ISSN 2310-5674

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The European Journal of Biomedical and Life Sciences

Premier Publishing s.r.o.

2023

1 2 3 4

European Journal of Biomedical and Life Sciences

2023, No 3

PREMIER Publishing

Vienna
2023

European Journal of Biomedical and Life Sciences

Scientific journal

№ 3 2023

ISSN 2310-5674

Editorial office Premier Publishing s.r.o.
Praha 8 – Karlín, Lyčkovo nám. 508/7, PSČ 18600
E-mail: pub@ppublishing.org
Homepage: ppublishing.org

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Scientific Journal Impact Factor

Scientific Journal Impact Factor Value for 2023 – 5.981

Typeset in Berling by Ziegler Buchdruckerei, Linz, Austria.
Printed by Premier Publishing s.r.o., Vienna, Austria on acid-free paper.

The European Journal of Biomedical and Life Sciences 2023, No 3
ISSN 2310-5674

PREMIER Publishing
ppublishing.org

Section 1. Clinical Medicine

DOI: 10.29013/EJBLS-23-3-3-7

D-DIMER DYNAMICS AND INFLAMMATION PARAMETERS IN THE FIRST DAYS OF HOSPITALIZATION IN PATIENTS WITH COVID-19

Albina Hasa [1], Alma Barbullushi [2], Emirvina Kolici [3], Aurora Xhixha[4], Admir Nake[5]

[1] PhD. C. Aldent University, Department of Medical Laboratory and Imaging, Tirana, Albania

[2] Prof. Assoc. Faculty of Technical Medical Sciences, Department of Diagnostics and Rehabilitation, University of Medicine, Tirana, Albania

[3] Ph.D. Faculty of Technical Medical Sciences, Department of Diagnostics and Rehabilitation, University of Medicine, Tirana, Albania

[4] Ph.D. Aldent University, Department of Medical Laboratory and Imaging, Tirana, Albania

[5] Prof. Assoc. Faculty of Technical Medical Sciences, Head of Department of Diagnostics and Rehabilitation, University of Medicine, Tirana, Albania

Cite: *Hasa A. Barbullushi A., Kolici E., Xhixha A., Nake, A. (2023). D-Dimer Dynamics and Inflammation Parameters in the First Days of Hospitalization in Patients With Covid-19. European Journal of Education and Applied Psychology 2023, No 3*. https://doi.org/10.29013/EJBLS-23-3-3-7

Abstract

The article provides data on the study of D-dimer dynamism, inflammation parameters and morphological blood parameters (neutrophil and lymphocyte) in 32 patients hospitalized with covid-19. The aim of the present study was an evaluation of inflammation, coagulation and fibrinolysis biomarkers and their possible associations with the severity and the prognosis of covid-19 disease.

Keywords: *covid-19, inflammation parameters, d-dimer, morphological blood, neutrophil, lymphocyte, hospitalization*

Introduction

CoV-19 is an infectious disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Named as the most significant global health crisis since the era of the influenzae pandemic of 1918. After the first cases of this predominantly respiratory disease reported in Hubei Province, Wuhan, China in December 2019, SARS-CoV-2 quickly had a worldwide distribution in a

short period of time, thus being declared by the WHO as a pandemic on March 11, 2020. Since the moment of the declaration as a pandemic, COVID-19 has affected many countries around the world, significantly affecting the health systems.

Materials and methods

The size of the samples taken in the study during this period is composed of 32 patients of the age groups; 20–30 years, 31–60 years and >61 years. The laboratory tests included in the study are inflammation parameters; ferritin, fibrinogen, PCR and D-dimer as a coagulation parameter as well as morphological blood parameters; leukocyte, neutrophil and lymphocyte. For the measurement of these laboratory tests, venous blood was obtained through the phlebotomy procedure. For the measurement of D-dimer and fibrinogen, plasma obtained through the centrifugation of venous blood taken with Na citrate laboratory tube in the ratio 9:1, the measurement was performed on the STA COMPACT MAX apparatus. For the measurement of ferritin and CRP, serum obtained through the centrifugation of venous blood taken with a gel tube, the measurement was performed on the cobas e411 apparatus. A tube with K3EDTA anticoagulant was used to measure blood morphology, the measurement was performed on the Erba Elite 580 device. The statistical analysis procedures used in this study are described as follows; all statistical analysis was performed in SPSS (Statistical Package for Social Sciences, Version 26.0). Descriptive data on the laboratory tests obtained in the study were processed. Correlations between different parameters obtained in the study were evaluated. In all cases, a value of $p \leq 0.05$ was considered statistically significant. The results were presented in absolute value and in percentage and were illustrated through tables and graphs.

Results

The data of the study showed that among the individuals included in the study, 59.4% are men and 40.6% are women, of which 3.1% are aged 20–30, 21.9% are aged 31–60 and 75% at age > 61 years. 68.8% turned out to be in serious condition and 31.2% in non-serious condition. The average values of the studied laboratory parameters in the first days of hospitalization varied as follows; d-dimer resulted with an average of 1.62(0.13–20), ferritin 1172.58 (76.1––1547.22), fibrinogen 484.83 (162––1792.04), CRP 5.19 (0.23–46.59), leukocyte 10.19 (1.28–29.98), neutrophil 81.7–51.7 96.60) and lymphocyte 11.65 (0.2–37.90). Ddimer has a positive linear relationship with ferritin r=.0.29, p=0.09. Fibrinogen has a negative linear relationship with Ddimer r= =–0.10, p=0.55. Ddimer has a positive linear relationship with CRP r=.0.41, p=0.01. Ferratin has a positive linear relationship with CRP r=0.06, p=0.73. Fibrinogen has a positive linear relationship with CRP r=0.39, p=0.02. A significant lymphopenia, leukocytosis and neutrocytosis are observed. Neutrophil has a negative linear relationship with lymphocyte r= –0.96, p=0.00. There is a statistically significant relationship between age and disease severity but not between gender and disease severity.

Table 1. *Spearman's correlation analysis of neutrophil and lymphocyte.*

			Neutrophil	Lymphocyte
Spearman's rho	Neutrophil	Correlation Coefficient	1.000	–.967**
		Sig. (2-tailed)	.	.000
		N	32	32
	Lymphocyte	Correlation Coefficient	–.967**	1.000
		Sig. (2-tailed)	.000	.
		N	32	32

In (table 1) Spearman's correlation analysis regarding neutrophil and lymphocyte is presented. From the correlative analysis we draw the following conclusions: the neutro-

phil has a negative linear relationship with the lymphocyte r= –0.96. Significance is .00.

Table 2. *Spearman's correlation analysis of inflammation parameters*

			The average value of Ddimer in the four days of hospitalization	The average value of Ferritine in the four days of hospitalization	The average value of Fibrinogen in the four days of hospitalization	The average value of CRP in the four days of hospitalization
Spearman's rho	The average value of Ddimer in the four days of hospitalization	Correlation Coefficient	1.000	.299	–.108	.418*
		Sig. (2-tailed)	.	.096	.556	.017
		N	32	32	32	32
	The average value of Ferritine in the four days of hospitalization	Correlation Coefficient	.299	1.000	–.120	.061
		Sig. (2-tailed)	.096	.	.512	.739
		N	32	32	32	32
	The average value of Fibrinogen in the four days of hospitalization	Correlation Coefficient	–.108	–.120	1.000	.398*
		Sig. (2-tailed)	.556	.512	.	.024
		N	32	32	32	32
	The average value of CRP in the four days of hospitalization	Correlation Coefficient	.418*	.061	.398*	1.000
		Sig. (2-tailed)	.017	.739	.024	.
		N	32	32	32	32

Table 2. shows Spearman's correlation analysis. From the correlative analysis we draw the following conclusions: Ddimer has a positive linear relationship with ferritin r = .0.29. Significance is .09. Ddimer has a negative linear relationship with fibrogen r = .–0.10. The significance is .55. Ddimer has a positive linear relationship with PCR r = .0.41. Significance is .01. Ferratin has a positive linear relationship with PCR r = =0.06. The significance is .73. Fibrinogen has a positive linear relationship with PCR r = 0.39. Significance is .02.

Discussions and conclusions

The infectious disease of COVID-19 has already spread around the world. Most infected patients manifest it with mild symptoms and a good prognosis, but some of them develop severe disease that can lead to death. From the studies there is no effective therapy for COVID-19. Therefore, it is essential to identify diagnostic markers that allow accurate monitoring of disease progression, because effective early interventions are essential measures to reduce mortality. There is much evidence to suggest that inflammatory responses play a critical role in the progression of COVID-19, and several markers have the potential to be used to accurately track and predict the severity and fatality of COVID-19 disease (Razu Rahman, S., Arif Binte, Y.T, T., Sh, I.S. Islam, Shariful Mohammed, H. Abrha, Gesesew and Ward, P. 2021).

The hematological profile of patients with COVID-19 showed differences between

severe and moderate cases. While hemoglobin, hematocrit and platelet count did not differ between these two groups, white blood cells and their differential count appeared to play an important role in terms of disease severity. We found that in severe cases, white blood cells were significantly increased compared to non-severe cases. More specifically, subjects with severe COVID-19 showed higher percentages of neutrophils and lower percentages of lymphocytes (Mardani, R., Namavar, M. E., Ghorbi, Z. Shoja, F. Zali, K. Hooman, M. Aghasadeghi Reza, S. Sadeghi Amir, S. Sabeti, I. Darzam Alavi, N. Ahmadi and Nasab Mousavi Dawood, S. 2022).

Lymphopenia has been concluded to be a characteristic of COVID-19 and to be useful in differentiating between COVID-19 pneumonia and non-COVID-19 pneumonia. Studies show that the decrease in lymphocytes is mainly caused by the depletion of T-lymphocyte subsets. Mainly T-helper and T-suppressor cells, and the presence of lymphopenia in patients with COVID-19 suggests significant inflammation and tissue damage. Our findings show that absolute lymphocyte counts are lower in severe cases (Mardani, R., Namavar, M. E., Ghorbi, Z. Shoja, F. Zali, K. Hooman, M. Aghasadeghi Reza, S. Sadeghi Amir, S. Sabeti, I. Darzam Alavi, N. Ahmadi and Nasab Mousavi Dawood, S. 2022). The results of our study showed the presence of lymphopenia and a significant relationship with the patient's health condition. A significant relationship between health status and leukocytes resulted. Neutrophils were found to have a significant relationship as well. A statistically significant relationship was found between neutrophil and lymphocyte.

CRP is a systemic marker of the acute-phase response to inflammation, infection, and tissue damage, which can be used as an indicator of inflammation. Previous studies have shown that CRP levels can be used to diagnose patients with COVID-19 and to predict the outcome of the infection (Razu Rahman, S., Arif Binte, Y.T, T., Sh, I. S. Islam, Shariful Mohammed, H. Abrha, Gesesew and Ward, P. 2021).

From the results of our study, an increased mean of CRP, ferritin, fibrinogen and dimer was observed and the degree of increase varied based on the severity of the patient's health condition.

Studies have shown that D-dimer is predictive of serious illness and death due to SARS-CoV-2 infection, and thus provides support for early triage of patients with COVID-19 presenting to the hospital emergency and for monitoring patients during the first week of hospitalization (E. M. D. A. G. O. Sayit, A. T., 2021).

Based on the studies conducted regarding the progress of ferritin in patients with covid, it was concluded that there is a significant correlation with the severity of the disease. D-dimer and ferritin had a particularly significant correlation between them (Sukrisman, L., Sinto, R., and Priantono, D. 2021).

Our found a significant correlation between fibrinogen and CRP, a significant correlation between dimer and CRP, no significant correlation was found between dimer and ferritin. Ddimer did not show a significant correlation with fibrinogen. No significant correlation was observed between ferritin and fibrinogen.

In conclusion we can say that the inflammatory markers can help doctors monitor and assess the severity and prognosis of COVID-19.

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submitted 22.08.2023;
accepted for publication 20.09.2023;
published 8.10.2023

Contact:

The European Journal of Biomedical and Life Sciences 2023, No 3
ISSN 2310-5674

PREMIER Publishing
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DOI: 10.29013/EJBLS-23-3-8-15

DESIGN OF ACETYLCHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE

Jiawei Ren [1]

[1] Lake Forest Academy, Illinois, USA

Cite: *Jiawei Ren. (2023). Design of Acetylcholinesterase Inhibitors for Alzheimer's Disease. European Journal of Education and Applied Psychology 2023, No 3.* https://doi.org/10.29013/EJBLS-23-3-8-15

Abstract

Introduction

Alzheimer's disease is a worldwide progressive neurodegenerative disease. In the past two decades, acetylcholinesterase (AChE) inhibitors have been the most popular medication in mitigating Alzheimer's disease symptoms. However, all common AChE inhibitors have side effects, and traditional inhibitor discovery is a very expensive and timely process. Replacing the traditional workflow with computational experiments, this research selected novel candidate AChE inhibitors for future drug development.

Methods

18 compounds were retrieved after virtually screening for pharmacophore structures affinitive to AChE. After compounds' interaction simulations with the AChE, their inhibition efficiencies were ranked based on Gibb's free energy of. Then the research further evaluated the compounds' oral bioavailability and ability to across the blood brain barrier by comparing their properties with the Lipinski's rule of 5.

Results

Overall, 17 out of 18 compounds passed the Lipinski's rule of 5, qualifying good absorption and permeation. While compound ZINC04713297 featured the best inhibition efficiency (–9.37kcal/mol), both ZINC92926669 and ZINC08756522 required the second lowest reaction energy (–9.20kcal/mol). ZINC92926669 stood out among the two in the absorption assessment for its stability and portability in the blood stream.

Conclusion

This research discovered 17 novel AChE inhibitors through the workflow combining virtual screening, interaction simulation and absorption assessment. It highlighted compound ZINC04713297 and ZIN92926669, which served as a starting point for development of novel acetylcholinesterase inhibitors for Alzheimer's disease.

Keywords: *Alzheimer Disease, Acetylcholinesterase, Drug Discovery, Computational Molecular Biology*

Introduction

Alzheimer's disease (AD), a neurodegenerative disease, is the most common cause of dementia (Breijyeh, Z. and R. Karaman, 2020). There are currently 55 million people worldwide suffering from dementia. The

number is projected to double every 20 years, reaching 78million by 2030 (Yiannopoulou, K.G. and Papageorgiou S.G., 2020).The most popular current medicine for AD is acetylcholinesterase (AChE) inhibitor (Marucci, G., et al. 2021). By hindering the activity of AChE, this class of drug maintains a healthy level of the neurotransmitter acetylcholine at synapses (Sharma, K. 20190).

Most physicians would recommend AChE inhibitors donepezil, galantamine and rivastigmine as the first-line drug to cope with mild to moderate AD symptoms (Birks, J. 2006). However, all of them posted side effects such as nausea, vomiting and insomnia (in *Liver Tox: 2012;* Birks, J.S. and Harvey R.J., 2018; Hager, K., et al., 2014).

Considering the limitations of popular medicines, personalized drugs are brought to attention. Some current researches begin to design novel AChE inhibitor. Research in 2021 used virtual screening to test on 1220 galantamine derivatives (GAL–L-Ar) for anti-AChE activities (Stavrakov, G., et al., 2016). However, more drug options are still needed for doctors to match the drug with patients' physical characters. To meet the need for more candidate AChE inhibitors, this research virtually screened for compounds with high affinity to AChE as a start point for novel drug development.

Methods

Virtual screening

The virtual screening process aimed to find drugs that mimicked binding structures of AChE antibodies. These structures allowed drugs to have a high affinity to AChE.

PocketQuery

Fab410 is an AChE antibody, one of the largest peptide inhibitors targeting the peripheral site of AChE (Bourne, Y., et al., 2013). The entire antibody-protein complex has total six chains, and all antibodies constitute of a heavy chain and a light chain. This experiment chose to study two interactions: **a.** the interaction of AChE's chain A with antibody's light Chain E, **b.** the interaction between AChE's chain A with heavy Chain F (Charles A. Janeway, J., Paul Travers, Mark Walport, and Mark J. Shlomchik, 2001).

I entered the PDB code of the Fab410-BfAChE complex, 4QWW, on PocketQuery (http://pocketquery.csb.pitt.edu/). Clicked "search" to run the search for binding clusters with high affinity to AChE. Pocke tQuery yielded Fab410's residue clusters at the interface of the interaction. The interactive clusters were ranked by scores, based on a support vector machine (SVM) classifier (Koes, D.R. and C.J., 2012).

Pharmacophore Screening

I uploaded three highest ranking clusters each from chain E and chain F onto ZINCPharmer. ZINCPharmer (http://zincpharmer.csb.pitt.edu) found matching compound hits that shared similar structure with the cluster. For each residue clusters, three compounds that had the highest RMSD (similarity scores) were chosen for further study.

Docking Experiment

SwissDock (http://www.swissdock.ch) calculated the Gibbs free energy of interaction between compounds and AChE. On the "Submit Docking" page, I selected "targets" by uploading the structure file for 3LII. Then ligands were entered by either using their identifiers from PDB or their structure files (Grosdidier, A., Zoete, V., and Michielin, O., 2011). Entering the job name and email, clicked "submit" to run the experiment. After approximately twelve hours, results were sent via email. I ranked the compounds' inhibition efficiencies based on their interactions' Gibbs free energy. A negative value of energy of interaction indicated that the reaction was spontaneous. Therefore, the lower the value was, the more likely a compound could inhibit AChE.

Absorption Assessment

In order to qualify as applicable drugs, the compounds had to meet specific features — Lipinski's Rule of 5 (Nogara, P.A., et al., 2015). This set of rules included restrictions on number of hydrogen bond acceptor, number of hydrogen bond donor, iLOGP, and molecular weight.

Swiss ADME

To prepare the input from Swiss ADME, SMILES format of the eighteen compounds were copied from ZINC database. By pasting

them on the Swiss ADME page and clicking "run", the program generated a range of compound data. The compound couldn't have more than ten H-bond acceptors, more than five H-bond donors, a iLOGP value greater than five, or the molecular weight bigger than five hundred gram per mole. Any compounds that violated the rules were eliminated.

Results

Virtual Screening

PocketQuery

Fab410 was a non-competitive AChE antibody that had promise in further research (Bourne, Y., Renault, L. and Marchot P., 2015). After submitting the PDB code for Fab410-BfAChE complex on Pocket Query, three clusters with the highest score each were chosen from chain E and chain F. Size represented the number of amino acid residues in the cluster, and the distance embodied the longest distance in Angstroms between the centroids of any two residues in the cluster. Overall, clusters from chain E earned a better score than clusters of chain F (Table 1).

Table 1. *Chain, size, distance and score of the six clusters*

Name	Chain	Size	Distance	Score
Cluster1	E	2	7.3511	0.981743
Cluster2	E	3	7.3511	0.981391
Cluster3	E	2	9.9599	0.979564
Cluster4	F	1	0	0.969102
Cluster5	F	2	11.1823	0.95847
Cluster6	F	2	5.8989	0.956513

Finding Matching Hits

The six clusters were sent to ZINCPharmer. The system searched for structurally similar compounds for each cluster. The compounds were given a value of RMSD (root mean square deviation) — a larger value indicated a more significant deviation from the original cluster structure (Koes, D. R. and Camacho, C. J., 2011). The best three compound with the lowest RMSD were selected for each cluster (Figure1) (Table 2).

Figure1. *Structures of the compounds*

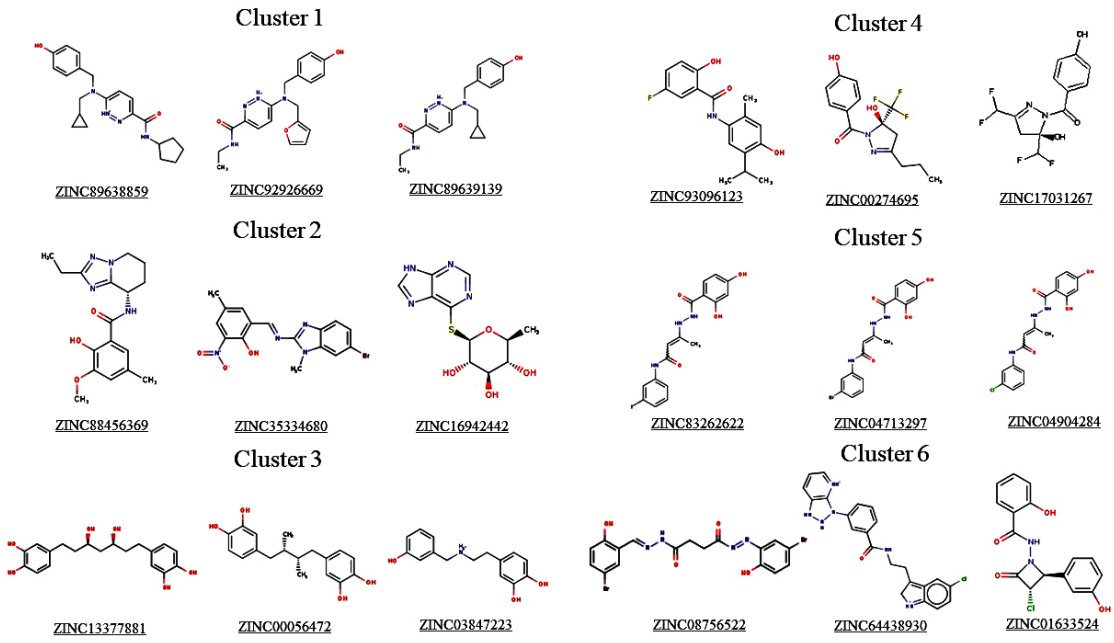

Table 2. *Chain, cluster and RMSD value of compounds*

Chain	Cluster	Compound	RMSD
		ZINC89638859	0.465
	Cluster 1	ZINC92926669	0.480
		ZINC89639139	0.480
		ZINC88456369	0.337
Chain E	Cluster 2	ZINC35334680	0.398
		ZINC16942442	0.453
		ZINC13377881	0.234
	Cluster 3	ZINC00056472	0.247
		ZINC03847223	0.456
		ZINC93096123	0.268
	Cluster 4	ZINC00274695	0.272
		ZINC17031267	0.272
		ZINC83262622	0.315
Chain F	Cluster 5	ZINC04713297	0.359
		ZINC04904284	0.402
		ZINC08756522	0.242
	Cluster 6	ZINC64438930	0.289
		ZINC01633524	0.338

Docking Experiment

The docking algorithm worked by first generating 5000 to 15000 binding models. The binding energy were later evaluated, and those that had the most favorable energies were selected to the file shown as results (Grosdidier, A., Zoete, V., and Michielin, O., 2011). Every compound's lowest Gibbs free energy of reaction were sorted into the table (Table 3). The lowest ΔG ranged from –9.37kcal/mol of ZINC04713297 to –7.36 kcal/mol of ZINC64438930. The compounds were ranked based on the estimated ΔG indicating the spontaneity of its interaction with AChE.

Table 3. *Estimated ΔG and rank of the interactions between compounds and AChE*

Cluster	Compound	Estimated ΔG (kcal/mol)	Rank
	ZINC89638859	– 7.69	14
Cluster 1	ZINC92926669	– 9.20	2
	ZINC89639139	– 8.13	7
	ZINC88456369	– 7.65	16
Cluster 2	ZINC35334680	– 9.19	4
	ZINC16942442	– 8.90	5
	ZINC13377881	– 7.64	17
Cluster 3	ZINC00056472	– 7.72	13
	ZINC03847223	– 8.68	6
	ZINC93096123	– 7.75	12
Cluster 4	ZINC00274695	– 7.88	9
	ZINC17031267	– 7.80	11

Cluster	Compound	Estimated ΔG (kcal/mol)	Rank
Cluster 5	ZINC83262622	– 7.89	8
	ZINC04713297	– 9.37	1
	ZINC04904284	– 7.82	10
Cluster 6	ZINC08756522	– 9.20	2
	ZINC64438930	– 7.36	18
	ZINC01633524	– 7.67	15

Absorption Assessment

Swiss ADME

According to the Lipinski's Rule of 5, a compound would have a poor absorption or permeation if it had more than ten H-bond acceptors, more than five H-bond donors, a iLOGP value greater than five, or the molecular weight bigger than five hundred gram per mole (Lipinski, C.A., et al., 2001). Based on the data acquired from SwissADME (Table 4), all of the compounds passed Lipinski's Rule of 5, except ZINC13377881 of cluster 3. Therefore, 17 out of 18 compounds qualified the assessment with good absorption and ability to cross blood brain barrier.

Table 4. *Number of H-bond acceptors, donors, Log Po/w, and molecular weight of compounds*

Cluster	Compound	Num. H-bond acceptors	Num. H-bond donors	Log Po/w (iLOGP)	Molecular weight
Cluster 1	ZINC89638859	3	3	3.40	367.46 g/mol
	ZINC92926669	4	3	3.03	353.40 g/mol
	ZINC89639139	3	3	2.34	327.40 g/mol
Cluster 2	ZINC88456369	5	2	2.87	330.38 g/mol
	ZINC35334680	5	1	2.25	389.20 g/mol
	ZINC16942442	7	4	1.01	298.32 g/mol
Cluster 3	ZINC13377881	6	6	2.13	348.39 g/mol
	ZINC00056472	4	4	2.44	302.36 g/mol
	ZINC03847223	3	4	2.06	260.31 g/mol
Cluster 4	ZINC93096123	4	3	3.09	303.33 g/mol
	ZINC00274695	7	2	2.32	316.28 g/mol
	ZINC17031267	8	2	1.91	306.21 g/mol
Cluster 5	ZINC83262622	4	5	2.16	453.23 g/mol
	ZINC04713297	4	5	2.21	406.23 g/mol
	ZINC04904284	4	5	2.08	361.78 g/mol
Cluster 6	ZINC08756522	7	3	3.03	498.13 g/mol
	ZINC64438930	2	5	3.02	420.89 g/mol
	ZINC01633524	4	3	1.51	332.74 g/mol

Discussion

Virtual screening and docking experiment

AChE antibody was screened to locate structures highly affinitive to AChE. Then, a searching tool discovered compounds similar to those structures. Results from ZINCPharmer showed that compounds mimicking cluster 4 had the lowest RMSD. Although this group of compounds were most structur-

ally similar to the original cluster, they only ranked at the 9th, 11th, and 12th in the docking experiment. ZINC04713297 (–9.37kcal/mol) with a higher RMSD score showed the best inhibition efficiency, followed by ZINC92926669 (–9.20kcal/mol) and ZINC08756522 (–9.20kcal/mol). Therefore, duplicating the original cluster structure didn't guarantee the best inhibition. A slight deviation might lead to a better effect.

Absorption assessment

Last part of the research was to test the absorption and permeation of the candidate AChE inhibitors using SwissADME. Compounds' properties had to pass the Lipinski's Rule of 5 by having no more than five H-bond donors, no more than ten H-bond acceptors, Log Po/w value smaller than five, and molecular weight less than 500g/mol. Number of H-bond donor and acceptors correlate to reactivity of the compounds. If a compound had too many reacting groups, it could interact with other molecules in the blood before reaching the brain. Log Po/w and molecular weight couldn't be too high either. A high Log Po/w value would lead to poor solubility in water and fast metabolism rate. A heavy molecular weight would render a compound harder to be transported through the blood stream. While Lipinski's rule of 5 wasn't a hard cutoff line for absorption and permeation, it was a good standard to compare with. For the results, ZINC13377881 had six H-bond donors, making it potentially overly reactive. The rest seventeen compounds passed the Lipinski's Rule of 5, which made them qualified with good absorption and ability to cross the blood brain barrier.

Best candidate compounds

The docking experiment highlighted ZINC04713297, ZINC92926669 and ZINC08756522 as the three best compounds at inhibiting AChE. Since the virtual screening didn't aim for a specific pharmacophore structure, there wasn't an established mechanism that contributed to the high inhibition efficiencies of all three compounds. However, possible interactions included hydrophobic interactions, hydrogen bonding, and ionic bonds. In addition, the carbon oxygen double bonds in all three compounds resembled the acetyl group, which might facilitate the binding to the anionic site of acetylcholinesterase.

While both ZINC92926669 and ZINC08756522 had the same Gibb's free energy, ZINC08756522 weighed 498.13 g/mol, which almost violated the Lipinski's rule of 5. This left our focus on ZINC04713297 and ZINC92926669. Compared to ZINC04713297 which had the lowest Gibb's free energy of –9.37kcal/mol, ZINC92926669 featured a better absorption with lower molecular weight (353.40 g/mol) and only 3 H-bond donors. It's not reasonable to decide on the best compound without the context. ZINC92926669 had a more comprehensive performance with good absorption and inhibition. But once the compound reaches the target site, ZINC04713297 would inhibit AChE more spontaneously. Therefore, ZINC04713297 and ZINC92926669 were the two best compounds discovered from this research

Workflow evaluation

This study established the workflow combining binding site identification, virtual screening, docking experiment, and ADME assessment to identify compounds that inhibit the acetylcholinesterase. The research introduced candidate compounds as a starting point for production of effective drug in Alzheimer's Disease therapy. All the experiment were on computer, which didn't involve real chemicals. Therefore, there were no exposures to dangerous compounds. In addition, all the compound data and interactions simulations were online. So, the research required neither purchasing nor shipping of any molecules, which saved both money and time. However, due to the lack of real experiments, the actual inhibition efficiency, properties and toxicity of the candidate drugs required future studies. The next step of this research would be testing compounds through in vivo study, particularly reaction with AChE for inhibition efficiency and trial on mice for toxicity study.

Conclusion

Through this virtual screening, seventeen compounds were chosen as potential therapeutics for Alzheimer's Diseases. Overall, ZINC04713297 and ZINC92926669 from

heavy chain F of AChE antibody stood out for their outstanding inhibition efficiencies. While ZINC04713297 exhibits a more spontaneous inhibition, ZINC92926669 featured better absorption and permeation. This research recognized the necessity of testing the compounds properties in person. Before going into future drug development, candidate compounds had to be reacted with AChE for actual inhibition efficiency. It's also crucial conduct in vivo studies to research on the effect of drugs on living organism and their toxicities.

Acknowledgement

I want to thank Dr. Gabr for mentoring me throughout the research. And I really appreciate the developers of all the websites that I used, including but not limited to PocketQuery, ZINCPharmer, SwissDock, SwissADME. Finally, as far as I am aware, except for the reference, the research paper does not include any content that has been published. If the statement above doesn't hold truthful, I am willing to take all responsibilities.

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submitted 22.08.2023;
accepted for publication 20.09.2023;
published 8.10.2023

Contact: ren.jiawei@outlook.com

The European Journal of Biomedical and Life Sciences 2023, No 3
ISSN 2310-5674

PREMIER Publishing
ppublishing.org

DOI: 10.29013/EJBLS-23-3-16-20

POST-TRAUMATIC DIAPHRAGMATIC HERNIA IN A CHILD (CASE REPORT)

Rene Tandilava [1], Tengiz Tebidze [2], Tamara Bakhtadze [3], Zurab Tandilava [4]

[1] MD, PhD (Med), Associate Professor, Department of Clinical Medicine, Shota Rustaveli State University M. Iashvili Maternal and Child Central Hospital, Batumi, Georgia

[2] Department of Surgery, M. Iashvili Maternal and Child Central Hospital, Batumi, Georgia

[3] MD, PhD (Med), Assistant Professor, Department of Clinical Medicine, Shota Rustaveli State University, Director of M. Iashvili Maternal and Child Central Hospital Batumi, Georgia

[4] Department of Vascular Surgery. Klinikum Fulda, Germany

Cite: *Tandilava, R., Tebidze, T., Bakhtadze, T., Tandilava, Z. (2023). Post-Traumatic Diaphragmatic Hernia in a Child (Case Report). European Journal of Education and Applied Psychology 2023, No 3*. https://doi.org/10.29013/EJBLS-23-3-16-20

Abstract

We describe the clinical case of a 9-year-old girl operated for diaphragmatic hernia. The probable cause of the diaphragm defect in the girl is a blunt abdominal injury with the subsequent formation of a false diaphragmatic hernia with clinic of acute respiratory failure, making it difficult for early diagnosis. A complex of instrumental methods of investigation was used to visualize a traumatic diaphragmatic hernia, the most effective of which was contrast computed tomography. The discussed clinical case is interesting for its rarity. The peculiarity of the disease is marked in a specific case, and the problem of early diagnosis of traumatic diaphragmatic hernias due to the lack of early pathognomonic symptoms of this pathology is considered. We conclude that managing children who had severe injuries requires being cautious in terms of the possibility of traumatic diaphragmatic hernia formation.

Keywords: *post-traumatic diaphragmatic hernia, acute respiratory failure, surgical treatment, children*

Introduction

Diaphragmatic hernia is the displacement of abdominal organs into the thoracic cavity through natural or pathological openings in the diaphragm, as well as by protrusion of its thinned section. Diaphragmatic hernias in children are most often congenital. Acquired hernias are extremely rare and are usually the result of trauma, injury. In closed trauma to the torso, the rupture of the diaphragm is caused by a strong shock, occurs in its thinnest place.

Depending on the type of trauma or injury, a number of other points, the surgeon can meet with acute and chronic diaphragmatic hernia. It is usually false (Struchkov, V.I.,

Pugachev, A. G., 1975; Adler, D. H., 2002; De Nadai, T. R., Lopes J. C., Inaco Cirino C. C., Godinho M., Rodrigues A. J., 2015).

Abdominal organs (stomach, intestines, spleen, etc.) move into the pleural cavity through the formed wound defect, compressing the lung, shifting the mediastinum to the opposite side. This condition is commonly referred to as acute traumatic diaphragmatic hernia. Rupture of the diaphragm is usually one of the components of a combined abdominal trauma. It is less common for an isolated injury to the diaphragm to occur. In such cases, the rupture may be unrecognised. Subsequently, the abdominal organs are periodically displaced into the thoracic cavity through the diaphragm defect. There is a "chronic" post-traumatic diaphragmatic hernia. In this disease, the need for urgent surgical intervention arises only in cases of complications, which are similar in nature to those observed in false congenital diaphragmatic hernia (Bairov G. A., 1997; Falidas E., Gourgiotis S., Vlachos K., Villias C., 2015; Hajong R., Baruah A., 2012). In the diagnosis of chronic posttraumatic diaphragmatic hernia, anamnesis (indication of trauma or injury) is of great importance.

Case study

Patient E., 9 years old, was admitted to the Department of Critical Care Medicine of the M. Iashvili Central Mother and Child Hospital of Batumi at 02:16 with the diagnosis of acute respiratory failure. Complaints of dyspnoea, breathing difficulties, abdominal pain in the epigastric region and left subcostal area. From anamnesis it is known that abdominal pain appeared in the afternoon, in the evening she vomited. Later she had difficulty breathing, vomiting became more frequent, and dyspnoea appeared. The girl's general condition is severe. The severity of the condition is due to respiratory failure. Her skin was pale, her face was covered with sweat, cyanosis of the nasolabial triangle, marked tachycardia, tachypnoea, respiratory rate – 42 per minute, SPO_2–92%, HR – 130 per minute, BP – 80/55 mmHg. Chest is cylindrical, symmetrical, auscultatory – no breath sounds on the left, percussion – boxy sound. Heart tones are muffled, the boundaries of absolute and relative cardiac bluntness are shifted to the right. The abdomen is not distended, participates in the act of breathing, palpatorily soft, painful in the epigastric region, left subcostal area, symptoms of peritoneal irritation are negative.

The child underwent emergency examinations – general blood and urine analysis, biochemical blood analysis, blood electrolytes, ECG, echocardioscopy, ultrasound of abdominal cavity and chest organs. A review radiograph of the chest organs revealed mediastinal displacement to the right, horizontal fluid levels were visualised in the left side of the chest (Fig. 1).

Contrast computed tomography of the abdominal cavity and chest organs was performed. The obtained slices show a collapsed left lung, the stomach is sharply dilated, displaced into the thoracic cavity, and fluid with horizontal levels in the lumen (Fig. 2).

Additional history with the parents revealed blunt abdominal trauma five months ago. She was examined and observed by a surgeon, no damage to the abdominal cavity organs was detected.

The girl was diagnosed with diaphragmatic hernia. A laparotomy was performed as an emergency. A defect of 5.0 × 3.5 cm was found in the left dome of the diaphragm, through which the inflated stomach, omentum, part of the transverse colon and spleen prolapsed into the pleural cavity. Abdominal organs are evacuated from the pleural cavity with difficulty, especially the stomach. The diaphragm defect was sutured with separate nodular sutures. Complete haemostasis, drainage of the abdominal cavity, pleural cavity, layer-by-layer sutures on the wound.

The postoperative period was satisfactory, without complications. Drains from the abdominal and pleural cavities were removed. On the control X-ray of the chest on the left side, the lung was flattened, the heart was within normal limits.

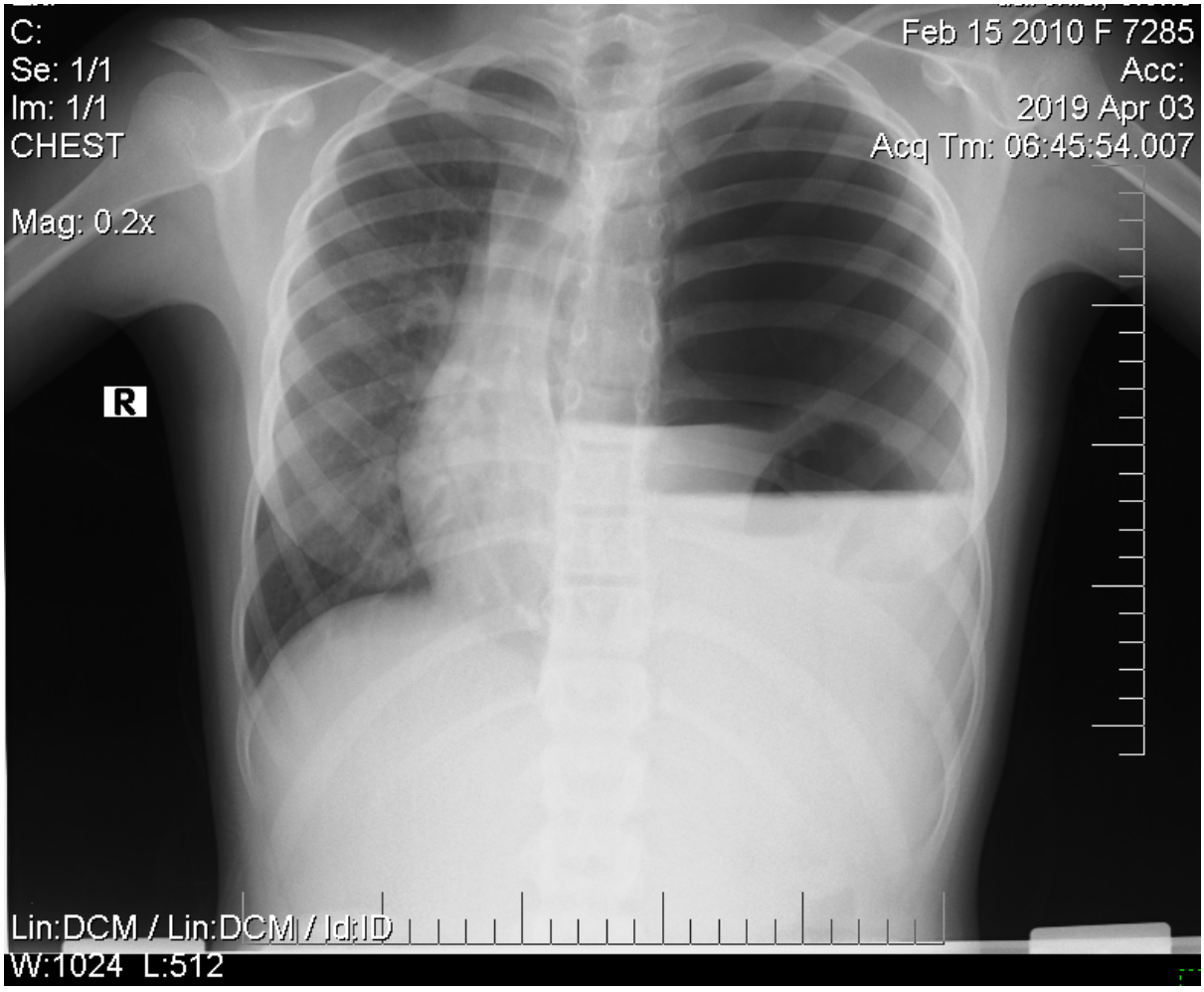
The girl was discharged from the clinic in satisfactory condition.

Discussion

The case presented here was a rather rare pathology for this age. The probable cause of the diaphragm defect in the girl was blunt abdominal trauma five months ago. After examination, the child's satisfactory general con-

dition and absence of distinct symptoms of abdominal cavity organ damage removed the suspicion of a possible diaphragm injury. Subsequently, a false diaphragmatic hernia was formed. Clinical manifestations and complications developed five months after the injury in the form of acute respiratory failure clinic, which made early diagnosis difficult. Because of the process under the guise of acute respiratory failure, the patient was admitted to the Department of Critical Care Medicine, where an examination was performed and a diaphragmatic hernia was diagnosed.

Figure 1. *Overview radiograph of the chest organs. The mediastinum is displaced to the right, horizontal fluid levels are visualised in the left side of the chest*



Standard chest radiological examination is the first diagnostic method in childhood. The main signs of diaphragm injury on review radiographs are detection of abdominal internal organs (gas bladder with horizontal fluid level is detected), elevation of the diaphragm dome on the affected side and contralateral displacement of the mediastinum, as in our 9-year-old patient.

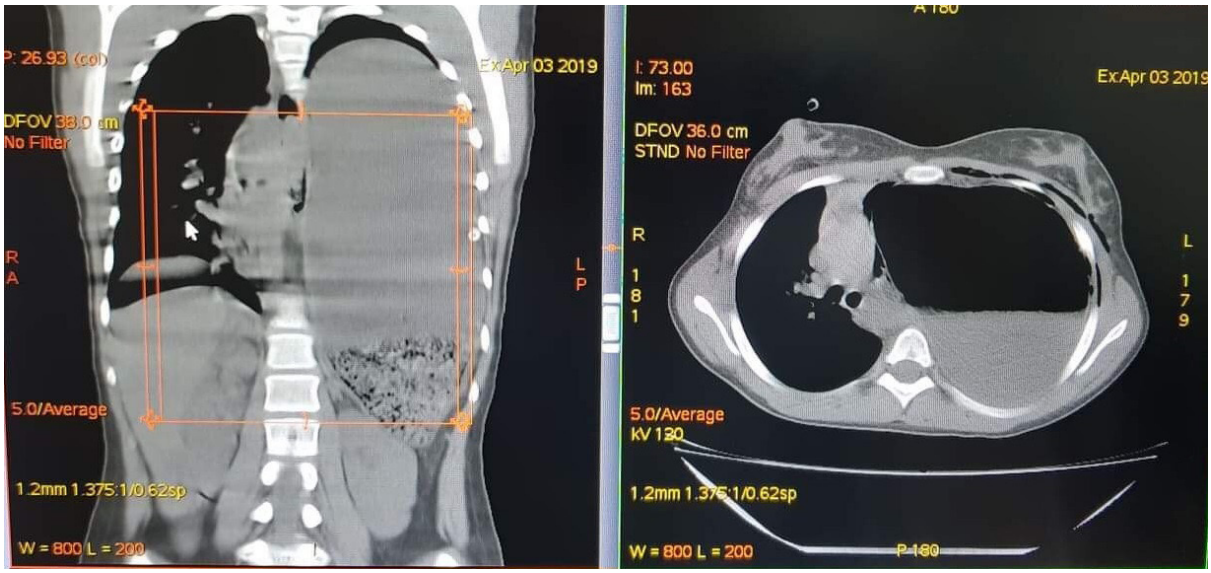
For visualisation of traumatic diaphragmatic hernia, ultrasound of abdominal and thoracic organs is also an available diagnostic method. However, it is not the main, but only an auxiliary method, which allows in the absence of computed tomography to tentatively differentiate the drained effusion in the pleural cavity from the stomach and intestinal loops.

The method of choice in the diagnosis of the disease is computed tomography of the chest and abdomen, which allows to convincingly diagnose diaphragmatic hernia, identify associated damage to the organs of the thoracic and abdominal cavity, differential diagnosis, as well as the correct choice of surgical access. Our girl, having previously conducted radiological and ultrasound studies, the final diagnosis was made after contrast

computed tomography of the chest and abdominal cavity.

The only possible method of treatment of diaphragm injuries and defects, as well as diaphragmatic hernia is surgery. The aim of surgery is to eliminate the compression syndrome (return the abdominal organs to their natural anatomical conditions) and eliminate the diaphragm defect.

Figure 2. *Contrast CT scan of the chest and abdominal cavity. Collapsed left lung is visualised, stomach is sharply dilated, displaced into the thoracic cavity, fluid with horizontal level in the lumen*



Conclusion

Patients with severe abdominal trauma in satisfactory general condition and absence of distinct symptoms from the thoracic and abdominal cavities should not dismiss the suspicion of possible diaphragm injury. Clinical manifestations and complications may develop several months after the injury, making early diagnosis difficult. Children who have suffered severe trauma should be alert to the possibility of traumatic diaphragmatic hernia formation.

Therefore, the problem of early diagnosis of traumatic diaphragmatic hernia is not completely solved, as there are no early pathognomonic symptoms of this pathology. Diagnosis requires the use of a set of instrumental methods of investigation, the most effective of which is contrast computed tomography.

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submitted 22.08.2023;
accepted for publication 20.09.2023;
published 8.10.2023

Contact: retandilava@vian.health

The European Journal of Biomedical and Life Sciences 2023, No 3
ISSN 2310-5674

PREMIER Publishing
ppublishing.org

Section 2. Life Sciences

DOI: 10.29013/EJBLS-23-3-21-27

EFFECTS OF REGULAR EXERCISE ON COGNITION IN CHILDREN

***Elton Spahiu*[1]*, Altin Erindi*[2]**

[1] Department of Physical Activity, Recreation and Tourism, Sports University of Tirana

[2] Department of Kinesiology, Sports University of Tirana

Cite: *Spahiu, E., Erindi, A. (2023). Effects of Regular Exercise on Cognition in Children. European Journal of Education and Applied Psychology 2023, No 3.* https://doi.org/10.29013/EJBLS-23-3-21-27

Abstract

Regular exercise has been demonstrated to improve children's physical and mental health in a variety of ways. However, there has been little study on the precise influence of exercise on reaction time, especially among children. The purpose of this study is to investigate the potential effect of regular physical activity on intelligence and reaction time in children. The hypothesis was that engaging in regular physical activity would positively affect cognitive abilities and reaction time. A sample of 40 boys, aged 13-15 was recruited for the purpose of the study. Subjects were divided into two groups, 20 active boys who were part of a local team and 20 inactive boys selected from a local school. Participants were subjected to anthropometric measurements effect of abstract is to summarise the available literature on the effects of regular exercise on children's response time. Participants were also subjected to an IQ Test consisting of 30 questions fitted for their age group, to measure their level of intelligence. While to gauge their ability to react in relation to time and space, subjects were subjected to an audio reaction time test (beep test) while exercising on a treadmill. The differences between the IQ test were in favour of those who didn't participate in sports. The BMI had a strong relationship with physical activity. The relationship between IQ test and reaction time was not significant, however, physical activity affected reaction time positively in both groups. The results of the study did not reveal a significant correlation between regular physical activity and intelligence. Furthermore, no significant correlation was found between physical activity and reaction time. Several factor might contribute to these results. Further research is warranted to explore potential indirect effects of physical activity on cognitive abilities, such as improvements in mood, attention, and overall well-being. In conclusion, these findings emphasize the importance of considering multiple factors when examining cognitive abilities in children and highlight the need for further research in this area.

Keywords: *intelligence, reaction time, children, physical activity, IQ test*

Introduction

Physical activity has always been part of the humankind history. Anthropological studies and historical evidence trace back the existence of such practice since the early prehistoric culture, as means of religious, social and cultural expression (US Department of Health and Human Servicesж Kig, A.C., Martin, J.E., 1994).

Nowadays, physical exercise is an absolute need for all people. With the scientific and technological development that came since the industrial revolution as well as due to the technological evolution we are passing by, we are always facing high levels of stress, anxiety, and sedentary level that compromises the health of a major part of populations around the world both in developed and developing countries.

Epidemiological data on different studies show that moderately active persons have a lower risk to have mental disorders than the sedentary ones, showing that the physical exercise exerts benefits in the physical and psychological sphere (Chodzko-Zajko, W.J., Moore, K.A. 1994; Chodzko-Zajko, W.J., 1991) and the physically active individuals probably have better cognitive skills (Elsayed, M., Ismail, A.H., Young, R.J., 1980; Van Boxtel, M.P., Langerak, K., Houx, P.J., Jolles J. 1996).

Despite of this, Heyn et al. (Heyn, P., Abreu, B.C., Ottenbacher, K.J., 2004), in a meta-analysis, have also found a significant increase in the physical and cognitive performance and a better situation in the elderly people's behavior with impairment of cognitive abilities and dementia. Confirming that practicing physical exercises can be an important protector against the cognitive decline and dementia in elderly individuals (Laurin, D., Verreault, R., Lindsay, J., Mac Pherson, K., Rockwood, K., 2001; Tomporowski, P.D., 2003).

The alert state created by the effects of the exercise is based on the Yerkes-Dodson Law (Yerkes, R.M., Dodson, J.D., 1908). Such law shows the existence of a connection between the cognitive performance and physical activity, similar to what happens to the alert level, as it could promote an initial improvement in the performance, followed by a decline after the increased alert above the resting state. So, it seems there is a clear evidence of the "U" invert relationship between cognition and performance.

Increased physical activity was related to cognitive performance for eight measurement categories, and results indicated a beneficial connection for all of these, with the exception of memory (Sibley, B.A , and Etnier, J.L., 2003).

Recent studies confirm what was observed by Levitt and Gutin (Levitt, S., Gutin, B., 1971, Salmela and Ndoye 1986, and Reilly and Smith 1986), when they investigated the cognitive and perceptive-motor performance after 6 minutes of exercise on bicycle at different intensities of theVO2 max. The individuals completed perceptive-motor tasks in the end of each intensity of the exercise; in the second step, all individuals performed arithmetic tasks on a computer. For both tasks, it was an inverted "U" behavior, with an improvement in the psychomotor performance at each increment on the workload up to 40% of the VO2max.

The aerobic fitness is connected with aspects of cognition in children but it is not explored. A meta-analysis conducted on 16 studies using true experimental designs found a positive relationship between physical activity and cognition or academic achievement in school-age children (Sibley, B.A , and Etnier, J.L., 2003). These findings suggest that fitness may be related to improvements in cognitive function, but do not show the mechanisms by which aerobic fitness may affect brain and cognition in children. Also, other factors such as the socioeconomic status may contribute to children's physical activity participation, making it difficult to determine the influence of fitness, on cognitive function during the early stages of the human life span.

Method

The aim of the present study was to investigate the effect of physical activity on reaction time in children. 40 boys of six to eight grade (aged 13 to 15 years) were selected for the study after receiving approval from the Ethics Committee and informed consent on the part of parents. The study was conducted in accordance with the Declaration of Helsinki, and the protocol approved by the

Ethics Committee of the Sports University of Tirana. The subjects were divided into two groups. The first group consisted of physically active boys who engaged in sports training for 2 hours every day as members of a local football team. The second group consisted of 20 inactive boys selected from a local secondary school and did not participate in any kind of sports activity. First, participants of both groups were subjected to anthropometric measurements. Height of the participants was measured barefoot to the nearest 1 mm. Weight of the participants was measured in without shoes and underwear with an electronic scale to the nearest 0.1 kg. BMI was calculated using a computer software as body weight in kilograms divided by the square of height in meters, and the percentage of body fat was measured with a fat caliper. Participants were also subjected to an IQ Test consisting of 30 questions fitted for their age group, to measure their level of intelligence. While to gauge their ability to react in relation to time and space, subjects were subjected to an audio reaction time test (beep test) while exercising on a treadmill. Subjects were asked to press a key every time they heard a "beep" sound. The Bruce Treadmill test protocol was used to measure at what point during the test, participants had their best reaction time. Subjects were made to run on a treadmill till to exhaustion. At timed stages during the test, the speed (km/hr) and grade of slope (%) of the treadmill were increased. At stage 1, the treadmill's speed was set to 2.74 km/hr and the slope grade was 10%. 3 minutes into the test, the speed was adjusted to 4.02 km/hr and the slope to 12%, and after 6 minutes into the test, speed increased to 5.47 km/hr and the slope to 14%. When children were not able to continue the test, normally this should be within 9 and 15 minutes of the test (Bruce, R.A., 1972), the assistant stopped the stopwatch and the test was ended. VO2 max was calculated using the formula as follows:

$VO2\ max = 14.8 - (1.379 \times T) + (0.451 \times \times T^2) - (0.012 \times T^3)$

"T" is the total time of the test expressed in minutes and fractions of a minute.

Results

More than 30 percent (7 boys) of the 20 inactive boys didn't fulfill the entire test due to the fact that they were exhausted. The BMI had a strong relationship with the outdoors Physical Activity and the difference between the active and inactive for the BMI was significant ($p < 0.01$). The BMI was of 26 kg/m^2 for the inactive children and 18.6 kg/m^2 for the active children. The IQ tests showed a percentage of 54% for the inactive children of the right answer and a 48 percent for the active children statistically not significant ($p < 0.01$). BMI and IQ results for both groups are presented in (Table 1 and Table 2).

Table 1. *BMI and IQ Test results of the Active Children*

Name/Surname	Weight/kg	Height/m	BMI	Timeof training/month	IQ Test results Percentage %
Average	**49.84**	**1.60**	**18.45**	**24.00**	**48.17**
SD	**9.9191**	**0.0886**	**2.2**	**0.00**	**7.9215**

Table 2. *BMI and IQ Test Results of the Inactive Children*

Name/Surname	Weight/kg	Height/m	BMI	VO2max	IQ Test results Percentage %
Average	**73.365**	**1.6715**	**26.29**	**18.848**	**54.5**
SD	**5.549**	**0.0798**	**1.521**	**1.992**	**5.4**

The results of the reaction time before the exercise were of 473 m/s for the active children and of 408 m/s for the inactive children, the difference was statistically significant ($p < < 0.01$). The reaction time was of nearly the same values till the end of the test, the differences were not significant ($p < 0.01$). Reaction time results for both groups are presented in (Table 3 and Table 4).

Table 3. *Reaction Time Results of the Active Children*

	Cardiac Frequency	Reac time before	Cardiac Frequency	Reac time 2	Cardiac Frequency	Reac time 3	Cardiac Frequency	Reac time 4	Cardiac Frequency	Reac time 5
Average	86.85	0.443	110.5	0.496	146.65	0.45	162.1	0.502	190.85	0.406
SD	3.93	0.086	7.59	0.12	11.5	0.08	14.17	0.11	12.12	0.05

Table 4. *Reaction Time Results of the Inactive Children*

	Cardiac Frequency	Reac time before	Cardiac Frequency	Reac time 2	Cardiac Frequency	Reac time 3	Cardiac Frequency	Reac time 4	Cardiac Frequency	Reac time 5
Average	85.6	0.431	123.15	0.498	161.05	0.44	177.85	0.502	197.85	0.409
SD	2.703	0.045	7.71	0.048	7.89	0.04	7.25	0.06	3.82	0.053

The correlation between cardiac frequency and reaction time for both groups is presented in (Figure 1 and Figure 2).

Figure 1. *Active children reaction time and Cardiac Frequency*

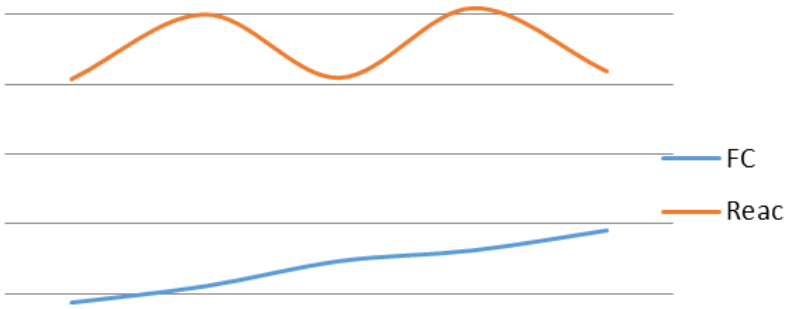
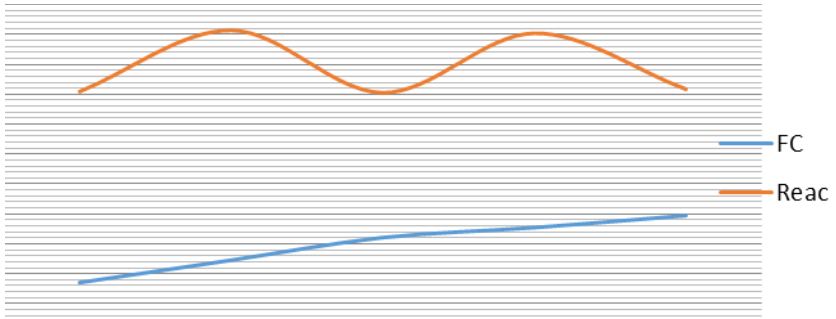


Figure 2. *Inactive children reaction time and Cardiac Frequency*



Discussion

The study of the relationship between physical fitness, and more specifically aerobic fitness, and cognition dates back several decades. The questions of whether or not such direct relationship does indeed exist, to what extent, and what variables make this connection the strongest have been the subject of many studies.

For the purposes of this paper, it is important to define exercise and cognition. According to the Webster's online dictionary the definition of exercise is: "the bodily exertion for the sake of developing and maintaining physical fitness" (The Journals of Gerontology Series A: 2003). Many different definitions of exercise do exist though. Another commonly used definition from Webster's dictio-

nary: "something that is performed or practiced in order to develop, improve, or display a specific power" (The Journals of Gerontology Series A: 2003). This definition does not include physical fitness, but leaves it open by using the word something.

For this paper, the first meaning will be the one utilized here. Exercise and fitness training are used interchangeably, along with some other substitutes in this paper. All the descriptions are in line with the above-presented definition of exercise. Although different type of cognition tests reviewed in this paper test various parts of the information processing, this definition sufficiently addresses the meaning of cognition used for the purposes of this paper.

Other researchers have, either explicitly or implicitly, assumed that fitness effects would be most likely observed in tasks such as simple reaction time or finger tapping, which presumably tap low-level central nervous system function uncontaminated by subject strategies or high-level cognition (Dustman, R.E., Ruhling, R.O., Russell, E.M., Shearer, D.E., Bonekat, W., Shigeoka, J.W., Wood, J.S. & Bradford D.C., 1984). This theoretical hypothesis is known as the speed hypothesis. Still, other researchers have suggested that fitness effects might be most readily observed for visuospatial tasks (Stones, M., & Kozma, A., 1989), because visuospatial processes have been demonstrated to be more susceptible to ageing than verbal skills. This is termed as the visuospatial hypothesis.

Finally, Kramer et al. (Kramer, A.F., Hahn S., Cohen N.J., Banich M.T., McAuley E., Harrison C.R., Chason J., Vakil E., Bardell L., Boileau R.A., & Colcombe A., 1999) argue that better fitness would be reflected in enhancements in executive-control processes such as coordination, inhibition, scheduling, planning, and working memory. Executive-control processes and the brain areas that support them have shown disproportionate sensitivity to aging. This is the executive-control hypothesis.

The action of the physical exercise on the cognitive function can be direct or indirect depending on age or other causes. The mechanisms that actuate in a direct way increasing the velocity of the cognitive processing would be an improvement in the cerebral circulation and in the synthesis and degradation of neurotransmitters in the brain. Besides these direct mechanisms, there are other mechanisms such as a decreasing blood pressure, decrease in the LDL, etc., that seem to have an indirect action, improving this function. Added to an improvement in the general function capability it has a reflection as an increase in the quality of life. The researchers have suggested some mechanisms which are responsible by the mediation of the effects of the exercising on the cognitive functions. It is believed that the physical exercise could increase the blood flow into the brain, consequently the Oxygenation, making an improvement in the cognitive function. Another hypothesis that has been formulated is about the effects of the oxidant stress on the CNS, because the aerobic physical exercises maybe increases the activity of the oxidant enzymes, as in other tissues such as the skeletal muscle, increasing the defense against the damages caused by oxygen specimens as Radák et al show in their article (Radák, Z., Kaneko, T., Tahara, S., Nakamoto, H., Pucsok, J., Sasvári, M., et al., 2001).

The hypothesis that the physical exercise per se increases the release of several neurotransmitters, such as the nor epinephrine and its precursors (Ebert, M.H., Post, R.M., Goodwin, F.K., 1972; Strüder, H.K., Weicker, H., 2001), in the serotonin (Bortz, W.M. 2nd, Angwin, P., Mefford, I.N., Boarder, M.R., Noyce, N., Barchas, J.D., 1981; Schuit, A.J., Feskens, E.J., Launer, L.J., Kromhout, D., 2001) and β-endorphin (Etnier, J.L., Salazar, W., Landers, D.M., Petruzzello, S.J., Han, M., Nowell, P., 1997) blood concentration after an acute exercise session, cannot be rejected.

Our data also suggest that there is more research necessary to actually do an examination of brain structure and functioning, and the impact of interventions such as children fitness and cognitive training. Although many theories exist on how to approach the study of correlation between cognition and exercise, a formation of one main theory will facilitate better results in the future. Nevertheless, theoretical accounts of fitness effects on human cognition can only rarely be neatly and precisely fit into the processing components of existing theories.

The differences between the IQ test were of in the favour of those that don't participate in sports. The BMI had a strong relationship with the outdoors Physical Activity. The relationship with the IQ test and with the reaction time was not significant, however the physical activity affected the reaction time positively in both groups. The results of reaction time during the Treadmill protocol showed that it improves at the pulse of 146 bpm to the active children and at 155 bpm to the inactive children. The results of the study did not reveal a significant correlation between regular physical activity and intelligence. Furthermore, no significant correlation was found between physical activity and reaction time. Several factor might contribute to these results. It is possible that the duration and intensity of the physical activity was not sufficient to elicit cognitive improvements. Additionally, other factors such as genetics, socio-economic status and educational opportunities may play a more significant role in determining intelligence and reaction time in children. Further research is warranted to explore potential indirect effects of physical activity on cognitive abilities, such as improvements in mood, attention, and overall well-being. In conclusion, these findings emphasize the importance of considering multiple factors when examining cognitive abilities in children and highlight the need for further research in this area.

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submitted 22.08.2023;
accepted for publication 20.09.2023;
published 8.10.2023

Contact: espahiu@ust.edu.al

The European Journal of Biomedical and Life Sciences 2023, No 3
ISSN 2310-5674

PREMIER Publishing
ppublishing.org

Section 3. Preventive Medicine

DOI: 10.29013/EJBLS-23-3-28-40

FACTORS ASSOCIATED WITH COGNITIVE FUNCTION IN THE ELDERLY: EVIDENCE FROM NHANES 2011–2014

Steven Wang [1], Xin Yang [2]

[1] Whippany Park High School, 165 Whippany Rd, Whippany, NJ 07981

[2] Ph.D., The University of Alabama, 201 Bidgood Hall, Tuscaloosa, AL 35406

Cite: *Steven Wang, Xin Yang. (2023). Factors Associated With Cognitive Function in the Elderly: Evidence From Nhanes 2011–2014. European Journal of Education and Applied Psychology 2023, No 3.* https://doi.org/10.29013/EJBLS-23-3-28-40

Abstract

Introduction: With global life expectancy on the rise, cognitive impairment increasingly strains individuals and healthcare systems due to age being a primary risk factor. This study seeks to elucidate the influence of age on other risk factors associated with cognitive impairment.

Methods: To assess the risk factors of cognitive impairment, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) from 2011–2014, totaling 2569 participants. By conducting multivariable logistic regression models and stratifying participants based on age (≤ 70 years old; > 70 years old), we further investigated the relationship between several risk factors and cognitive function status. Cognitive function status was defined by a Z-score (cognitive impairment defined as a z-score < −1), consisting of four cognitive tests (CERAD-WL, CERAD-DR, AFT, and DSST).

Results: The study found that participants over 70, particularly those of Mexican American, non-Hispanic Black, and multi-racial backgrounds, who were unmarried with lower education and family income levels, faced higher risks of cognitive impairment. As participant age increased, many risk factors diminished, though some, like being overweight and belonging to non-Hispanic White or multi-racial groups, remained exceptions.

Conclusion: This research studied age's significant impact on cognitive function development. Our findings can guide policy-making for cognitive impairment, benefiting both patients and healthcare professionals. Future research should explore why risk factors in non-Hispanic Whites aren't reduced with age and explore other potential risk factors that are not available in this study.

Keywords: *cognitive impairment, cognitive function status, cross-sectional, logistic regression, body mass index (BMI), risk factor*

Introduction

Cognitive impairment is when an aging individual has a cognitive decline greater than expected, ranging from minor problems with cognition (mild cognitive impairment) to severe problems with cognition (dementia). Individuals affected by cognitive impairment tend to have poorer quality of life (Lawson et al. 2014) and shorter life expectancy. Men with mild cognitive impairment can expect to live for 3.5 years, and women can expect to live for 4.2 years (Hale et al. 2020).

Over 55.7 million Americans were aged 65 and over in 2020, representing 17% of the US population; with this number projected to grow to 22% by 2040 (Administration of Community Living, 2022) With the rapid growth of the older population, an increasingly greater number of individuals will be at risk of developing cognitive impairment. At an average age of 70, approximately two out of three Americans develop cognitive impairment (Hale et al. 2020). Cognitive impairment is putting an increasingly heavy burden on both healthcare systems and families, with total payments for individuals with dementia projected to reach $345 billion in 2023 (2023 Alzheimer's Disease Facts and Figures, 2023).

Numerous studies have been conducted on the risk factors of cognitive impairment, including demographic (Díaz-Venegas et al. 2016; Chen and Cao 2020; Bloomberg et al. 2023), nutritional (Huang et al. 2021; Shen et al. 2023), and medical risk factors (Feinkohl et al. 2018). Obesity has been shown to be positively associated with cognitive impairment, with each 1 kg/m^2 increment in body mass index (BMI) associated with a 3% increased prevalence of cognitive impairment (Feinkohl et al. 2018). Other studies have found that older age, lower education level, lower income, lower social participation, no spouse, worse psychological well-being, being female, and less fruit/vegetable consumption increase the risk of cognitive impairment (Zhang et al. 2019; Aartsen et al. 2002). Some studies have found that poverty is associated with an increased risk of developing cognitive impairment (Chen and Cao 2020). A few studies have studied the association of country of residence on risk factors such as gender and education concerning cognitive function status. Education was found to be less accessible to women in middle-income countries compared to high-income countries, which is associated with a higher risk of developing cognitive impairment (Bloomberg et al. 2023). Although risk factors of cognitive impairment have been intensively studied, the literature is scarce on the effects of risk factors conditioned on a demographic variable, particularly age. Cognition deteriorates disproportionally as age increases. For this reason, cognitive impairment most often develops at age 70 or older (Aartsen et al. 2002). Therefore, the effects of the risk factors on cognitive impairment may differ significantly among different age groups.

The purpose of this study is to observe whether age influences the association between risk factors — such as gender, age, obesity, education, race, marital status, and annual family income — and cognitive function status. Since age has already been reported as a significant risk factor for cognitive impairment (Murman 2015), further research on how age affects other risk factors is necessary. Additionally, many studies have assessed cognitive function status by combining four cognitive tests (CERAD-WL, CERAD-DR, DSST, AFT), but very few have examined risk factors for each test individually. This study aims to contribute to the literature on the risk factors of cognitive impairment and provide insights that can help inform policies that benefit patients and healthcare providers. We hypothesized that between age groups, many risk factors would have a significant difference in effect on the development of cognitive impairment.

Methods

Datasets and Participants

We extracted data from the National Health and Nutrition Examination Survey (NHANES) between 2011 and 2014 since cognitive functioning test data was only available for these two cycles. The NHANES datasets are based on multistage, stratified surveys with a probability cluster design, and conducted by the National Center of Health Statistics of the Centers for Disease Control and Prevention (Huang et al. 2021). In this study, we selected a population aged 60 and over (n = 3472), excluding participants with no records of cognitive function status (559) or other covariates (344), leaving a final sample of 2569.

Outcomes

To assess cognitive function status, we used four cognitive tests: The Consortium to Establish a Registry for Alzheimer's Disease — Word Learning (CERAD-WL), Delayed Recall (CERAD-DR) (Fillenbaum et al. 2008), Digit Symbol Substitution Test (DSST) (Jaeger 2018) and Animal Fluency Test (AFT) (Canning et al. 2004). The CERAD-WL and CERAD-DR tests assess delayed and immediate learning for new verbal information. The CERAD-WL test consists of three learning tests, in which participants are presented with ten unrelated words on a computer one at a time. Participants are prompted to read aloud the words as they appear. Immediately after, participants try to recall as many of the words as possible, with each correct recall earning a point. This learning test is repeated two more times, with only the order of the words changing each time. The CERAD-DR test is completed after the DSST and AFT are completed (8–10 minutes after the start of the learning tests). Participants try to recall words from the learning tests, with each correct recall earning a point. The DSST assesses sustained attention, processing speed, and working memory. Participants are given a paper test with 133 boxes, each of which contains a number from 1 to 9. The test has a key containing 9 numbers paired with symbols, and participants are given two minutes to copy the corresponding symbols in each of the 133 boxes. Each correct match earns a point. The AFT evaluates categorical verbal fluency. Participants are given one minute to name as many animals as possible, with each animal earning a point (Sebaldt et al. 2009). We used a Z-score as a total cognitive function status score, consisting of the CERAD-WL test, CERAD-DR test, AFT, and DSST. Z-score was calculated with $Z = (x-u)/\sigma$, where x was the total number of points from the four tests, u was the population mean, and σ was the standard deviation. A Z-score of < -1 indicated that the participant had cognitive impairment (Wirth et al. 2017; Frith et al. 2018).

Covariates

Gender, age, education, race, marital status, and annual family income data were all obtained from household interviews. BMI data was measured in a NHANES Mobile Examination Center (MEC). Age was categorized into two groups: participants aged 70 and under and participants over 70. Education was categorized by each participant's highest grade or degree, with the four levels being less than high school, high school, college (or an AA degree), and college graduate. Race was categorized as Mexican American, non-Hispanic white, non-Hispanic black, and other race/multi-racial. Marital status was classified as married and not currently married (widowed, divorced, separated, or never married). Annual family income was divided into under $35,000, from $35,000 to $75,000, and over $75,000. Obesity was categorized according to the CDC's definitions of healthy weight (BMI from 18.5 to < 25), overweight (BMI from 25.0 to < 30), and obese (BMI over 30).

Statistical Analysis

All categorical variables were presented as frequencies, weighted percentages, and standard errors (SE). Chi-square tests were used to determine the association between covariates and cognitive function status. To assess the strength of the association between covariates and outcomes, we conducted weighted logistic regression models, where crude models include only one variable at one time and adjusted models include all variables. The results of the logistic regression models were reported as odds ratios (OR), 95% confidence intervals (CI), and p-values. We conducted additional logistic regression models for each of the four cognitive tests to assess the possible relationships between individual tests and covariates. We also employed a stratified logistic regression analysis to assess whether each covariate has a different effect on cognitive function status when separated by participants aged 70 and under and participants over 70. A p-value less than .05 was considered statistically significant. All analyses were conducted using R (http://www.r-project.org; version 4.3.1, The R Foundation).

Results

We extracted data from two continuous NHANES cycles (2011–2012 and 2013–2014), totaling 2569 participants after excluding participants with incomplete interviews. Table 1 shows the number and proportions of respondents grouped by cognitive function status. The percentage of respondents

over 70 years old with cognitive impairment (69.1%) was significantly higher than those without (35.1%), with a p-value of less than .001. Similarly, the percentage of respondents with an education level of high school (26.1%) or less (45.6%) was higher than those without (21.2% and 12.1% respectively), with a p-value of less than .001. Conversely, the percentage of cognitively impaired non-Hispanic White Americans (54.2%) was much less than those without (83.1%), with a p-value of less than .001. The percentage of not currently married participants with cognitive impairment (53.6%) was much greater than those without (33.9%), with a p-value of less than .001. Likewise, the percentage of respondents with an annual family income of under $35,000 (66.8%) was significantly greater than those without (32.4%), with a p-value of less than .001. In summary, compared to normal participants, participants with cognitive impairment were more likely to be over 70 years old, not non-Hispanic White, and not currently married. Participants with cognitive impairment were also more likely to have an education level less than high school and an annual family income under $35,000. Neither the participants' gender nor obesity was significantly associated with cognitive function status.

Table 1. *Sample characteristics by cognitive function status*

	Normal		Impaired		p-value
	n(%)	SE	n(%)	SE	
Gender					
Male	1010(45.6)	1.1%	221(42.5)	2.2%	0.277
Female	1139(54.4)	1.1%	199(57.5)	2.2%	
Age					
70 and Under	1341(64.9)	1.4%	166(30.9)	3.7%	<0.001
Over 70	808(35.1)	1.4%	254(69.1)	3.7%	
Obesity					
Healthy	568(25.4)	1.4%	129(32.8)	2.7%	
Overweight	763(36.8)	1.2%	135(31.8)	2.7%	0.06
Obese	818(37.8)	1.4%	156(35.4)	3.4%	
Education					
Less than HS	378(12.1)	1.4%	249(45.6)	4.1%	
HS/GED	514(21.2)	1.4%	86(26.1)	3.2%	<0.001
Some College/AA	685(33.3)	1.3%	52(17.8)	2.8%	
College Grad or above	572(33.4)	2.3%	33(10.5)	2.5%	
Race					
Mexican American	163(2.7)	0.6%	55(9.3)	2.6%	
Non-Hispanic Black	468(7.0)	1.0%	136(19.9)	3.3%	<0.001
Non-Hispanic White	1141(83.1)	1.5%	124(54.2)	4.8%	
Other Race/Multi-Racial	377(7.3)	0.8%	105(16.6)	2.2%	
Marital Status					
Married	1266(66.1)	1.1%	189(46.4)	3.1%	<0.001
Not Currently Married	883(33.9)	1.1%	231(53.6)	3.1%	
Annual Family Income					
Under $35.000	942(32.4)	2.2%	299(66.8)	4.3%	
$35,000-$75.000	686(35.7)	2.0%	82(22.4)	3.4%	<0.001
Over $75.000	521(31.9)	2.4%	39(10.8)	2.4%	

Abbreviations: SE, standard error; HS, high school graduate; GED, General Educational Development diploma; AA, associate's degree

To investigate the relationship between cognitive function status and risk factors such as gender, age, obesity, education, race, marital status, and annual family income, we created a crude model (univariate logistic regression) and an adjusted model (multivariate logistic regression). Table 2 shows the association between cognitive function status and various risk factors. We found that age was significantly associated with cognitive function status in both the crude and adjusted models. The odds of developing cognitive impairment among participants over 70 was 4.15 times of those under 70 in the crude model (OR = 4.15, 95% CI (2.83.6.09), p < .001) and 4.77 after adjusting for other covariates (OR = 4.77, 95% CI (3.05.7.46), p < .001). Obesity was also significantly associated with cognitive function status in both crude and adjusted models. Overweight participants were 33% less likely to develop cognitive impairment compared to participants with a healthy weight in the crude model (OR = 0.67, 95% CI (0.49.0.91), p = .015) and 36% less likely to after adjusting for other covariates (OR = 0.64, 95% CI (0.46, 0.89), p = .015). The education level of the participants was significantly associated with cognitive function status, with higher levels of education having lower odds of cognitive impairment. Compared with an education level of less than high school, participants with an higher education level were less likely to have cognitive impairment based on individual tests, such as high school (OR = 0.33, 95% CI (0.23,0.47), p < .001), college (OR = 0.14, 95% CI (0.10,0.20), p < .001) and college graduate (OR = 0.08, 95% CI (0.05,0.14), p < .001) all had lower odds of developing cognitive impairment. We observed similar results after adjusting for covariates (high school: OR = 0.46, 95% CI (0.31,0.67), p = =.001; college: OR = 0.24, 95% CI (0.16,0.36), p < .001; college graduate: OR = 0.17, 95% CI (0.11,0.26), p < .001). Compared to Mexican American participants, non-Hispanic White participants were 81% less likely to develop cognitive impairment in the crude model (OR = 0.19, 95% CI (0.13,0.27), p < .001) and 76% less likely after adjusting for other covariates (OR = 0.24, 95% CI (0.16,0.35), p < .001). Participants who were not currently married had 2.26 times the odds of developing cognitive impairment compared with married participants in the crude model (OR = 2.26, 95% CI (1.76,2.90), p < .001) and 1.38 after adjusting for other covariates (OR = 1.38, 95% CI (1.02,1.87), p = .05). Annual family income was also significantly associated with cognitive function status in both models. Compared with participants with an annual family income under $35,000, participants with an annual family income between $35,000 and $75,000 (OR = = 0.30, 95% CI (0.20,0.47), p < .001) and over $75,000 (OR = 0.16, 95% CI (0.09,0.31), p < .001) had lower odds of developing cognitive impairment. We observed similar results after adjusting for covariates ($35,000 to $75,000: OR = 0.51, 95% CI (0.32,0.80), p = .009; over $75,000: OR = 0.45, 95% CI (0.25,0.83), p = .019 respectively).

Table 2. *Association between risk factors and cognitive function status by logistic regression models*

	Crude model (univariable)		Adjusted model (multivariable)	
	OR(LCI, UCI)	p-value	OR(LCI, UCI)	p-value
Gender				
Male			Ref.	
Female	1.14(0.91,1.42)	0.278	0.82(0.64,1.05)	0.139
Age				
70 and Under			Ref.	
Over 70	4.15(2.83,6.09)	<0.001	4.77(3.05,7.46)	<0.001
Obesity				
Healthy			Ref.	
Overweight	0.67(0.49,0.91)	0.015	0.64(0.46,0.89)	0.015

	Crude model (univariable)		Adjusted model (multivariable)	
	OR(LCI, UCI)	p-value	OR(LCI, UCI)	p-value
Obese	0.72(0.50,1.06)	0.107	0.67(0.46,0.98)	0.051
Education				
Less than HS			Ref.	
HS/GED	0.33(0.23,0.47)	<0.001	0.46(0.31,0.67)	0.001
Some College/AA	0.14(0.10,0.20)	<0.001	0.24(0.16,0.36)	<0.001
College Grad or above	0.08(0.05,0.14)	<0.001	0.17(0.11,0.26)	<0.001
Race				
Mexican American			Ref.	
Non-Hispanic Black	0.82(0.50,1.33)	0.418	0.90(0.55,1.46)	0.675
Non-Hispanic White	0.19(0.13,0.27)	<0.001	0.24(0.16,0.35)	<0.001
Other Race/Multi-Racial	0.65(0.39,1.08)	0.111	0.81(0.49,1.33)	0.409
Marital Status				
Married			Ref.	
Not Currently Married	2.26(1.76,2.90)	<0.001	1.38(1.02,1.87)	0.05
Annual Family Income				
Under $35,000			Ref.	
$35,000-$75,000	0.30(0.20,0.47)	<0.001	0.51(0.32,0.80)	0.009
Over $75,000	0.16(0.09,0.31)	<0.001	0.45(0.25,0.83)	0.019

Note: The crude model includes only the predictor variable, the adjusted model includes the predictor variable while factoring in all other covariates

Abbreviations: Ref., reference category of a predictor variable; OR, odds ratio of developing cognitive impairment; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

Table 3 shows the association between the four cognitive tests (CERAD-WL, CERAD-DR, DSST, AFT) used to determine cognitive function status and risk factors. We observed that gender, age, education, race, marital status, and annual family income had a significant association with at least one of the four cognitive tests, while obesity did not. Compared to male participants, female participants were 48% less likely to develop cognitive impцairment as assessed by the CERAD-DR (OR = 0.52, 95% CI (0.42,0.65), p < .001) and 36% less likely to as assessed by the DSST (OR = 0.64, 95% CI (0.49,0.83), p = .003). Age had a significant association with all four tests. When compared to participants 70 and under, participants over 70 had much higher odds of developing cognitive impairment(CERAD-WL: OR = 3.63, 95% CI (2.81,4.70), p < .001; CERAD-DR: OR = =3.08, 95% CI (2.34,4.06), p < .001; DSST: OR = 4.57, 95% CI (3.11,6.72), p < .001; AFT: OR = 2.71, 95% CI (2.09,3.51), p < .001). Compared with an education level of less than high school, participants with an education level of high school (CERAD-WL: OR = 0.62, 95% CI (0.42,0.92), p = .027; DSST: OR = 0.37, 95% CI (0.28,0.48), p < .001), college (CERAD-WL: OR = 0.40, 95% CI (0.23,0.68), p = .003; CERAD-DR: OR = 0.57, 95% CI (0.38,0.85), p = .013; DSST: OR = 0.20, 95% CI (0.15,0.27), p < .001; AFT: OR = 0.43, 95% CI (0.31,0.61), p < .001) and college graduate (CERAD-WL: OR = 0.28, 95% CI (0.16,0.48), p < .001; DSST: OR = 0.10, 95% CI (0.07,0.15), p < .001; AFT: OR = 0.29, 95% CI (0.21,0.41), p < .001) all had lower odds of developing cognitive impairment. Compared to Mexican American participants, non-Hispanic White (CERAD-WL: OR = 0.63, 95% CI (0.42,0.93), p = .032; DSST: OR = 0.22, 95% CI (0.15,0.32), p < < .001) and Other Race/Multi-Racial (DSST: OR = 0.61, 95% CI (0.41,0.89), p = .019) participants had lower odds of developing cognitive impairment shown by the CERAD-WL and DSST, but non-Hispanic Black (OR =

Table 3. *Logistic regression models for individual tests*

	CERAD-WL		CERAD-DR		DSST		AFT	
	OR(LCI, UCI)	p-value	OR(LCI, UCI)	p-value	OR(LCI, UCI)	p-value	OR(LCI, UCI)	p-value
Gender								
Male	Ref.							
Female	0.82(0.51,1.33)	0.428	0.52(0.42,0.65)	<0.001	0.64(0.49,0.83)	0.003	0.90(0.65,1.24)	0.521
Age								
70 and Under	Ref.							
Over 70	3.63(2.81,4.70)	<0.001	3.08(2.34,4.06)	<0.001	4.57(3.11,6.72)	<0.001	2.71(2.09,3.51)	<0.001
Obesity								
Healthy	Ref.							
Overweight	0.90(0.60,1.36)	0.633	1.06(0.77,1.46)	0.718	0.72(0.53,0.98)	0.051	0.82(0.63,1.07)	0.159
Obese	0.79(0.57,1.09)	0.169	0.84(0.60,1.17)	0.309	0.74(0.47,1.19)	0.231	0.77(0.55,1.08)	0.140
Education								
Less than HS	Ref.							
HS/GED	0.62(0.42,0.92)	0.027	0.86(0.52,1.41)	0.554	0.37(0.28,0.48)	<0.001	0.83(0.56,1.21)	0.344
Some College/AA	0.40(0.23,0.68)	0.003	0.57(0.38,0.85)	0.013	0.20(0.15,0.27)	<0.001	0.43(0.31,0.61)	<0.001
College Grad or above	0.28(0.16,0.48)	<0.001	0.58(0.35,0.97)	0.052	0.10(0.07,0.15)	<0.001	0.29(0.21,0.41)	<0.001
Race								
Mexican American	Ref.							
Non-Hispanic Black	0.78(0.53,1.14)	0.213	0.86(0.58,1.28)	0.48	1.06(0.77,1.47)	0.72	2.20(1.49,3.23)	<0.001
Non-Hispanic White	0.63(0.42,0.93)	0.032	0.73(0.51,1.05)	0.111	0.22(0.15,0.32)	<0.001	0.66(0.46,0.95)	0.038
Other Race/Multi-Racial	1.02(0.72,1.45)	0.896	0.69(0.46,1.04)	0.093	0.61(0.41,0.89)	0.019	1.69(1.16,2.47)	0.014
Marital Status								
Married	Ref.							
Not Currently Married	1.29(1.01,1.65)	0.057	0.99(0.75,1.32)	0.97	1.35(1.06,1.72)	0.023	1.04(0.71,1.54)	0.833
Annual Family Income								
Under $35,000	Ref.							
$35,000-$75,000	0.65(0.48,0.87)	0.01	0.56(0.42,0.76)	0.001	0.46(0.34,0.62)	<0.001	0.83(0.58,1.18)	0.31
Over $75,000	0.65(0.43,0.99)	0.06	0.52(0.36,0.74)	0.002	0.33(0.18,0.61)	0.002	0.67(0.46,0.99)	0.056

Note: These models include the predictor variable while factoring in all other covariates

= 2.20, 95% CI (1.49,3.23), p < .001) and Other Race/Multi-Racial (OR = 1.69, 95% CI (1.16,2.47), p = .014) participants were found to have greater odds of developing cognitive impairment in the AFT, with the exception of non-Hispanic White (OR = 0.66, 95% CI (0.46,0.95), p = .038) participants. Participants who were not currently married had 1.35 times the odds of developing cognitive impairment compared with married participants (OR = 1.35, 95% CI (1.06,1.72), p = = .023) as assessed by the DSST. Finally, compared with participants with an annual family income under $35,000, participants with an annual family income between $35,000 and $75,000 (CERAD-WL: OR = 0.65, 95% CI (0.48,0.87), p = .01; CERAD-DR: OR = 0.56, 95% CI (0.42,0.76), p = .001; DSST: OR = = 0.46, 95% CI (0.34,0.62), p < .001) and over $75,000 (CERAD-DR: OR = 0.52, 95% CI (0.36,0.74), p = .002; DSST: OR = 0.33, 95% CI (0.18,0.61), p = .002) all had lower odds of developing cognitive impairment as assessed by the CERAD-WL, CERAD-DR and DSST.

Abbreviations: Ref., reference category of a predictor variable; OR, odds ratio of developing cognitive impairment; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval.

To investigate whether age moderates the association between other risk factors and cognitive function status, we conducted a stratified multiple logistic regression analysis for participants aged 70 and under and participants over 70. Table 4 shows the association between cognitive function status and risk factors stratified by age (≤ 70 and > 70). Overall, several risk factors differed significantly in ORs between the two age groups. Obesity was not significantly associated with cognitive function status in participants 70 and under. However, among participants over 70, being overweight (OR = 0.6, 95% CI (0.39,0.93), p = .033) or obese (OR = 0.51, 95% CI (0.31,0.87), p = .021) was significantly associated with lower odds of developing cognitive impairment. Higher education levels were protective for CF impairment for both age groups, but there was a reduction in the protective effects for the participants over 70 (high school: OR = 0.58, 95% CI (0.39,0.87), p = .014; college: OR = 0.36, 95% CI (0.23,0.58), p < .001; college grad: OR = 0.24, 95% CI (0.14,0.42), p < .001) compared to participants 70 and under (high school: OR = 0.32, 95% CI (0.18,0.55), p < .001; college: OR = 0.11, 95% CI (0.04,0.26), p < .001; college grad: OR = 0.09, 95% CI (0.03,0.28), p < .001). Non-Hispanic White participants had lower odds of developing cognitive impairment, with an increase in the protective effects of the participants over 70 (OR = 0.19, 95% CI (0.11,0.31), p < .001) compared to participants 70 and under (OR = 0.26, 95% CI (0.11,0.61), p = .006). Other Race/Multi-Racial participants 70 and under were not significantly associated with cognitive function status, but participants over 70 were less likely to develop cognitive impairment (OR = 0.46, 95% CI (0.24,0.89), p = .032). For participants 70 and under, participants who were not currently married had higher odds of developing cognitive impairment (OR = 1.94, 95% CI (1.08,3.49), p = .038) compared to married participants. However, for participants over 70, marital status was not significantly associated with cognitive function status. Similar to obesity, annual family income was not significantly associated with cognitive function status in participants 70 and under. However, among participants over 70, an annual family income between $35,000 and $75,000 (OR = 0.48, 95% CI (0.28,0.83), p = .015) or over $75,000 (OR = 0.49, 95% CI (0.26,0.91), p = .036) was significantly associated with lower odds of developing cognitive impairment.

Table 4. *Logistic regression models stratified by age (≤ 70 and > 70)*

	≤ 70		> 70		
	OR(LCI, UCI)	p-value [a]	OR(LCI, UCI)	p-value [a]	p-value [*]
Gender					
Male					
Female	0.63(0.33,1.19)	0.17	0.96(0.67,1.38)	0.825	0.4930
Obesity					

	≤ 70		> 70		
	OR(LCI, UCI)	p-value [a]	OR(LCI, UCI)	p-value [a]	p-value [*]
Healthy					
Overweight	0.76(0.42,1.4)	0.393	0.6(0.39,0.93)	0.033	0.2646
Obese	1.17(0.6,2.28)	0.651	0.51(0.31,0.87)	0.021	
Education					
Less than HS					
HS/GED	0.32(0.18,0.55)	<0.001	0.58(0.39,0.87)	0.014	
Some College/AA	0.11(0.04,0.26)	<0.001	0.36(0.23,0.58)	<0.001	0.0192
College Grad or above	0.09(0.03,0.28)	<0.001	0.24(0.14,0.42)	<0.001	
Race					
Mexican American					
Non-Hispanic Black	0.92(0.49,1.73)	0.795	0.75(0.38,1.46)	0.4	
Non-Hispanic White	0.26(0.11,0.61)	0.006	0.19(0.11,0.31)	<0.001	0.2269
Other Race/Multi-Racial	1.39(0.76,2.55)	0.296	0.46(0.24,0.89)	0.032	
Marital Status					
Married					
Not Currently Married	1.94(1.08,3.49)	0.038	1.2(0.76,1.88)	0.445	0.2593
Annual Family Income					
Under $35,000					
$35,000-$75,000	0.6(0.27,1.32)	0.219	0.48(0.28,0.83)	0.015	0.6036
Over $75,000	0.49(0.13,1.82)	0.299	0.49(0.26,0.91)	0.036	

Note: These models include the predictor variable while factoring in all other covariates. P-value [a] refers to each level of the predictor in a multiple logistic regression model. p-value [*] refers to the interaction term between predictors and age, and p-value[*] < .05 indicates significant difference in the effects between ≤ 70 and > 70

Discussion

In this study of 2569 participants aged 60 and over, we explored the relationship between several risk factors and cognitive function status. Mexican American, non-Hispanic Black, and other race/multi-racial participants who were over 70, not currently married, and had a low level of education and low annual family income were the most likely to develop cognitive impairment. Non-Hispanic White participants who were 70 or under, married, and had a high level of education and high annual family income were the least likely to develop cognitive impairment. Consistent with our hypothesis, many risk factors had significantly different effects on cognitive function status across age groups. Compared with the lower age group, many of the risk factors' effects on cognitive function status were attenuated in the older age group. Exceptions include the non-Hispanic White and overweight risk factors, which both saw an increase in protective effect. Obesity and being other race/multi-racial were associated with an increased risk of developing cognitive impairment for participants 70 and under but were associated with a decreased risk for participants over 70. Additionally, being either overweight or obese is protective against developing cognitive impairment, although only in the older age group. We found no significant association between gender and cognitive function status.

Overall, our findings were consistent with much of the existing literature. A study on the association between numerous risk

factors and cognitive impairment (Zhang et al. 2019) found that older age, lower education level, less income, being female, and no spouse are associated with greater risk of developing cognitive impairment. These results are consistent with ours, with the exception of gender as we found that gender did not have a significant association with cognitive function status. This inconsistency in results could be due to the use of the Mini-Mental State Examination instead of the four tests we used to determine cognitive function status, or that the study's sample was Chinese participants aged 64 and above while our sample was American participants aged 60 and above. One study found that poverty is associated with a greater chance of developing cognitive impairment (Chen and Cao 2020). We found similar results, as participants with an annual family income of under $35,000 had approximately a 2 times greater risk of developing cognitive impairment when compared to participants with an income of $35,000 or over. Another study (Bloomberg et al. 2023) found that education was associated with cognitive function status, with lower levels of education associated with a higher risk of cognitive impairment. These findings are consistent with our study, with each higher level of education providing a greater resistance to developing cognitive impairment. Finally, a study on obesity and cognitive impairment (Feinkohl et al. 2018) found that obesity is positively associated with cognitive impairment, with an 1 kg/m2 increase in BMI associated with a 3% increased prevalence of cognitive impairment. We found that being overweight or obese decreased the risk of developing cognitive impairment for those over 70 years of age. The difference in results could be due to a smaller sample size (1545 vs. 2569), the use of log-binomial regression analyses instead of logistic regression analyses. This disparity of obesity status's effects between our study and Feinkohl et al indicate other confounding variables may play a role in the association between obesity and cognitive impairment.

Our study showed that age significantly moderated the association between risk factors and cognitive function status. Higher levels of education correspond with a lower risk of developing cognitive impairment in both age groups, with a similar pattern found in both the crude and adjusted models. Education plays a larger role in the development of cognitive impairment for participants 70 and under, consistent with other studies (Hale et al. 2020). Compared to participants with an education level lower than high school in the lower age group, participants with an education level of high school (68% decrease), college (89% decrease), and college graduate (91% decrease) all had lower odds of developing cognitive impairment compared with the higher age group (42%, 64%, 76% decrease respectively). While higher levels of education are associated with a higher cognitive ability and slower cognitive decline, levels of education up until high school are associated with slower cognitive decline while levels of education past high school are associated with higher income, which in turn is negatively associated with the development of cognitive impairment (Zahodne, Stern, and Manly 2015). Overweight and obese participants who were 70 and under were not associated with cognitive function status, but both overweight and obese participants over 70 had a lower chance of developing cognitive impairment when compared to participants with a healthy weight. In our crude and adjusted models, only overweight participants were significantly associated with a 36% decrease in the odds of developing cognitive impairment after adjusting for covariates. For overweight participants over 70, this reduction increases to 40%. Although the underlying mechanism is still unknown for this relationship, weight may be confounded by economic status since obesity is inversely associated with income (Andoy-Galvan et al. 2020).

Notably, the only case where the risk of developing cognitive impairment was higher for the lower age group than the older age group was for non-Hispanic White participants. Non-Hispanic White participants who were 70 and under had a 74% decrease in the odds of developing cognitive impairment, while non-Hispanic White participants who were over 70 had an 81% decrease in the odds. No association was found with non-Hispanic black participants, and other race/multi-racial participants over 70 had a 54% decrease in the odds of developing cognitive impairment. Being married plays

a huge role in protecting against cognitive impairment in participants 70 and under, as participants who were not currently married were 94% more likely to develop cognitive impairment. For participants over 70, there is no significant association between marital status and cognitive function status. Finally, compared with participants over 70 with an annual family income of less than $35.000, an annual family income of $35,000-$75.000 and over $75.000 is associated with a 52% and 51% decrease in the likelihood of developing cognitive impairment respectively. For participants 70 and under, there is no significant association between annual family income and cognitive function status. Age attenuates the effect of many protective factors, indicating that to create a more effective and personalized prevention/treatment plan, healthcare providers or policymakers need to allocate more resources to individuals who have protective factors more vulnerable to age. Further research is needed to identify risk factors for the lower age group.

Our study has several strengths. First, we used a large sample from NHANES, creating a more accurate representation of our population. In addition, we individually assessed the relationship between each risk factor and the four cognitive tests to provide more insight than would be possible with only the total score. Moreover, we assessed the risk factors stratified by age group, enabling us to delve into the disparities of the risk factors' effects between the two age groups. However, our study is not without limitations. First, this study is cross-sectional, preventing us from demonstrating any causality between the risk factors and cognitive function status. Furthermore, not all possible variables are included and adjusted for in the study, so unmeasured variables could yield different results. Additionally, some risk factors like annual family income are self-reported, so the data could contain inaccuracies. Finally, although we used a large sample, the study population is limited to US residents.

Conclusion

Age, obesity, education, race, marital status, and annual family income are all significantly associated with cognitive function status. Many of the risk factors are attenuated by age, some are significant only for participants 70 and under (marital status), and others are significant only for participants 70 and over (obesity and annual family income). Our results can help inform policies related to cognitive impairment to benefit patients and healthcare providers. Further studies could investigate why certain risk factors are not attenuated by age or include covariates not present in this study such as alcohol use or smoking.

Declaration

Ethics Statement

The CDC's National Center for Health Statistics Institutional Research Ethics Review Board approved the NHANES survey protocol. Every participant provided written informed consent, and this study was approved by the NCHS Research Ethics Review Board (https://wwwn.cdc.gov/nchs/nhanes/default.aspx).

Author Contributions

SW conducted data collection, conducted analyses, and wrote the manuscript. XY modified the manuscript. SW and XY conducted data interpretation. SW and XY made the tables. XY designed the study and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was not supported by any funding.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

Data is available upon request.

Acknowledgment

I want to thank my co-author and mentor Xin Yang for his continual guidance and encouragement throughout the project. I also want to thank my parents for their advice and support throughout the project.

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submitted 22.08.2023;
accepted for publication 20.09.2023;
published 8.10.2023

Contact: stevenszwang@gmail.com

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