site A	Site B	Young
AD		0.012	0.422	0.148	0.182	AD	/	0.001	0.659	0.009	0.010	AD	/	0.002	0.323	0.020	0.035	AD	/	< 0.001	0.493	0.006	0.002	AD	/	0.001	0.547	0.020	0.003
Control	$\overline{}$		0.005	0.629	0.225	Control			0.011	0.896	0.313	Control	$\overline{\ }$		0.024	0.795	0.217	Control	$\overline{\ }$		0.005	0.987	0.059	Control	$\overline{\ }$		0.019	0.891	0.105
Site A				0.059	0.004	Site A		\sim		0.011	0.002	Site A				0.012	0.001	Site A				0.017	< 0.001	Site A		\sim		0.046	< 0.001
C'to D				<u> </u>	0.124	C'to D				<hr/>	0.269	C'to D			$\overline{}$	<hr/>	0.165	6% P				<hr/>	0.052	C'to D		\sim		<u> </u>	0.062
Site B	$\langle \rangle$	\sim	\rightarrow	\rightarrow	0.134	Site B		>	$\langle \rangle$		0.208	Site B		\sim		\rightarrow	0.105	Site B		$\langle \rangle$		\rightarrow	0.033	Site B		$ \rightarrow $	$ \rightarrow $	$\langle \rangle$	0.002
Young					$ \geq $	Young		\geq	\geq		\geq	Young				\geq	\geq	Young		\geq		\geq	$ \geq $	Young			$ \geq $	$ \geq $	
		c	6						.7						8					c	9					с	10		
	AD	C Control	6 Site A	Site B	Young		AD	C Control	7 Site A	Site B	Young		AD	Control	8 Site A	Site B	Young		AD	C Control	9 Site A	Site B	Young		AD	C Control	10 Site A	Site B	Young
AD	AD	Control 0.009	56 Site A 0.610	Site B 0.249	Young 0.931	AD	AD	Control 0.018	27 Site A 0.213	Site B 0.250	Young	AD	AD	Control 0.006	8 Site A 0.991	Site B 0.022	Young	AD	AD	Control 0.002	9 Site A 0.636	Site B 0.028	Young 0.117	AD	AD	C Control <0.001	10 Site A 0.845	Site B 0.002	Young 0.123
AD	AD	Control 0.009	56 Site A 0.610	Site B 0.249	Young 0.931	AD	AD	Control 0.018	7 Site A 0.213	Site B 0.250 0.438	Young 0.864	AD	AD	Control 0.006	8 Site A 0.991	Site B 0.022	Young 0.136	AD	AD	Control	9 Site A 0.636	Site B 0.028	Young 0.117 0.910	AD	AD	C Control <0.001	10 Site A 0.845	Site B 0.002	Young 0.123
AD Control	AD	Control 0.009	6 Site A 0.610 0.005	Site B 0.249 0.307	Young 0.931 0.071	AD Control		Control 0.018	7 Site A 0.213 0.001	Site B 0.250 0.438	Young 0.864 0.046	AD Control	AD	Control 0.006	8 Site A 0.991 0.027	Site B 0.022 0.680	Young 0.136 0.868	AD Control	AD	Control	9 Site A 0.636 0.069	Site B 0.028 0.962	Young 0.117 0.910	AD Control	AD	Control <0.001	10 Site A 0.845 0.009	Site B 0.002 0.658	Young 0.123 0.534
AD Control Site A	AD A	Control 0.009	56 Site A 0.610 0.005	Site B 0.249 0.307 0.133	Young 0.931 0.071 0.661	AD Control Site A	AD V	Control 0.018	7 Site A 0.213 0.001	Site B 0.250 0.438 0.060	Young 0.864 0.046 0.517	AD Control Site A	AD V	Control 0.006	8 Site A 0.991 0.027	Site B 0.022 0.680 0.050	Young 0.136 0.868 0.195	AD Control Site A	AB	Control 0.002	9 Site A 0.636 0.069	Site B 0.028 0.962 0.172	Young 0.117 0.910 0.320	AD Control Site A	AD	Control <0.001	10 Site A 0.845 0.009	Site B 0.002 0.658 0.035	Young 0.123 0.534 0.315
AD Control Site A Site B		Control 0.009	6 Site A 0.610 0.005	Site B 0.249 0.307 0.133	Young 0.931 0.071 0.661 0.297	AD Control Site A Site B		Control 0.018	7 Site A 0.213 0.001	Site B 0.250 0.438 0.060	Young 0.864 0.046 0.517 0.146	AD Control Site A Site B		Control 0.006	8 Site A 0.991 0.027	Site B 0.022 0.680 0.050	Young 0.136 0.868 0.195 0.866	AD Control Site A Site B		Control 0.002	9 Site A 0.636 0.069	Site B 0.028 0.962 0.172	Young 0.117 0.910 0.320 0.926	AD Control Site A Site B		Control <0.001	10 Site A 0.845 0.009	Site B 0.002 0.658 0.035	Young 0.123 0.534 0.315 0.206
AD Control Site A Site B Young		Control 0.009	56 Site A 0.610 0.005	Site B 0.249 0.307 0.133	Young 0.931 0.071 0.661 0.297	AD Control Site A Site B Young		Control 0.018	7 Site A 0.213 0.001	Site B 0.250 0.438 0.060	Young 0.864 0.046 0.517 0.146	AD Control Site A Site B Young		Control 0.006	8 Site A 0.991 0.027	Site B 0.022 0.680 0.050	Young 0.136 0.868 0.195 0.866	AD Control Site A Site B Young		Control 0.002	9 Site A 0.636 0.069	Site B 0.028 0.962 0.172	Young 0.117 0.910 0.320 0.926	AD Control Site A Site B Young		C Control <0.001	10 Site A 0.845 0.009	Site B 0.002 0.658 0.035	Young 0.123 0.534 0.315 0.206
AD Control Site A Site B Young	AD	Control 0.009	6 Site A 0.610 0.005	Site B 0.249 0.307 0.133	Young 0.931 0.071 0.661 0.297	AD Control Site A Site B Young		Control 0.018	7 Site A 0.213 0.001	Site B 0.250 0.438 0.060	Young 0.864 0.046 0.517 0.146	AD Control Site A Site B Young	AD VVV	Control 0.006	8 Site A 0.991 0.027	Site B 0.022 0.680 0.050	Young 0.136 0.868 0.195 0.866	AD Control Site A Site B Young	₽ ////	Control 0.002	9 Site A 0.636 0.069	Site B 0.028 0.962 0.172	Young 0.117 0.910 0.320 0.926	AD Control Site A Site B Young	AD AD	C Control <0.001	10 Site A 0.845 0.009	Site B 0.002 0.658 0.035	Young 0.123 0.534 0.315 0.206
AD Control Site A Site B Young	AD AD	Control	6 Site A 0.610 0.005 V6 Site A	Site B 0.249 0.307 0.133 Site B	Young 0.931 0.071 0.661 0.297 Young	AD Control Site A Site B Young		Control 0.018 Control	7 Site A 0.213 0.001	Site B 0.250 0.438 0.060 Site B	Young 0.864 0.046 0.517 0.146 Young	AD Control Site A Site B Young		Control	8 Site A 0.991 0.027 V8 Site A	Site B 0.022 0.680 0.050 Site B	Young 0.136 0.868 0.195 0.866 Young	AD Control Site A Site B Young		Control 0.002 Control Control	9 Site A 0.636 0.069 V9 Site A	Site B 0.028 0.962 0.172 Site B	Young 0.117 0.910 0.320 0.926 Young	AD Control Site A Site B Young		Control <0.001	10 Site A 0.845 0.009	Site B 0.002 0.658 0.035 Site B	Young 0.123 0.534 0.315 0.206 Young
AD Control Site A Site B Young AD		Control 0.009 Control 0.006	6 Site A 0.610 0.005 V6 Site A 0.292	Site B 0.249 0.307 0.133 Site B 0.001	Young 0.931 0.071 0.661 0.297 Young 0.021	AD Control Site A Site B Young AD		Control 0.018 0.018 C Control <0.001	7 Site A 0.213 0.001 V7 Site A 0.182	Site B 0.250 0.438 0.060 Site B	Young 0.864 0.046 0.517 0.146 Young 0.002	AD Control Site A Site B Young AD		Control 0.006 0.007 0.007 0.007 0.001	8 Site A 0.991 0.027 V8 Site A 0.440	Site B 0.022 0.680 0.050 Site B 0.002	Young 0.136 0.868 0.195 0.866 Young 0.029	AD Control Site A Site B Young AD		C Control 0.002 C C Control <0.001	9 Site A 0.636 0.069 V9 Site A 0.157	Site B 0.028 0.962 0.172 Site B	Young 0.117 0.910 0.320 0.926 Young 0.013	AD Control Site A Site B Young AD		Control <0.001 <0.001 Control <0.001	10 Site A 0.845 0.009 V10 Site A 0.071	Site B 0.002 0.658 0.035 Site B 0.008	Young 0.123 0.534 0.315 0.206 Young 0.006
AD Control Site A Site B Young AD Control		Control 0.009 Control 0.006	6 Site A 0.610 0.005 V6 Site A 0.292 0.214	Site B 0.249 0.307 0.133 Site B 0.001 0.275	Young 0.931 0.071 0.661 0.297 Young 0.021 0.437	AD Control Site A Site B Young AD Control		Control 0.018 0.018 Control <0.001	7 Site A 0.213 0.001 V7 Site A 0.182 0.039	Site B 0.250 0.438 0.060 Site B <0.001 0.808	Young 0.864 0.046 0.517 0.146 Young 0.002 0.396	AD Control Site A Site B Young AD Control		Control 0.006 Control <0.001	8 Site A 0.991 0.027 V8 Site A 0.440 0.021	Site B 0.022 0.680 0.050 Site B 0.002 0.930	Young 0.136 0.868 0.195 0.866 Young 0.029 0.986	AD Control Site A Site B Young AD Control		Control 0.002 Control <0.001	9 Site A 0.636 0.069 V9 Site A 0.157 0.030	Site B 0.028 0.962 0.172 Site B <0.001 0.528	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705	AD Control Site A Site B Young AD Control		Control <0.001 Control <0.001	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.008 0.518	Young 0.123 0.534 0.315 0.206 Young 0.006 0.820
AD Control Site A Site B Young AD Control Site A		Control 0.009 Control 0.006	6 Site A 0.610 0.005 V6 Site A 0.292 0.214	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029	Young 0.931 0.071 0.661 0.297 Young 0.021 0.021 0.437 0.099	AD Control Site A Site B Young AD Control Site A		Control 0.018 Control Control <0.001	7 Site A 0.213 0.001 V7 Site A 0.182 0.039	Site B 0.250 0.438 0.060 Site B <0.001 0.808 0.059	Young 0.864 0.046 0.517 0.146 Young 0.002 0.396 0.042	AD Control Site A Site B Young AD Control Site A		Control 0.006 Control <0.001	8 Site A 0.991 0.027 V8 Site A 0.440 0.021	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046	Young 0.136 0.868 0.195 0.866 Young 0.029 0.986 0.163	AD Control Site A Site B Young AD Control Site A		Control 0.002 0.001 Control 0.001	9 Site A 0.636 0.069 V9 Site A 0.157 0.030	Site B 0.028 0.962 0.172 Site B <0.001 0.528 0.009	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705 0.049	AD Control Site A Site B Young AD Control Site A		Control <0.001 Control Control <0.001	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497	Young 0.123 0.534 0.206 Young 0.006 0.820 0.238
AD Control Site A Site B Young AD Control Site A Site B		Control 0.009 Control 0.006	6 Site A 0.610 0.005 V6 Site A 0.292 0.214	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971	AD Control Site A Site B Young AD Control Site A Site B		Control 0.018 Control <0.001	7 Site A 0.213 0.001 V7 Site A 0.182 0.039	Site B 0.250 0.438 0.060 Site B <0.001 0.808 0.059	Young 0.864 0.046 0.517 0.146 Voung 0.002 0.396 0.042 0.485	AD Control Site A Site B Young AD Control Site A Site B		Control 0.006 Control <0.001	8 Site A 0.991 0.027 V8 Site A 0.440 0.021	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046	Young 0.136 0.868 0.195 0.866 Young 0.029 0.986 0.163 0.956	AD Control Site A Site B Young AD Control Site A Site B			9 Site A 0.636 0.069 V9 Site A 0.157 0.030	Site B 0.028 0.962 0.172 Site B <0.001 0.528 0.009	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705 0.049 0.938	AD Control Site A Site B Young AD Control Site A Site B		Control <0.001 CV Control <0.001	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497	Young 0.123 0.534 0.315 0.206 Voung 0.006 0.820 0.238 0.455
AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.009 Control 0.006	6 Site A 0.610 0.005 V6 Site A 0.292 0.214	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029	Young 0.931 0.071 0.661 0.297 Young 0.021 0.437 0.099 0.971	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.018 Control	7 Site A 0.213 0.001 V7 Site A 0.182 0.039	Site B 0.250 0.438 0.060 Site B <0.001 0.808 0.059	Young 0.864 0.046 0.517 0.146 Voung 0.002 0.396 0.042 0.485	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.006 Control <0.001	8 Site A 0.991 0.027 V8 Site A 0.440 0.021	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046	Young 0.136 0.868 0.195 0.866 Voung 0.029 0.986 0.163 0.956	AD Control Site A Young AD Control Site A Site B Young			9 Site A 0.636 0.069 Site A 0.157 0.030	Site B 0.028 0.962 0.172 Site B <0.001 0.528 0.009	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705 0.049 0.938	AD Control Site A Site B Young AD Control Site A Site B Young		Control <0.001 Control <0.001 <0.001	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497	Young 0.123 0.534 0.315 0.206 Voung 0.006 0.820 0.238 0.455
AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.009 Control 0.006 Control 0.006	6 Site A 0.610 0.005 V6 Site A 0.292 0.214	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029	Young 0.931 0.071 0.661 0.297 Young 0.021 0.437 0.099 0.971	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.018 Control	7 Site A 0.213 0.001 V7 Site A 0.182 0.039	Site B 0.250 0.438 0.060 Site B <0.001 0.808 0.059	Young 0.864 0.046 0.517 0.146 Voung 0.002 0.396 0.042 0.485	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.006 Control	8 Site A 0.991 0.027 V8 Site A 0.440 0.021	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046	Young 0.136 0.868 0.195 0.866 Voung 0.029 0.986 0.163 0.956	AD Control Site A Site B Young AD Control Site A Site B Young			9 Site A 0.636 0.069 V9 Site A 0.157 0.030	Site B 0.028 0.962 0.172 Site B <0.001 0.528 0.009	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705 0.049 0.938	AD Control Site A Site B Young AD Control Site A Site B Young		Control <0.001 Control Control <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497	Young 0.123 0.534 0.315 0.206 Voung 0.006 0.820 0.238 0.455
AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.009 Control 0.006 F Control	6 Site A 0.610 0.005 V6 Site A 0.292 0.214	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.018 Control	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 V7 Site A	Site B 0.250 0.438 0.060 Site B <0.001 0.808 0.059 Site B	Young 0.864 0.046 0.517 0.146 Young 0.002 0.396 0.042 0.485	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.006 Control Control Control Control Control Control Control Control Control	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.163 0.956 Young	AD Control Site A Site B Young AD Control Site A Site B Young			9 Site A 0.636 0.069 V9 Site A 0.157 0.030	Site B 0.028 0.962 0.172 Site B -0.001 0.528 0.009	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705 0.049 0.938	AD Control Site A Site B Young AD Control Site A Site B Young		Control Control Control Control P Control	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.518 0.497 Site B	Young 0.123 0.534 0.315 0.206 Voung 0.006 0.820 0.238 0.455 Young
AD Control Site A Site B Young AD Control Site A Site B Young AD		Control 0.009 Control 0.006 F Control 0.006 0.006 Control 0.0006 Control 0.000	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.027	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236	Young 0.931 0.071 0.661 0.297 Young 0.021 0.437 0.099 0.971 Voung 0.247	AD Control Site A Young AD Control Site A Site B Young		Control 0.018 Control 0.001 Control 0.262	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.146	Site B 0.250 0.438 0.060 Site B 0.808 0.059 Site B 0.044	Young 0.864 0.046 0.517 0.146 Young 0.002 0.396 0.042 0.485 Young 0.867	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.006 Control Control Control Control 0.001 Control 0.001 Control 0.020 Control 0.020 Control	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A 0.218 8	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046 Site B	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.163 0.956 Voung 0.973	AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.002 Control 0.001 Control 0.001 Control 0.001 Control 0.002	9 Site A 0.636 0.069 Site A 0.157 0.030 9 Site A 0.344	Site B 0.028 0.962 0.172 Site B 0.001 0.528 0.009 Site B ≤0.001	Young 0.117 0.910 0.320 0.926 Young 0.013 0.705 0.049 0.938 Young 0.938	AD Control Site A Site B Young AD Control Site A Site B Young		Control <0.001 Control Control P Control 0.132	10 Site A 0.845 0.009 V10 Site A 0.071 0.162	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044	Young 0.123 0.534 0.315 0.206 Young 0.006 0.820 0.238 0.455 Young 0.603
AD Site A Site B Young AD Control Site A Site B Young		Control 0.009 Control 0.006 Control 0.006	6 Site A 0.610 0.005 Site A 0.292 0.214 6 Site A 0.027	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.236	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971 Voung 0.247	AD Site A Site B Young AD Control Site A Site B Young		Control 0.018 Control <0.001 Control 0.262	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.146	Site B 0.250 0.438 0.060 Site B 0.001 0.808 0.059 Site B 0.044	Voung 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.485 Voung 0.867	AD Site A Site B Young AD Control Site A Site B Young		Control 0.006 Control Control 0.001	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A 0.218 8	Site B 0.022 0.680 0.050 0.050 0.002 0.930 0.046 Site B 0.0017	Young 0.136 0.868 0.195 0.866 0.986 0.029 0.986 0.163 0.956 Voung 0.973	AD Site A Site B Young AD Site A Site B Young AD		Control 0.002 Control 0.002 Control 0.026 Control	9 Site A 0.636 0.069 Site A 0.157 0.030 9 Site A 0.344 0.344	Site B 0.028 0.962 0.172 Site B <0.001	Young 0.117 0.910 0.320 0.926 Voung 0.013 0.705 0.049 0.668 0.668	AD Site A Site B Young AD Site A Site B Young		Control <0.001 <0.001 <0.001 <0.001 <0.001 0.132	10 Sife A 0.845 0.009 V10 Sife A 0.071 0.162 10 Sife A 0.363	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044	Young 0.123 0.534 0.315 0.206 0.206 0.820 0.238 0.455 Young 0.603
AD Control Site A Site B Site B Site A AD Control AD		Control 0.009 Control 0.006 Control 0.006 Control 0.0090 Control 0.0090 Control 0.0090 Control 0.0090 Control 0.0090 Control C	6 Site A 0.610 0.005 Site A 0.292 0.214 6 Site A 0.027 0.269	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882	Young 0.931 0.071 0.661 0.297 0.021 0.437 0.099 0.971 Voung 0.2247 0.0247	AD Control Site A Site B Voung AD Control Site A Site B Voung AD		Control 0.018 Control 0.262	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.146 0.568	Site B 0.250 0.438 0.060 Site B <0.001	Voung 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.485 Voung 0.867 0.422	AD Site A Site B Young AD Control Site A Site B Young AD		Control 0.006 <0.001 <0.001 <0.001 Control 0.020	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A 0.218 0.573	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046 0.017 0.878	Young 0.136 0.868 0.195 0.866 0.986 0.029 0.986 0.163 0.956 Voung 0.956	AD Control Site A Site B Voung AD Site A Site B Young AD Control		Control 0.002 Control 0.002 Control 0.002 Control 0.026	9 Site A 0.636 0.069 V9 Site A 0.157 0.030 9 Site A 0.344 0.404	Site B 0.028 0.962 0.172 Site B <0.001	Young 0.117 0.910 0.320 0.926 Voung 0.013 0.705 0.049 0.938 Voung 0.668 0.139	AD Site A Site B Young AD Control Site A Site B Young		Control <0.001 <0.001 <0.001 <0.001 <0.001 P Control 0.132	10 Site A 0.845 0.009 V10 Site A 0.071 0.162 Site A 0.363 0.056	Site B 0.002 0.658 0.035 Site B 0.008 0.497 Site B 0.044 0.489	Young 0.123 0.534 0.206 Voung 0.006 0.820 0.455 Voung 0.603 0.695
AD Control Site A Site B Young AD Control Site A Control Site A		Control 0.009 Control 0.000 Econtrol	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.027 0.269	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971 Voung 0.247 0.026 0.021	AD Control Site A Site B AD Control Site A Site B Young AD Control Site A		Control 0.018 Control 0.001 Control 0.262	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.568	Site B 0.250 0.438 0.060 Site B <0.001	Young 0.864 0.046 0.517 0.146 0.002 0.002 0.396 0.042 0.485 0.867 0.822 0.241	AD Control Site A Site B AD Control Site A Site B Young AD Control Site A		Control 0.006 Control 0.001 E Control 0.020	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A 0.218 0.573	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046 Site B 0.017 0.878 0.500	Young 0.136 0.868 0.195 0.866 0.986 0.986 0.986 0.986 0.986 0.936 0.956 Voung 0.973 0.215 0.475	AD Control Site A AD Control Site A Site B Young AD Control Site A			9 Site A 0.636 0.069 V9 Site A 0.157 0.030 9 Site A 0.344 0.404	Site B 0.028 0.962 0.172 Site B 0.001 0.528 0.009 Site B 0.0097	Young 0.117 0.910 0.320 0.926 Voung 0.013 0.705 0.049 0.938 Voung 0.139 0.383	AD Control Site A AD Control Site A Site B Young AD Control Site A		Control Control Control Control Control 0.132	10 Site A 0.845 0.009 V10 Site A 0.071 0.162 Site A 0.363 0.056	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044 0.489 0.037	Young 0.123 0.534 0.206 Voung 0.006 0.238 0.455 Voung 0.603 0.695 0.369
AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B		Control 0.009 Control 0.006 Control 0.009 Co	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.027 0.269	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302	Young 0.931 0.071 0.661 0.297 Young 0.021 0.437 0.099 0.971 Voung 0.247 0.026 0.013 0.028	AD Control Site A Young AD Control Site A Site B Young AD Control Site A Site B		Control 0.018 Control 0.001	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.568	Site B 0.250 0.438 0.060 Site B 0.001 0.808 0.059 Site B 0.044 0.308 0.700	Young 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.485 Voung 0.864 0.867 0.482 0.241 0.043	AD Control Site A Site B AD Control Site A Site B Young AD Control Site A Site B		Control 0.000 Control 0.001 Control 0.020	Site A 0.991 0.027 0.027 Site A 0.440 0.021 Site A 0.218 0.218 0.573	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046 Site B 0.017 0.878 0.500	Young 0.136 0.868 0.195 0.866 0.986 0.986 0.986 0.986 0.996 0.986 0.957 Voung 0.973 0.215 0.475	AD Control Site A Site B Young AD Control Site A Site B Site A Site B			9 Site A 0.636 0.069 Site A 0.157 0.030 9 Site A 0.344 0.404	Site B 0.028 0.962 0.172 Site B <0.001	Young 0.117 0.910 0.320 0.926 0.013 0.013 0.705 0.049 0.938 0.668 0.139 0.383 0.002	AD Control Site A AD Control Site A Site B Young AD Control Site A Site B Site B		Control Control P Control P Control Co	10 Site A 0.845 0.009 V10 Site A 0.071 0.162 10 Site A 0.363 0.056	Site B 0.002 0.658 0.035 0.035 0.008 0.518 0.497 0.044 0.489 0.037	Young 0.123 0.534 0.315 0.206 0.206 0.238 0.455 Voung 0.603 0.695 0.359
AD Control Site A Site B Young AD Control Site A Site B Young Site A Site B Young		Control 0.009 Control 0.000 Control 0.000 Control 0.000 Control 0.000 Control 0.000 Control Co	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.027 0.269	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302	Young 0.931 0.071 0.661 0.297 0.021 0.437 0.099 0.9711 0.437 0.099 0.971 0.0247 0.026 0.013 0.028 0.028	AD Control Site A Site B Young AD Control Site A Site B Young Site A Site B Young		Control 0.018 Control	7 Site A 0.213 0.001 0.001 V7 Site A 0.182 0.039 7 Site A 0.146 0.568	Site B 0.250 0.438 0.060 Site B 0.001 0.808 0.059 Site B 0.044 0.308 0.700	Young 0.864 0.046 0.517 0.146 0.396 0.002 0.396 0.042 0.485 0.485 0.485 0.422 0.241 0.043	AD Control Site A Site B Young AD Control Site A Site B Young Site A Site B Young		Control Contro	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A 0.218 0.573	Site B 0.022 0.680 0.050 0.050 0.002 0.930 0.046 0.002 0.930 0.046 0.017 0.878 0.500	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.163 0.956 0.973 0.215 0.475 0.057	AD Control Site A Site B Young AD Control Site A Site B Young Site A Site B Young			9 Site A 0.636 0.069 Site A 0.157 0.030 9 Site A 0.344 0.404	Site B 0.028 0.962 0.172 Site B <0.001 0.528 0.009 Site B <0.001 0.386 0.097	Young 0.117 0.910 0.320 0.926 0.013 0.705 0.049 0.938 0.6668 0.139 0.383 0.002	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young		Control Control Control Control Control Control P P Control 0.132	10 Site A 0.845 0.009 V10 Site A 0.071 0.162 10 Site A 0.363 0.056	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044 0.489 0.037	Young 0.123 0.534 0.315 0.206 0.006 0.820 0.238 0.455 Voung 0.603 0.695 0.369 0.359
AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.009 Control 0.006 Control 0.006 FG Control 0.009 FG FG Control 0.009 FG	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 0.214 0.227 0.214 0.229 0.214 SD	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971 Voung 0.247 0.026 0.013 0.028	AD Control Site A Site B Young AD Control Site A Site B Young AD Control		Control 0.018 Control 0.001 0.001 Control 0.262 P7	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.146 0.568 SD	Site B 0.250 0.438 0.060 Site B <0.001 0.808 0.059 Site B 0.044 0.308 0.700	Young 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.485 Voung 0.867 0.422 0.241 0.043	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A		Control Control Control Rev P8	8 Site A 0.991 0.027 V8 Site A 0.218 0.218 0.218 0.573 SD	Site B 0.022 0.680 0.050 0.050 0.002 0.930 0.046 Site B 0.017 0.878 0.500	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.956 0.956 0.973 0.215 0.475 0.057	AD Control Site A Site B Voung AD Control Site A Site B Young AD Control Site A			9 Site A 0.636 0.069 V9 Site A 0.157 0.030 9 Site A 0.404 SD	Site B 0.028 0.962 0.172 Site B <0.001 0.528 0.0097 Site B <0.001 0.386 0.097	Young 0.117 0.910 0.320 0.926 Voung 0.013 0.705 0.049 0.938 0.668 0.139 0.383 0.002	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Site A Young AD Site A AD Site A Young AD Site A Young AD Site A Site A Site B Site A Site A		C Control Control Control Control 0.132 P10 P10	10 Site A 0.845 0.009 V10 Site A 0.071 0.162 10 Site A 0.363 0.056 SD	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044 0.037	Young 0.123 0.534 0.315 0.206 Voung 0.006 0.238 0.455 Voung 0.603 0.695 0.369 0.359
AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.009 Control 0.000 Control 0.000 F6 Control 0.009 P6 Control 0.009	6 Site A 0.610 0.005 V6 Site A 0.222 0.214 6 Site A 0.027 0.269 Site A 0.027 Site A Site A Sit	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302 Site B	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.9711 Voung 0.2247 0.026 0.013 0.028 Voung	AD Control Site A Site B Young AD Control Site A Site B Young Control Site A		Control 0.018 Control 0.001 Control 0.262 P7 Control	7 Site A 0.213 0.001 V7 Site A 0.182 0.039 7 Site A 0.568 Site A SD Site A	Site B 0.250 0.438 0.060 Site B 0.001 0.808 0.059 Site B 0.044 0.308 0.700 Site B	Young 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.867 0.485 0.422 0.241 0.422 0.241 0.433	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A		Control Control Control Control Control Ref Control Re	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 8 Site A 0.573 Site A Site A S	Site B 0.022 0.680 0.050 0.046 0.002 0.930 0.046 0.017 0.878 0.500 Site B	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.986 0.956 0.956 0.973 0.215 0.475 0.057 Voung	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A		Control 0.002 Control 0.001 Control 0.026 Control Con	9 Site A 0.636 0.069 Site A 0.157 0.030 9 Site A 0.404 Site A Site A Site A	Site B 0.028 0.962 0.172 Site B 0.001 0.528 0.009 Site B Site B	Young 0.117 0.910 0.320 0.926 Voung 0.013 0.705 0.049 0.938 0.6668 0.139 0.383 0.002 Young	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD		Control Control Control PIO Control PIO Control PIO Control	10 Site A 0.009 V10 Site A 0.0071 0.162 Site A 0.363 0.056 Site A Site A S	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044 0.489 0.037 Site B	Voung 0.123 0.534 0.315 0.206 0.206 0.238 0.455 0.603 0.605 0.369 0.359 Voung
AD Control Site A Site B Young AD Control Site A Site B		Control 0.009 Control 0.009 Control 0.009 F Control 0.009 F Control 0.009 Control 0.009 Control 0.009 F Control 0.017 Control 0.	5 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.027 0.269 SD Site A 0.527	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302 Site B 0.302 Site B 0.302	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971 Voung 0.247 0.026 0.021 0.026 0.021 0.026 0.021 0.026 0.021 0.026 0.021 0.026 0.028 Young <0.013	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B		Control 0.018 Control 0.262 P7 Control 0.229	7 Site A 0.182 0.039 7 Site A 0.182 0.039 7 Site A 0.568 SD Site A 0.090	Site B 0.250 0.438 0.060 Site B 0.080 0.080 0.059 0.044 0.308 0.044 0.308 0.700 Site B 0.044	Young 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.485 0.485 0.485 0.485 0.422 0.433 0.433 Young <0.043	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.006 <0.001 <0.001 Control 0.020 P8 Control 0.023	8 Site A 0.991 0.027 V8 Site A 0.440 0.021 Site A 0.218 Site A 0.218 Site A 0.218 Site A 0.218 Site A 0.127	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046 0.017 0.878 0.500 Site B 0.500 Site B 0.177 0.878 0.500	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.163 0.956 0.957 0.0475 0.057 Young <0.057	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B			9 Site A 0.636 0.069 Site A 0.157 0.030 Site A 0.344 0.404 SD Site A 0.244	Site B 0.028 0.962 0.172 Site B 0.001 0.528 0.009 Site B 0.009 0.386 0.097 Site B 0.097	Young 0.117 0.910 0.320 0.926 0.033 0.705 0.049 0.668 0.139 0.383 0.002 Young Voung 0.383	AD Site A Site B Young AD Control Site A Site B Young AD Control AD Control AD Control AD		C Control <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.	10 Sife A 0.845 0.009 V10 Sife A 0.363 0.056 Sife A 0.363 0.056 Sife A 0.238	Site B 0.002 0.658 0.035 Site B 0.044 0.497 Site B 0.044 0.489 0.037 Site B 0.294	Young 0.123 0.534 0.315 0.206 Voung 0.006 0.238 0.455 0.603 0.695 0.369 Voung 0.359 Young <0.001
AD Control Site A Site B Young AD Control Site A Site B Young AD Control Contr		Control 0.009 Control 0.000 Control 0.000 F Control 0.009 F Control 0.009 F Control 0.001 Control 0.001 Control 0.001 Control 0.001 Control Co	5 Site A 0.610 0.005 Site A 0.292 0.214 0.292 0.214 0.292 0.214 0.007 0.269 Site A 0.027 0.269 Site A 0.527 0.015	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302 Site B 0.003 0.0236 0.0236	Young 0.931 0.071 0.661 0.297 Voung 0.021 0.437 0.099 0.971 0.029 0.971 0.029 0.971 0.029 0.097 0.021 0.029 0.021 0.021 0.028 Voung 0.021 0.028 Voung 0.028 0.021 0.028 0.021 0.029 0.021 0.029 0.021 0.029 0.021 0.022 0.021 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.022 0.021 0.022 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.021 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.022 0.020 0.022 0.020 0.022 0.020 0.000 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.020 0.0200 0.0200 0.0200 0.0200000000	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Contro		Control 0.018 Control 0.001 Control 0.262 P7 Control 0.029	7 Site A 0.213 0.001 0.001 0.182 0.039 7 Site A 0.146 0.568 SD Site A 0.090 0.000	Site B 0.250 0.438 0.060 Site B 0.001 0.808 0.059 0.044 0.308 0.700 Site B 0.044 0.308 0.700 Site B 0.036 0.036	Young 0.864 0.046 0.317 0.146 0.3396 0.042 0.396 0.485 0.485 0.485 0.422 0.422 0.433 Young <0.043	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Control Control Control Control Control Control Control Control Site A Site B Young AD Control		Control Contro	8 Site A 0.991 0.027 V8 Site A 0.211 8 Site A 0.218 0.573 Site A 0.218 0.573 Site A 0.127 0.021 0.021 0.021 0.021 0.021 0.027 0	Site B 0.022 0.680 0.050 Site B 0.046 0.930 0.046 Site B 0.017 0.878 0.500 Site B 0.035 0.046	Young 0.136 0.868 0.195 0.866 0.029 0.028 0.986 0.163 0.956 Voung 0.973 0.215 0.475 0.475 0.057 Young <0.001	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A AD Control Con			9 Site A 0.636 0.069 V9 Site A 0.157 0.030 9 Site A 0.344 0.404 0.404 SD Site A 0.244 0.004	Site B 0.028 0.962 0.172 Site B 0.001 0.528 0.009 Site B 0.009 Site B 0.009 Site B 0.009 Site B 0.009	Young 0.117 0.910 0.320 0.926 0.926 0.033 0.705 0.049 0.938 0.668 0.139 0.383 0.002 Young <0.001	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control		C Control Control Control P10 Control 0.152	10 Sife A 0.845 0.009 V10 Sife A 0.071 0.162 10 Sife A 0.363 0.056 Sife A 0.238 0.238 0.238	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044 0.489 0.037 Site B 0.044 0.489 0.037 Site B 0.294 0.893	Young 0.123 0.534 0.315 0.206 0.206 0.238 0.455 0.455 0.369 0.359 0.359 Voung 0.001 0.359
AD Control Site A Site B Voung AD Control Site A Site B Young AD Control Site A Site B Site B Site A Site B Control Site A Site B Site A Site B Site A Control Site A Contr		Control 0.009 Control 0.006 Control 0.007 Control 0.017 Co	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.527 0.015 Site A	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302 Site B 0.003 Site B 0.003 0.004	Young 0.931 0.071 0.661 0.297 0.021 0.437 0.999 0.971 Voung 0.247 0.026 0.013 0.028 Young <0.013	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A		Control 0.018 Control 0.001 Control 0.262 P7 Control 0.029	7 Sife A 0.213 0.001 0.182 0.039 7 Sife A 0.146 0.568 SD Sife A 0.003	Site B 0.250 0.438 0.060 Site B 0.059 Site B 0.044 0.308 0.700 Site B 0.044 0.308 0.700 Site B 0.036 0.036 0.036	Young 0.864 0.046 0.517 0.146 0.317 0.302 0.396 0.042 0.485 Voung 0.867 0.422 0.241 0.043 Voung <0.041	AD Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A		Control 0.006 Control Control 0.020 P8 Control 0.023 P8 Control 0.023 Control 0.023 Control 0.023 Control Con	8 Site A 0.991 0.027 V8 Site A 0.021 V8 Site A 0.021 8 Site A 0.218 0.573 Site A 0.127 0.003	Site B 0.022 0.680 0.050 Site B 0.002 0.930 0.046 Site B 0.017 0.878 0.035 0.777 0.7177 0.011	Young 0.136 0.868 0.195 0.866 0.29 0.986 0.163 0.956 Voung 0.973 0.215 0.475 0.057 Voung <0.001	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Site A Site A Site B Site B Sit			9 Site A 0.636 0.069 0.8 0.069 9 Site A 0.157 0.030 9 Site A 0.344 0.404 9 Site A 0.244 0.004	Site B 0.028 0.962 0.172 Site B <0.001	Young 0.117 0.910 0.320 0.926 0.926 0.033 0.049 0.938 0.668 0.139 0.383 0.002 Young <0.001	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Site A Site A Site B Site A Site A		Control Control PP0 Control 0.132 P10 Control 0.152	10 Sife A 0.845 0.009 V10 Sife A 0.363 0.056 Sife A 0.238 0.038	Site B 0.002 0.658 0.035 Site B 0.008 0.518 0.497 Site B 0.044 0.489 0.294 0.294 0.893 0.893	Young 0.123 0.534 0.315 0.206 0.820 0.238 0.455 0.603 0.635 0.359 0.359 Voung <0.001
AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young Site A Site B Young Site A Site B Young Control Site A Site B Young Site		Control 0.009 Control 0.006 Control 0.000 F Control 0.007 Control 0.017	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.269 Site A 0.527 0.015 Site A	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.236 0.882 0.302 Site B 0.003 0.276 0.004	Young 0.931 0.071 0.661 0.297 0.021 0.437 0.099 0.971 Voung 0.247 0.026 0.013 0.024 0.024 0.024 0.024 0.024 0.024 0.024 0.024 0.024 0.024	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site S Young AD Control Site A		Control 0.018 Control 0.262 P7 Control 0.202	7 Sife A 0.213 0.001 0.014 0.146 0.568 Sife A 0.090 0.003	Site B 0.250 0.438 0.060 Site B 0.044 0.048 0.044 0.044 0.0308 0.044 0.0308 0.044 0.0308 0.044 0.0308 0.0308 0.0308 0.041 0.0308 0.041 0.0308 0.0308 0.0308 0.0308 0.041 0.0308 0.041 0.0308 0.0308 0.0308 0.0308	Young 0.864 0.046 0.517 0.146 0.396 0.002 0.396 0.042 0.485 Young 0.867 0.422 0.241 0.043 0.001 0.003	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A AD Control Site A		Control 0.020 Control 0.020 P8 Control 0.023	8 Site A 0.991 0.027 0.028 Site A 0.440 0.021 Site A 0.573 Site A 0.573 SD Site A 0.127 0.033	Site B 0.022 0.680 0.050 0.050 0.002 0.930 0.046 0.017 0.017 0.017 0.017 0.035 0.003 0.035 0.777 0.011	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.163 0.956 0.973 0.215 0.475 0.057 0.475 0.001 0.047 0.002 0.001 0.002	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A			9 Site A 0.636 0.069 0.030 0.157 0.030 9 Site A 0.344 0.0404 0.404 SD Site A 0.0404 0.0404	Site B 0.028 0.962 0.172 Site B <0.001	Young 0.117 0.910 0.320 0.926 0.926 0.033 0.705 0.049 0.938 0.6688 0.139 0.6668 0.133 0.002 Voung <0.001	AD Control Site A Site B AD Control Site A Site B Young AD Control Site A AD Control Site A Site B		C Control 40.001 C Control 40.001 Prol Control 0.132 P10 Control 0.132 P10	10 Sife A 0.845 0.009 V10 Sife A 0.363 0.056 Sife A 0.238 0.038	Site B 0.002 0.658 0.035 Site B 0.044 0.489 0.044 0.489 0.037	Young 0.123 0.534 0.315 0.206 0.206 0.238 0.455 0.369 0.603 0.603 0.605 0.369 0.359 Voung 0.603 0.695 0.359 Voung 0.603
AD Control Site A Site B Young Control Control Control Site A Site B Young Control Contr		Control 0.009 Control 0.000 Control Contro	6 Site A 0.610 0.005 V6 Site A 0.292 0.214 6 Site A 0.227 0.2269 SD Site A 0.527 0.015	Site B 0.249 0.307 0.133 Site B 0.001 0.275 0.029 Site B 0.302 Site B 0.003 0.276 0.003 0.276	Young 0.931 0.071 0.661 0.297 0.021 0.437 0.099 0.971 Voung 0.247 0.061 0.028 Voung 0.028 Voung 0.028	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site A Site A Site A Site A		Control 0.262 F7 Control 0.229	7 Sife A 0.213 0.001 0.001 0.182 0.039 7 Sife A 0.568 SD SD SD	Site B 0.250 0.438 0.060 Site B 0.0011 Site B 0.0360 0.0360 0.0361 0.0361	Voung 0.864 0.046 0.517 0.146 0.002 0.396 0.042 0.396 0.485 Voung 0.867 0.422 0.241 0.043 voung 0.043 0.074 0.074	AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young AD Control Site A Site B Young		Control 0.000 Control 0.000 F Control 0.020 F Control 0.023 F S Control 0.023 F Control 0.02 F Con	8 Site A 0.991 0.027 Site A 0.440 0.021 8 Site A 0.573 SD Site A 0.127 0.003	Site B 0.022 0.680 0.050 Site B 0.017 0.878 0.500 Site B 0.035 0.046	Young 0.136 0.868 0.195 0.866 0.029 0.986 0.163 0.973 0.215 0.057 Voung <0.057	AD Control Site A Site B Young AD Control Site A Young AD Control Site A Site B Young AD Control Site A			9 Site A 0.636 0.069 0.030 0.157 0.030 9 Site A 0.157 0.0344 0.404 SD Site A 0.244 0.004	Site B 0.028 0.962 0.172 Site B <0.001	Young 0.117 0.910 0.320 0.926 0.026 0.013 0.705 0.049 0.668 0.383 0.602 Voung 0.383 0.002 Voung <0.001	AD Control Site A Site B Young Control Control Control Site A Site B Young Control Contr		C Control Control Control 0.001 P Control 0.132 P10 Control 0.152	10 Sife A 0.363 0.009 0.009 0.009 0.009 0.010 0.010 0.010 0.056 0.038 0.038 0.038	Site B 0.002 0.658 0.035 Site B 0.044 0.489 0.037 Site B 0.044 0.489 0.037 Site B 0.037 Site B 0.037	Young 0.123 0.534 0.315 0.206 0.206 0.208 0.455 0.603 0.603 0.359 Voung 0.369 0.359 Young 0.001 0.002

Table 3. Probability values for comparisons of BPW harmonic indices (C_n , CV_n , P_n , and P_n_SD) between AD patients, controls, and community subjects. Significant differences were underlined.

For variability indices of BPW signals, Group AD had the largest values of all CV_n indices and $P_n_SD_1$ to $P_n_SD_5$. Group AD had larger values than Group Control of all CV_n indices (all significant) and P_n_SD indices (all significant except for $P_n_SD_{10}$). Site A had larger values than Site B of all CV_n indices (p < 0.05 for CV_3 , CV_5 , CV_6 , CV_8 , and CV_9 ; $0.05 for <math>CV_4$ and CV_7) and P_n_SD indices (p < 0.05 for $P_n_SD_2$ to $P_n_SD_{10}$, $0.05 for <math>P_n_SD_1$). Group Young had smaller values than Group AD of all P_n_SD indices among the groups (all significant except for $P_n_SD_1$).

Table 4 lists the machine-learning analysis results (accuracy, sensitivity, specificity, and AUC) for evaluating the performance in classifying the subjects into the AD and Control groups. MLP had the best AUC (70.32%) among the eight methods. Detailed results of the threefold cross-validation analysis for MLP are shown in Figure 4.



Figure 4. MLP analysis results for comparisons of BPW indices between AD patients and Group Control. Training and validation accuracy plots, AUC, and contradiction matrix are presented for the threefold cross-validation. The mean accuracy, sensitivity, specificity, and AUC were 70.32%, 0.68, 0.72, and 0.70, respectively. "1" indicates AD patients and "0" indicates Control. (**a**) 1st part; (**b**) 2nd part; (**c**) 3rd part of the threefold cross-validation.

The correlations found in the testing results between the prediction probability (using AD patients and Control as training data) and the MMSE scores for the community and young subjects are shown in Figure 5. There was a significant negative correlation for these testing subjects ($R^2 = 0.36$, p < 0.05 by *F*-test). When the young group was excluded to minimize the possible interference effects of different ages, there was still a significant negative correlation for the community subjects ($R^2 = 0.31$, p < 0.05 by *F*-test).



Figure 5. Correlation between the prediction probability and MMSE score. Group AD and Control were used as training data. Community subjects at Sites A and B, and Group Young were used as test subjects. (a), There was a significant negative correlation for the testing community subjects $(R^2 = 0.36, p < 0.05 \text{ by } F\text{-test})$. (b), When the young group was excluded, there was still a significant negative correlation $(R^2 = 0.31, p < 0.05 \text{ by } F\text{-test})$.

Table 4. Results of the machine-learning analyses comparing BPW indices between AD patients andControl. Results are presented for the threefold cross-validation.

Accuracy (%)	SVM	MLP	GNB	DT	RF	LR	LDA	KNN
1	70.61	72.50	61.34	63.57	64.26	71.47	76.80	64.94
2	56.35	71.64	55.84	64.77	69.41	62.37	71.64	62.37
3	60.30	66.83	60.48	59.79	63.40	62.71	56.87	63.91
average	62.42	70.32	59.22	62.71	65.69	65.52	68.44	63.74
Sensitivity	SVM	MLP	GNB	DT	RF	LR	LDA	KNN
1	0.66	0.66	0.38	0.61	0.72	0.61	0.64	0.60
2	0.46	0.63	0.21	0.62	0.71	0.47	0.61	0.51
3	0.78	0.76	0.75	0.81	0.91	0.77	0.68	0.78
average	0.63	0.68	0.45	0.68	0.78	0.62	0.64	0.63
Specificity	SVM	MLP	GNB	DT	RF	LR	LDA	KNN
1	0.74	0.78	0.84	0.65	0.56	0.81	0.89	0.69
2	0.66	0.80	0.90	0.66	0.67	0.77	0.81	0.73
3	0.41	0.57	0.45	0.37	0.35	0.48	0.45	0.49
average	0.60	0.72	0.73	0.56	0.53	0.69	0.72	0.64
AUC	SVM	MLP	GNB	DT	RF	LR	LDA	KNN
1	0.70	0.72	0.61	0.63	0.64	0.71	0.76	0.64
2	0.56	0.71	0.55	0.64	0.69	0.62	0.71	0.62
3	0.60	0.66	0.60	0.59	0.63	0.62	0.56	0.63
average	0.62	0.70	0.59	0.62	0.65	0.65	0.68	0.63

4. Discussion

The present study found significant differences in BPW spectral indices between AD patients and control subjects. Using AD patients and control subjects as training data, a significant correlation was found between the prediction probability of the test data (comparing community subjects at two sites and young subjects) and the MMSE score.

4.1. Differences in the Spectral Indices of the Pulse Waveform

Differences in the BPW spectral indices between AD patients and control subjects were similar to those noted in our previous study [11]. Figure 3 reveals that C_5 – C_{10} were significantly larger for AD patients than controls. Similarly for the subjects at the two community sites, C_n values were larger in Site-A subjects than in Site-B subjects (significant for C_8 and C_{10}). Site B is located in the educational area of the city, whereas Site A is located in the countryside, and so Site-B subjects are probably more likely to experience diverse kinds of cognitive stimulation, therefore leading differences in cognitive function between the subjects at the two sites. This conjecture is supported by the difference in the MMSE scores between the two sites: although not statistically significant, the MMSE score was slightly lower in Site-A subjects (21.84 ± 5.19) than in Site-B subjects (23.95 ± 4.39).

It has been demonstrated previously that dementia can occur in association with an increase in the arterial stiffness [4,5]. This implies that it is possible for dementia to be accompanied with changes in the arterial pulse transmission condition outside the cerebrovascular vascular system, and hence measuring and analyzing the pulse waveform acquired at some distal site could be used to aid the evaluation of dementia-induced vascular changes in the pulse waveform. It has also been suggested that the larger C_n values of dementia patients can be partly attributed to the increased transmission efficiency for the higher-frequency components of the pulse spectrum [11]. The present findings of cognitive function differing between subjects at different community sites suggest that this is associated with changes in the vascular stiffness that affect the arterial pulse wave transmission and hence change the C_n values. The MMSE scores of AD patients (12.16 \pm 5.52) were closer to those of Site-A subjects than Site-B subjects, which may therefore be associated with larger C_n values for several higher-frequency components of the pulse referency components of the pulse spectrum.

Regarding variability indices, Figure 3 indicates that AD patients had the largest values of all CV_n indices (all significant compared with Control) and many $P_n_SD_n$ indices (significant for $P_n_SD_1$ to $P_n_SD_9$ compared with Control). Variability indices such as HR and BP variability have been used in many studies to aid the monitoring of cardiovascular regulatory activities [21]. Variability indices of the pulse waveform in AD patients have previously been suggested to illustrate the presence of larger regulatory activities acting on vascular elastic properties [11]. This could be related to the greater effort needed to address the changes in the blood-flow perfusion condition when facing AD-induced changes in vascular stiffness.

Similar to the situation for C_n indices, since the values of many of the analyzed pulse variability indices were significantly larger for AD patients, comparison between Site-A and Site-B subjects revealed that those at Site A had larger values of all CV_n indices (some of them were significant) and P_n_SD indices (significant for $P_n_SD_2$ to $P_n_SD_{10}$). Based on the above-mentioned conjecture, the differences in the cognitive function of subjects between the two sites may induce different vascular regulatory activities, and hence may partly account for the observed differences in the CV_n and $P_n_SD_n$ indices.

Another finding supporting this conjecture is that Group Young had the smallest values of all $P_{n}SD$ indices (significant for $P_{n}SD_2$ to $P_{n}SD_{10}$ compared with AD patients). The MMSE scores of these young subjects were higher than those of Site-A and Site-B subjects. Based on the above-mentioned conjecture, the regulatory efforts may be smallest due to the high cognitive function of the young subjects. The vascular regulatory activities of Group Young may therefore be smallest, hence leading to the smallest values of $P_{n}SD$ indices.

Regarding phase-angle indices of BPW signals, Group AD had the largest values of P_2 – P_9 (significant for P_8 and P_9 compared with Control). The phase angle is related to the starting time point for each frequency component. A larger P_n value can therefore be partly attributed to faster propagation of that specific frequency component of the arterial pulse, and hence related to the spectral distribution of the vascular elasticity (increased vascular elasticity for some specific frequency components).

4.2. Correlation between Prediction Probability and MMSE Score

Further important support for the above-mentioned conjecture comes from the correlation between the MMSE score and the prediction probability identified in the machinelearning analysis using spectral pulse indices as features. While there have been advances in detecting early neuropathology, it may be necessary to consider a shift in the diagnostic paradigm so that milder dementia can be detected earlier in order to obtain greater benefits from interventions [22,23]. Identifying the symptoms of the early stages of dementia is often difficult among older adults living in residential care [24]. It has been reported that more than 10% of community-dwelling subjects older than 70 years suffer from very mild or mild dementia [22]. Data-informed decision-making strategies to identify individuals at high risk of dementia could be essential to facilitating large-scale prevention and early intervention [25]. Triage tests such as the MMSE are used in clinical practice to rapidly assess the cognitive condition [2]. We therefore used the MMSE in comparisons with the results of machine-learning pulse analysis in the present study.

In previous community studies, the diagnostic accuracy of MMSE was indicated by a sensitivity of 0.85 (95% CI = 0.74–0.92) and a specificity of around 0.90 (95% CI = 0.82–0.95) [1]. A previous study that applied machine-learning algorithms used the MMSE, the Montreal Cognitive Assessment, and the Korean Dementia Screening Questionnaire to evaluate participants, and achieved an overall screening accuracy of >90% for mild cognitive impairment, dementia, and cognitive dysfunction [26]. Although the MMSE has the largest body of evidence to support its use and has adequate test accuracy, its utility is limited by the relatively long administration time (10–15 min) and high cost [2]. The present results (Figure 4) indicated an AUC of 0.70 in the threefold cross-validation when using MLP, which represents acceptable discrimination performance.

The significant correlation between the prediction probability and the MMSE score noted in the present study provides further support for possible application in community subjects. Figure 5 indicates that a higher MMSE score was associated with a lower prediction probability. This illustrates that there could be a physiological connection between the MMSE evaluation and the pulse indices; that is, when the MMSE score is lower (which indicates worse cognition), the prediction probability is higher (indicating greater similarity of the pulse waveforms between the subject and the average of the AD group), and vice versa.

The young group was included in the test subjects for the data shown in Figure 5a. Subjects of different ages may exhibit different levels of vascular stiffness [27], which could interfere with arterial pulse transmission and hence the pulse indices. To elucidate the relationship between the prediction probability and the MMSE score, the young group was excluded in Figure 5b to minimize the possible effects of different ages in the comparisons. After removing these data points of the young group, there was still a significant correlation (with R^2 changing from 0.36 to 0.31). This illustrated that even when the age varied between groups of testing data, the correlation between the prediction probability and the MMSE score remained statistically significant.

Since the MMSE is a widely used tool for evaluating cognitive function in community subjects, the present finding of a significant correlation illustrates a possible connection of underlying physiological mechanisms between arterial pulse transmission and the MMSE score. Other efforts have been made to identify possible connections between physiological measurements and cognition evaluation indices. For example, one previous study focused on the activities of daily living of adults in a smart-home setting to monitor potential cognitive anomalies using a public data set, and achieved a 90.74% accuracy in detecting the onset of dementia by applying machine-learning analysis [24]. In the present study, the pulse data took only 3 min to acquire; this shorter administration time enhances the user-friendliness of the present method of pulse-wave measurements for discriminating cognitive conditions, and hence represents a potential method for the early screening of dementia.

This study was limited by the relatively small sample in the machine-learning analysis (although cross-validation was used). Future efforts could focus on accumulating more patients and community subjects in order to verify the present conjectures.

5. Conclusions

The findings of this study and the related conclusions to be drawn can be summarized as follows:

- Significant differences in spectral indices of the BPW were found between the AD patients and control subjects.
- The threefold cross-validation results indicated an AUC of 0.70 in the threefold cross-validation when using MLP, which indicated acceptable discrimination performance.
- Using AD patients and control subjects as training data, a significant correlation was found between the prediction probability of the test data (comprising community subjects at two sites and young subjects) and the MMSE score. Although significant, the correlation in Figure 5 was modestly correlated. Further collection of subject data in future work is necessary to strengthen the present conjecture.
- Age did not markedly interfere with the identified correlation between the prediction probability and the MMSE score.
- The present findings based on pulse waveform measurements and machine-learning analysis may be meaningful for the development of a noninvasive, rapid, and objective method for monitoring the cognitive condition.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/s22030806/s1.

Author Contributions: Conceptualization, H.H. and S.-K.L.; methodology, H.H. and S.-K.L.; software, W.-L.W.; validation, C.-C.L.; formal analysis, W.-L.W., C.-M.H. and C.-K.C.; investigation, W.-L.W. and C.-K.C.; resources, H.H. and S.-K.L.; data curation, H.H.; writing—original draft preparation, H.H.; writing—review and editing, H.H.; visualization, S.-K.L.; supervision, C.-T.C.; project administration, H.H. and S.-K.L.; funding acquisition, H.H. and S.-K.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Ministry of Science and Technology, grant number 109-2221-E-011-029 and Taipei City Hospital, grant number TPCH-110-30.

Institutional Review Board Statement: Approved by the Review Board of Taipei City Hospital; approval no. TCHIRB-10810016-E.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical concern.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Creavin, S.T.; Wisniewski, S.; Noel-Storr, A.H.; Trevelyan, C.M.; Hampton, T.; Rayment, D.; Thom, V.M.; Nash, K.J.; Elhamoui, H.; Milligan, R.; et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst. Rev.* 2016, 13, CD011145. [CrossRef]
- Patnode, C.D.; Perdue, L.A.; Rossom, R.C.; Rushkin, M.C.; Redmond, N.; Thomas, R.G.; Lin, J.S. Screening for Cognitive Impairment in Older Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2020, 323, 764–785. [CrossRef]
- Dequanter, S.; Buyl, R.; Fobelets, M. Quality indicators for community dementia care: A systematic review. *Eur. J. Public Health* 2020, 30, 879–885. [CrossRef]
- 4. Iadecola, C.; Gottesman, R.F. Cerebrovascular alterations in Alzheimer disease: Incidental or pathogenic? *Circ. Res.* 2018, 123, 406–408. [CrossRef] [PubMed]
- 5. Cortes-Canteli, M.; Iadecola, C. Alzheimer's disease and vascular aging: JACC Focus Seminar. J. Am. Coll. Cardiol. 2020, 75, 942–951. [CrossRef] [PubMed]

- Kuller, L.H.; Lopez, O.L.; Mackey, R.H.; Rosano, C.; Edmundowicz, D.; Becker, J.T.; Newman, A.B. Subclinical cardiovascular disease and death, dementia, and coronary heart disease in patients 80+ years. *J. Am. Coll. Cardiol.* 2016, 67, 1013–1022. [CrossRef]
 O'Rourke, M.F.; Adji, A.; Safar, M.E. Structure and Function of Systemic Arteries: Reflections on the Arterial Pulse. *Am. J.*
- O'Rourke, M.F.; Adji, A.; Safar, M.E. Structure and Function of Systemic Arteries: Reflections on the Arterial Pulse. Am. J. Hypertens. 2018, 31, 934–940. [CrossRef] [PubMed]
 Willingen LB: Conferent LB: Webb DL Pulse years analysis and enterial stiffness. L Conference Discussed 1998, 22 (Suppl. 2)
- Wilkinson, I.B.; Cockcroft, J.R.; Webb, D.J. Pulse wave analysis and arterial stiffness. J. Cardiovasc. Pharmacol. 1998, 32 (Suppl. 3), S33–S37.
- 9. Oh, Y.S. Arterial stiffness and hypertension. Clin. Hypertens. 2018, 24, 17. [CrossRef] [PubMed]
- 10. Hsiu, H.; Liu, J.C.; Yang, C.J.; Chen, H.S.; Wu, M.S.; Hao, W.R.; Lee, K.Y.; Hu, C.J.; Wang, Y.H.; Fang, Y.A. Discrimination of vascular aging using the arterial pulse spectrum and machine-learning analysis. *Microvasc. Res.* **2021**, *139*, 104240. [CrossRef]
- 11. Lin, S.K.; Hsiu, H.; Chen, H.S.; Yang, C.J. Classification of patients with Alzheimer's disease using the arterial pulse spectrum and a multilayer-perceptron analysis. *Sci. Rep.* **2021**, *11*, 8882. [CrossRef]
- Husmann, M.; Jacomella, V.; Thalhammer, C.; Amann-Vesti, B.R. Markers of arterial stiffness in peripheral arterial disease. *Vasa* 2015, 44, 341–348. [CrossRef] [PubMed]
- 13. Mackenzie, I.S.; Wilkinson, I.B.; Cockcroft, J.R. Assessment of arterial stiffness in clinical practice. QJM 2002, 95, 67–74. [CrossRef]
- 14. Liao, J.; Farmer, J. Arterial stiffness as a risk factor for coronary artery disease. *Curr. Atheroscler Rep.* 2014, *16*, 387. [CrossRef]
- 15. Lin, F.C.; Hsiu, H.; Chiu, H.S.; Chen, C.T.; Hsu, C.H. Characteristics of pulse-waveform and laser-Doppler indices in frozenshoulder patients. *Biomed. Signal Process. Control* 2020, *56*, 101718. [CrossRef]
- Chen, C.T.; Hsiu, H.; Hung, S.H.; Chen, G.Z.; Huang, Y.L. Characteristics of spectral indexes of the blood pressure waveform in patients with breast cancer. *Blood Press. Monit.* 2017, 22, 217–220. [CrossRef] [PubMed]
- 17. Chang, Y.W.; Hsiu, H.; Yang, S.H.; Fang, W.H.; Tsai, H.C. Characteristics of beat-to-beat photoplethysmography waveform indexes in subjects with metabolic syndrome. *Microvasc. Res.* **2016**, *106*, 80–87. [CrossRef] [PubMed]
- 18. Hsu, C.L.; Hsiu, H.; Hsu, W.C.; Chen, C.Y. Characteristics of harmonic indexes of the arterial blood pressure waveform in polycystic ovary syndrome. *Blood Press Monit.* **2014**, *19*, 226–232. [CrossRef] [PubMed]
- Chen, C.T.; Ting, C.T.; Chen, C.Y.; Lyu, Z.J.; Chen, C.C.; Chou, Y.S.; Cheng, C.F.; Hsu, C.H.; Hsiu, H. Pulse-waveform and laser-Doppler indices for identifying colorectal-cancer patients. *Biom. Eng. Appl. Basis Comm.* 2020, 33, 2150005. [CrossRef]
- 20. Sorelli, M.; Perrella, A.; Bocchi, L. Detecting vascular age using the analysis of peripheral pulse. *IEEE Trans. Biomed. Eng.* **2018**, *65*, 2742–2750. [CrossRef]
- 21. Stergiou, G.S.; Ntineri, A.; Kollias, A.; Ohkubo, T.; Imai, Y.; Parati, G. Blood pressure variability assessed by home measurements: A systematic review. *Hypertens. Res.* **2014**, *37*, 565–572. [CrossRef]
- Lam, L.C.; Tam, C.W.; Lui, V.W.; Chan, W.C.; Chan, S.S.; Wong, S.; Wong, A.; Tham, M.K.; Ho, K.S.; Chan, W.M.; et al. Prevalence of very mild and mild dementia in community-dwelling older Chinese people in Hong Kong. *Int. Psychogeriatr.* 2008, 20, 135–148. [CrossRef] [PubMed]
- 23. Trivedi, D. Cochrane Review Summary: Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Prim. Health Care Res. Dev.* **2017**, *18*, 527–528. [CrossRef]
- Ahamed, F.; Shahrestani, S.; Cheung, H. Internet of Things and Machine Learning for Healthy Ageing: Identifying the Early Signs of Dementia. Sensors 2020, 20, 6031. [CrossRef] [PubMed]
- Luo, H.; Lau, K.K.; Wong, G.H.Y.; Chan, W.C.; Mak, H.K.F.; Zhang, Q.; Knapp, M.; Wong, I.C.K. Predicting dementia diagnosis from cognitive footprints in electronic health records: A case-control study protocol. *BMJ Open* 2020, 10, e043487. [CrossRef] [PubMed]
- 26. Yim, D.; Yeo, T.Y.; Park, M.H. Mild cognitive impairment, dementia, and cognitive dysfunction screening using machine learning. *J. Int. Med. Res.* **2020**, *48*, 300060520936881. [CrossRef]
- Faconti, L.; Bruno, R.M.; Ghiadoni, L.; Taddei, S.; Virdis, A. Ventricular and vascular stiffening in aging and hypertension. *Curr. Hypertens. Rev.* 2015, 11, 100–109. [CrossRef]